Non-steroidal anti-inflammatory drugs and postoperative analgesia

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Table of Contents

List of Tables

List of Figures

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Our research nurse, Elizabeth Douglas, did the pain assessments, and also contributed in many practical aspects of the investigations.

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Declaration

I composed the thesis, and all books and papers were consulted by me personally. I performed the work between 1987 and 1991 while I was a Lecturer in the University Department of Anaesthetics in the Royal Infirmary, Edinburgh. The following publications include work presented, and are enclosed at the back of the thesis:

Power I, Noble DW, Douglas E, Spence AA. Comparison of i.m. ketorolac trometamol and morphine sulphate for pain relief after cholecystectomy. Br J Anaesth 1990;65:448-455.

Power I, Chambers WA, Greer IA, Ramage D, Simon E. Platelet function after intramuscular diclofenac. Anaesthesia 1990;45:916-919.

I designed all the studies described, and was directly responsible for collecting and analysing the data from all the investigations. In the studies of platelet function, I performed most of the skin bleeding times, and some (about 10%) of the *in vitro* platelet aggregation tests when the laboratory technician was not available.

The more specialized laboratory investigations of platelet and renal function were of necessity carried out in collaboration with Dr IA Greer of the MRC Reproductive Biology Unit, and Dr AD Cumming of the Medical Renal Unit, of the Royal Infirmary of Edinburgh. I collected the blood and urine samples for these investigations.

I analysed the data on an IBM compatible personal computer using the statistical programme 'Minitab', and constructed the figures using the graphics package 'SlideWrite Plus'.

Abbreviations

GFR	glomerular filtration rate
LAS	lysine acetyl salicylate
NSAID	non-steroidal anti-inflammatory drug
PCA	patient controlled analgesia
PG	prostaglandin
PID	pain intensity difference
SD	standard deviation
SE	standard error
SPID	summed pain intensity difference
TOTPAR	total pain relief score
Tx	thromboxane
VAS	visual analogue scale
VRS	verbal rating scale

Summary

The non-steroidal anti-inflammatory drugs (NSAIDs) are being promoted for use as postoperative analgesics, and diclofenac is already used widely for that purpose. Ketorolac is a new drug and early reports have indicated that it may be useful after surgery. The advantages claimed for these drugs are that they are effective analgesics which do not produce sedation, respiratory or gastrointestinal depression, or dependence. Unfortunately, NSAIDs do have important side-effects because they inhibit tissue prostaglandin production.

In this thesis, ketorolac is assessed both in comparison with, and as an adjunct to, morphine. The effects of ketorolac and diclofenac on platelets and the kidneys were studied.

Ketorolac compared with morphine

A double-blind, randomized pilot study compared intramuscular ketorolac 30 mg with morphine 10 mg in twenty patients having cholecystectomy. Assessments were made immediately after surgery by two observers using a simple rating scale. Ketorolac gave analgesia equivalent to morphine, and on the basis of these results, a larger study was carried out to investigate in detail the use of this new NSAID after upper abdominal surgery.

Intramuscular ketorolac 30 mg was compared with morphine sulphate 10mg after cholecystectomy in a double-blind, multiple dose, randomized study of one hundred patients. Specific assessments of pain were made immediately after operation (day 1), and the next morning (day 2). Pain intensity (verbal rating scale and visual analogue scale) was recorded before injection and then over a six hour period. Pain relief was also assessed. Time to commencing

oral intake and the duration of intravenous fluids were recorded. Adverse events were noted. Ketorolac produced significantly less analgesia than morphine on day 1 when pain intensity was severe, but on day 2 in the presence of moderate pain the two drugs gave a similar effect. Repeated intramuscular administration of ketorolac did not produce any serious adverse effects. The value of using an observer to assess pain in the immediate postoperative period was confirmed.

Ketorolac as an adjunct to morphine

The possible opioid sparing effect of ketorolac was investigated in seventy-five patients having thoracotomy who were given access to intravenous morphine using patient controlled analgesia. In a double-blind randomized study, patients were given six hourly intramuscular injections of ketorolac 30 mg, ketorolac 10 mg, or placebo for forty-eight hours from the end of surgery. The consumption of morphine, pain scores, sedation, compliance with physiotherapy, and respiratory effects were compared between the groups at intervals during the study. Ketorolac did not significantly reduce morphine requirements or improve pain assessments, but was associated with a higher study completion rate, and less sedation and lower arterial blood carbon dioxide tensions in the late postoperative period. No serious side-effects were encountered with ketorolac.

The effect of ketorolac and diclofenac on platelet function

The effect of ketorolac and diclofenac on platelet function and haemostasis was investigated in patients having surgery who had also been given prophylactic subcutaneous heparin. Platelet function was measured *in vivo* by the skin bleeding time, and *in vitro* by whole

blood platelet aggregation studies. During cholecystectomy, ketorolac 30 mg intramuscularly prolonged skin bleeding time, although not beyond the normal range, and inhibited platelet aggregation within one hour of administration, but operative blood loss was not increased. Diclofenac 75 mg given during thoracotomy similarly prolonged skin bleeding time and reduced platelet aggregation, and blood loss was not increased.

The effect of ketorolac in combination with dextran-70 was observed in healthy volunteers. Skin bleeding time, platelet aggregation, venous blood thromboxane generation, von Willebrand factor antigen, factor VIII coagulant activity, and tissue plasminogen activator antigen were measured for effects on platelets, coagulation factors, and fibrinolysis. Ketorolac markedly reduced blood thromboxane generation and inhibited platelet function. Dextran reduced factor VIII coagulant activity. There was evidence of a small but significant interaction between ketorolac and dextran in reducing thromboxane production.

The effect of ketorolac and diclofenac on renal function

The effect of ketorolac on renal function was assessed by measurement of plasma urea, creatinine, and electrolytes from the subjects enrolled in the cholecystectomy and thoracotomy analgesic studies. After cholecystectomy, there were few electrolyte abnormalities associated with ketorolac, although in contrast with the control group, postoperative decreases in urea and sodium were smaller, and potassium and creatinine concentrations did not decrease at all. After thoracotomy, plasma urea, creatinine and sodium concentrations rose in all groups, although high urea concentrations

were more common with ketorolac. The main finding after thoracotomy was that intramuscular ketorolac was associated with a significant rise in plasma potassium concentration.

The effect of intramuscular diclofenac 75 mg twelve hourly on renal function was investigated in twenty patients after oesophagogastrectomy in a double-blind randomized study. Urinary 6-keto-$PGF_{1\alpha}$ was used to estimate renal prostacyclin production. Assessments were made on the day before surgery and over the next two days. In the control group, urinary 6-keto-$PGF_{1\alpha}$ rose significantly after surgery and peaked in the first twenty four hours. In the diclofenac group, renal prostacyclin production did not change. Diclofenac was associated with lower urine flow rates and urinary sodium and potassium excretion on the first postoperative day, but on the next day there was no difference between the groups. The control group retained more free water on the first day after operation. One patient was withdrawn from the diclofenac group because of concern about persistently low urine output.

Other effects

No other serious side-effects were encountered. Muscle pain, often apparent after the injection of diclofenac, was not a significant problem with ketorolac.

Conclusion

In this thesis, an assessment of the appropriate use of NSAIDs in surgical patients is attempted. Ketorolac may be useful for the relief of mild to moderate pain, but it is unsuitable for the relief of severe discomfort after major surgery. Ketorolac and diclofenac inhibit platelet function soon after administration, but this should

not lead to increased bleeding. Renal prostaglandin production may be important in the immediate postoperative period, and because of this urinary output and plasma potassium should be monitored when ketorolac or diclofenac are used after major surgery.

CHAPTER 1

INTRODUCTION

1.1 The problem

Opioids have been the mainstay of post-operative pain relief, but there is now a recognition that new drugs are needed to both improve analgesia and reduce adverse effects. Increasing use is being made of the aspirin-like non-steroidal anti-inflammatory drugs which are given before, during, and after surgery. The attraction of these drugs is that they may have a significant analgesic action whilst avoiding many of the side-effects associated with opioids.

Diclofenac sodium (Voltarol, Geigy Pharmaceuticals) has been the most popular of these drugs until now. It is being promoted for post-operative analgesia and is available as oral, suppository, and intramuscular preparations. It is my impression that diclofenac has quickly become favoured by clinicians, and is being prescribed widely after many operations by anaesthetists and other medical staff.

Ketorolac trometamol (Toradol, Syntex Pharmaceuticals Ltd) is a new drug which is soon to be available for general prescription as intramuscular, intravenous, and perhaps oral preparations. Early clinical studies have indicated that it may be useful as an analgesic after surgery, and it is indeed already being promoted in other countries for that purpose.

Although many other drugs of this type have been used during surgery, it is likely that diclofenac and ketorolac will be the agents routinely used by anaesthetists and surgeons because of the encouraging clinical trials already published, and the availability of parenteral preparations.

However, there are concerns about the rapid introduction of ketorolac and diclofenac into anaesthetic and surgical practice because of the recognised side-effects of non-steroidal anti-

inflammatory drugs. The analgesic efficacy of ketorolac needs further investigation and the adverse effects of both drugs need to be assessed carefully in surgical patients.

Initial reports have indicated that these drugs may be used to relieve moderate to severe postoperative pain, and that they can be used to replace opioids. Such claims have to be substantiated because, although there have been clinical investigations using ketorolac, many have only been single-dose studies performed at different times after various types of surgical incisions, some of which would be less painful than others. Therefore, there is a need for a clinical investigation comparing ketorolac with conventional opioid therapy over a period of time after a standard surgical incision.

The non-steroidal anti-inflammatory analgesics do not have opioid-like effects, but they do unfortunately have adverse effects as a consequence of their mechanism of action, inhibition of tissue prostaglandin production. Such effects include (amongst others) impairment of platelet and renal function and peptic ulceration. It is not known whether such adverse effects will be seen when the drugs are given for a short time after surgery. Although some investigations have been performed in volunteers, there is an urgent need for careful assessment of these possible adverse effects of ketorolac and diclofenac in surgical patients, in whom any platelet and renal effects would be of prime importance.

In this thesis, the efficacy of ketorolac as a postoperative analgesic is further examined, and the potential adverse effects of these aspirin-like drugs investigated in surgical patients.

1.2 Aspirin

The analgesic, anti-inflammatory and anti-pyretic properties of an extract of willow bark was first described in the middle of the eighteenth century (1). The active ingredient was a glycoside, salicin, isolated in 1829 by Leroux. In 1875 sodium salicylate was introduced for the treatment of rheumatic and other fevers. Acetyl salicylate was synthesised by Hoffman and introduced into medical practice in 1899 by Dreser under the name 'aspirin', and quickly became accepted as an analgesic for the treatment of mild to moderate pain.

In the latter part of the nineteenth century more chemical compounds sharing some of the properties of the salicylates were synthesised. The most important of these were derivatives of para-aminophenol, and of these paracetamol is used today.

1.3 The non-steroidal anti-inflammatory analgesic drugs (NSAIDs)

In this century various synthetic substances have been developed with analgesic, anti-inflammatory and anti-pyretic properties like aspirin. One of the earliest was indomethacin, and now there are many compounds of different chemical structures in this group, known as the non-steroidal anti-inflammatory analgesic drugs or NSAIDs. These can be classed according to their basic chemical structure as pyrazolones, oxicams, and carboxylic acids:

The NSAIDs

Pyrazolones
Dipyrone

Oxicams
Piroxicam

Carboxylic acids
Salicylates: acetylsalicylic acid, diflunisal

Propionic acids: ibuprofen, naproxen, naproxen sodium, fenbufen, fenoprofen, ketoprofen.

Acetic acids:
Indolacetic acids: indomethacin
Pyrrolacetic acids: ketorolac
Phenylacetic acids: diclofenac

Anthranilic acids: mefenamic acid, floctafenine

As a group, the NSAIDs have anti-inflammatory, anti-pyretic, and analgesic actions like aspirin. Those offering the greatest potential for postoperative use have marked analgesic effects with a relatively mild anti-inflammatory action (2).

1.4 Prostaglandins

These substances were first described by Von Euler as locally active tissue agents which produce smooth muscle contraction. Their name results from the early discovery of their high rate of release from the prostate (3).

Various types of prostaglandins have now been recognised, and are all based on a 20-carbon chain molecule. The names given to individual prostaglandins relate to the chemical methods originally used to isolate them. For example, prostaglandin E (PGE) was isolated in ether, and prostaglandin F (PGF) in phosphate (fosfate in Swedish). Prostaglandins are one family of the eicosanoids ('eicosa' indicating 20), oxygenated metabolites of arachidonic acid and other polyunsaturated fatty acids of about 20 carbons in length, including leukotrienes and other lipoxygenase products (4).

1.4.1 Synthesis The basal rate of prostaglandin production is low, and synthesis is activated in response to various tissue stimuli or trauma when tissue phospholipases release arachidonic acid from membrane phospholipids (4,5). Prostaglandins are produced from arachidonic acid by the enzyme prostaglandin endoperoxide (PGH) synthase which is a membrane bound glycoprotein (molecular weight 72,000 daltons) which has cyclo-oxygenase and hydroperoxidase catalytic activities (4,6). Initially the cyclo-oxygenase inserts two molecules of oxygen into arachidonate to yield the intermediate endoperoxide PGG_2, which is converted by the hydroperoxidase to PGH_2, from which prostaglandins and thromboxanes are produced. It has been demonstrated that one gene controls the production of prostaglandin endoperoxide synthase (6). This gene has been characterised and the structure of human cyclo-oxygenase deduced as being similar to the enzyme in various animals (7). The principal products of cyclo-oxygenase are the cyclic endoperoxides PGG_2 and PGH_2, prostaglandins E_2, D_2, $F_{2\alpha}$, I_2 (prostacyclin), and thromboxane A_2 (4).

Arachidonic acid can also be metabolized by a different pathway involving the lipoxygenase enzyme, to produce various substances including leukotrienes and slow reacting substance (4). This metabolic pathway is not directly affected by cyclo-oxygenase inhibitors.

1.4.2 Catabolism Prostaglandins are broken down rapidly after being formed to inactive metabolites and are not thought to circulate in the bloodstream unchanged (8,4). There are specific enzymatic pathways for the catabolism of prostaglandins but, in addition, some cyclo-oxygenase products are chemically unstable. For example, prostacyclin (PGI_2) spontaneously undergoes rapid nonenzymatic

hydrolysis to 6-keto-$PGF_{1\alpha}$ which is then enzymatically metabolized to 2,3-dinor 6-keto-$PGF_{1\alpha}$. Similarly thromboxane A_2 is very unstable, degrading quickly to thromboxane B_2 (TxB_2). The rapid spontaneous breakdown of these substances means that measurement of the inactive metabolite is often used as a reliable indicator of the rate of synthesis of the parent compound.

Enzymatic and nonenzymatic breakdown tend to limit the action of prostaglandins to the site of synthesis, and they can be thought of as local hormones allowing tissues to react to local conditions in response to specific stimuli without having systemic effects (5).

1.5 Mechanisms of action of aspirin and the NSAIDs

Many of the effects of these drugs, including analgesia, can be attributed mainly to inhibition of tissue prostaglandin synthesis. This may not explain all the actions of the NSAIDs, which may additionally be produced by the inherent ability of these chemical substances to interfere with the cellular processes involved in neutrophil activation by inflammatory stimuli.

1.5.1 Inhibition of prostaglandin synthesis (figure 1)

Although salicylates had been used clinically since the nineteenth century it was not until the middle of the twentieth century that their mechanism of action was discovered. In 1971 aspirin and indomethacin were shown to inhibit the production of prostaglandins in various tissues (9,10,11).

It has now become clear that NSAIDs work by inhibiting the cyclo-oxygenase component of prostaglandin endoperoxide (PGH) synthase (12,13,1,6), and thus prevent the synthesis of prostaglandins from membrane phospholipids. The NSAIDs and aspirin are sometimes

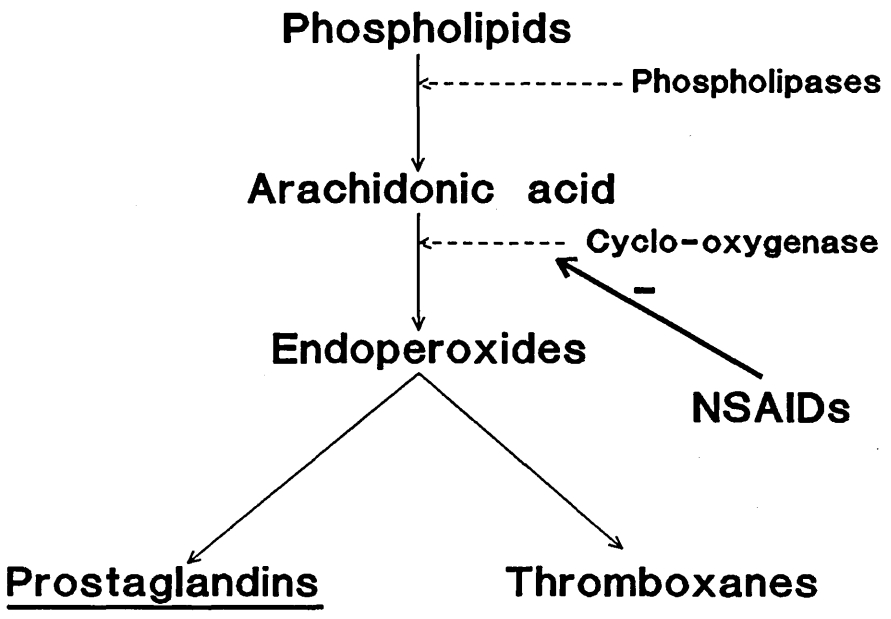

Figure 1 The mechanism of action of the NSAIDs.

therefore described as "cyclo-oxygenase inhibitors". Aspirin first binds with the cyclo-oxygenase site of PGH synthase and then acetylates the protein at Ser530, thereby interfering irreversibly with arachidonic acid interaction (6). Acetylation of PGH synthase at the serine group by aspirin leads to loss of the cyclo-oxygenase, but not hydroperoxidase, activity (14). Unlike aspirin, the NSAIDs do not acetylate cyclo-oxygenase, but inhibit it reversibly and therefore only affect prostaglandin synthesis while there are effective plasma levels of the drug present. By inhibiting cyclo-oxygenase, aspirin and the NSAIDs also prevent the production of thromboxanes.

Paracetamol, which has anti-pyretic and analgesic but not anti-inflammatory effects, may primarily inhibit cyclo-oxygenase in the central nervous system, whereas the NSAIDs affect the enzyme in various tissues (15).

1.5.2 Other mechanisms of action Although the mechanism described above is accepted for the analgesic and antipyretic effect of aspirin and the NSAIDs, it has become obvious that it may not fully explain their anti-inflammatory effects (16). Certain problems have persisted in explaining the anti-inflammatory action of NSAIDs solely by an effect on prostaglandin synthesis. For example, sodium salicylate has no effect on prostaglandin synthesis but is an effective anti-inflammatory agent, and aspirin itself exhibits anti-inflammatory effects only at doses far higher than those required to inhibit prostaglandin synthesis.

It seems that some of the anti-inflammatory action of these drugs may result additionally from a completely different mechanism; inhibition of neutrophil activation by inflammatory stimuli (16,17). When exposed to certain ligands, neutrophils are activated by 'twin

signals', intracellular calcium and protein kinase C, and NSAIDs seem to affect these signals, inhibiting neutrophil aggregation *in vivo* and *in vitro* (18). This may be a chemical effect related to NSAID molecular structure, as they are planar lipophilic molecules which inhibit many membrane processes. NSAID inhibition of cell aggregation extends even to primitive marine cell cultures which do not synthesise prostaglandins (16,18), suggesting that these effects are a basic chemical property of the drugs.

1.5.3 The analgesic effect of NSAIDs Tissue injury leads firstly to nociception by damage to nerve endings, secondly to inflammation with the release of chemical substances, including prostaglandins, from damaged tissues, and thirdly to hyperalgesia produced by sprouting of damaged nerves and capillaries, and invasion of phagocytes and fibroblasts (19,20,21).

Prostaglandins are involved in the tissue reaction to injury, and PGI_2 and PGE_2 produced at the site of tissue damage sensitise pain receptors to histamine and bradykinin and produce hyperalgesia (12,19,22). It is unclear whether prostaglandins produce pain themselves or whether they only increase the effect of other painful stimuli on nerve endings. Nociceptors are known to be sensitised by painful stimuli and prostaglandins may have a role in this process (23). In addition, PGE increases the response from isolated single afferent C fibres in response to heat and bradykinin, an effect prevented by lysine salicylate (24). By preventing prostaglandin synthesis, NSAIDs inhibit nociceptor sensitisation and act as analgesics (12,22,5).

Because they are thought to act by inhibiting cyclo-oxygenase in damaged tissues, NSAIDs have been described as peripherally acting analgesics. Although this is the case, paracetamol, which is not usually classed as an NSAID, differs in that it is thought to act by inhibition of cyclo-oxygenase in the central nervous system (15) without the peripheral side-effects of the aspirin-like drugs. It may be that different drugs inhibit cyclo-oxygenase and prostaglandin production in different tissues. The NSAIDs may also have a central effect in addition to their peripheral action, as aspirin has been shown to have effects on the central nervous system (25) and NSAIDs do diffuse into the cerebrospinal fluid (26). Indomethacin, ibuprofen, and diclofenac depress the evoked response of rat thalamic neurones to peripheral nerve stimulation in a dose-dependent fashion, and this central action may contribute to their analgesic effect (27).

1.6 Pain relief after surgery

Despite the widespread availability of powerful analgesics, patients can still experience severe pain for an appreciable time after surgery (28,29). This seems unacceptable when modern anaesthesia allows the painless performance of surgery. The importance of improving postoperative analgesia has been emphasised in the findings of a recent joint anaesthetic and surgical commission on this subject (30). Opioids are the mainstay of postoperative analgesia, with local anaesthetic techniques being used increasingly commonly. NSAIDs are now available in parenteral forms, and may be a useful addition to existing techniques for postoperative analgesia (31,19).

1.6.1 Opioids At present, opioids are normally used to provide analgesia after operation, but, although they are powerful analgesics, they are often not employed effectively. Fear by the prescribers of overdosage and creating dependence seems to limit their administration (32,28). In addition, opioids are associated with harmful side-effects even at normal doses. Sedation, respiratory depression, disturbances of breathing patterns, nausea and vomiting are all associated with their use (33).

1.6.2 Local anaesthetic techniques Nerve blockade can give excellent postoperative pain relief, but circumstances may limit the application of local anaesthesia. Peripheral nerve blocks cannot be performed for all operations, and there is often a problem of providing analgesia when the effect wears off. Spinal analgesia can be used for many types of operation, and continued into the postoperative period to provide analgesia, but potential side-effects restricts the use of this technique to high-dependency areas.

1.6.3 NSAIDs There is therefore a need for alternative pharmacological agents to complement or replace existing methods for pain relief after operation. The NSAIDs may fulfill that role (31), and are mentioned in the report of the commission into postoperative pain as drugs worthy of further investigation, although their side-effects are noted (30). Potentially, they offer effective analgesia without the morphine-like side effects of respiratory, central nervous, or gastrointestinal depression, and they do not produce addiction.

1.7 The NSAIDs as postoperative analgesics

To be useful after surgery, when the patient usually cannot take oral medications, a NSAID would have to be available as a parenteral preparation. Intravenous forms of salicylates are available, but not widely used. Indomethacin can be given intravenously and by suppository, but side-effects have limited its use. Diclofenac (Voltarol, Geigy Pharmaceuticals) is available as an injection for intramuscular use, as well as tablet and suppository preparations, and is increasingly being used to relieve pain after operation. Ketorolac trometamol (Toradol, Syntex Pharmaceticals Ltd) is a new drug which has been licensed recently for intramuscular use as an analgesic, but has not yet been marketed in the United Kingdom by the manufacturer.

1.7.1 Salicylates Aspirin is normally considered to be an oral analgesic for relief of mild or moderate pain, but intravenous preparations of salicylates have been compared with opioids in the presence of severe pain after surgery (34,35,36). Lysine acetyl salicylate (LAS) 1.8g intravenously is equivalent to 1g of aspirin, and a single intravenous bolus gave poor relief of severe, immediate, postoperative pain compared with morphine 10 mg intramuscularly (36). Studies using continuous infusions of LAS have, however, produced more encouraging results. After inguinal herniorrhaphy, LAS infusions were as effective as morphine and associated with less drowsiness, nausea, and vomiting (34). Following thoracic surgery, LAS 7.2g over 24 hours gave equivalent analgesia to morphine 40mg, but the authors did note that the salicylate was not as effective in the face of severe pain present in the immediate postoperative period (35). After major gynaecological surgery, LAS was at least as good an analgesic

as morphine, and tended to produce less nausea, vomiting, and respiratory impairment (37). Although such studies give a favourable view of infusions of LAS, the drug is not used in practice, perhaps as a result of the high incidence of injection site problems including venous thrombosis.

1.7.2 Indomethacin Indomethacin has marked anti-inflammatory activity, and is normally used for the treatment of specific conditions as gout. A limited number of investigations have used indomethacin after surgery, but the lack of an intramuscular preparation has probably restricted the use of this drug.

An early study using indomethacin (100mg by suppository, 8 hourly for 3 days) found an impressive reduction in pain intensity and morphine requirement, and some evidence of improved respiratory function after major abdominal surgery (38). Although the analgesic effect was promising, the platelet side-effects were noted because indomethacin was associated with bleeding problems, including wound haematoma, haematemesis, and increased loss from surgical drains (38).

Efficacy has been confirmed in other clinical studies mostly using indomethacin by suppository. 0.8 mg/kg intravenously given before surgery, followed by 100 mg rectally 8 hourly, reduced opiate requirements and improved analgesia a little after hysterectomy, but again there was an associated increase in bleeding (39), a side-effect also confirmed in other studies (40). Given by suppository after thoracotomy, indomethacin (400mg, then 100 mg 12 hourly) improved analgesia and reduced opioid requirements, without side-effects (41). Indomethacin has been used in paediatric surgery, and in children after general surgical operations a bolus of intravenous

indomethacin 0.35 mg/kg followed by 0.07 mg/kg/h improved analgesia and reduced the incidence of pyrexia with no serious adverse effects, although bleeding was increased a little (42).

1.7.3 Piroxicam Piroxicam (Feldene, Pfizer) is not available in a parenteral preparation, but oral administration after hip surgery performed under spinal anaesthesia reduced patient requirements for morphine by half, with no significant side-effects (43). Pretreatment with piroxicam before oral surgery reduced analgesic requirements and increased the time before analgesia was requested (44).

1.7.4 Diclofenac Diclofenac (Voltarol, Geigy Pharmaceuticals) is available as tablets and suppositories as well as a preparation for intramuscular use. The injection has been promoted for postoperative use in a dose of 75 mg intramuscularly twelve hourly. There have been a considerable number of studies concerning the postoperative use of diclofenac (45), although no direct comparison has been made with opioids after upper abdominal surgery.

Intramuscular diclofenac can be given in a dose of 75 mg up to twice daily, and because of the short half-life (45) injections can be repeated after only thirty minutes (Data sheet, Voltarol, Geigy Pharmaceuticals). Parenteral diclofenac should only be given for up to two days by deep intramuscular injection because of injection site problems, and the total daily dose should not exceed 150 mg (data sheet). These safety restrictions on diclofenac administration are often misinterpreted as meaning that intramuscular diclofenac is long acting and only has to be given every twelve hours. In fact, the elimination half-life of diclofenac is only one to two hours (45, data sheet, Voltarol) suggesting that any effect is short lived, and

the safety restrictions on dosage should be recognised as a clear disadvantage. As with most NSAIDs, there is a lack of information concerning safety evaluation of this drug when used after surgery.

In a double blind, randomized, study performed the day after hip surgery, diclofenac 75 mg produced better analgesia than pethidine 50 mg, with fewer side-effects (46). After hip replacement, diclofenac 75 mg was a better analgesic than papaveretum 10, 15, and 20 mg (47). In the same study, the diclofenac patients also resumed walking more quickly, had less cognitive impairment, and were better in overall nursing scores of well being. This study can be criticised because it was not completely blinded. The analgesic regimens were different: the diclofenac group were given regular injections while the papaveretum patients only received injections on demand.

After major abdominal surgery, diclofenac 75 mg twelve hourly significantly reduced morphine requirements by 30% on average as delivered by a patient controlled analgesic device, although concern was expressed about the effect on platelets and bleeding (48). In contrast, other studies have found that single doses of diclofenac confer no advantage after upper abdominal surgery. Rectal diclofenac did not augment opioid analgesia after upper abdominal surgery (49), and intravenous diclofenac showed no analgesic effect in the immediate postoperative period (50).

Diclofenac is an effective analgesic after minor surgery. After day-stay arthroscopy surgery, diclofenac given at induction of anaesthesia was as effective as fentanyl (51). Pretreatment with diclofenac markedly reduces pain after removal of impacted wisdom teeth, intravenous administration giving better analgesia than fentanyl (52).

Various studies have found that diclofenac is useful in paediatric surgery. In children having tonsillectomy, rectal diclofenac is as effective as pethidine (53) and papaveretum (54). After inguinal herniotomy in children, rectal diclofenac was as effective as caudal local anaesthetic block with bupivacaine (55).

1.7.5 Ketorolac Ketorolac trometamol (Toradol, Syntex Pharmaceuticals Ltd) (56) is a new drug which is being assessed as a postoperative analgesic (2), and will be available for general use in the near future. Ketorolac is available already in the United States for short-term management of pain, and it is the first injectable NSAID to be marketed as an analgesic in that country (57).

Chemically it is a pyrroloacetic acid and is similar to tolmetin and zomepirac. It is prepared as the trometamol salt to increase solubility (the US terminology is tromethamine). The intramuscular preparation is a 3% solution in water with ethanol.

In animal models, ketorolac has analgesic, antipyretic, and anti-inflammatory actions attributed to prevention of prostaglandin synthesis by inhibition of the enzyme cyclo-oxygenase, and at clinically used doses it has a much greater analgesic than anti-inflammatory effect (58). In animal experiments, the systemic analgesic effect of ketorolac was some 800 times more than aspirin, and was greater than the systemic anti-inflammatory action (58,59).

Ketorolac does not have the side-effects associated with opioids. It does not produce respiratory depression (60,61), reduction of gastrointestinal motility (62), addiction (63), or psychomotor effects (64).

The absorption of ketorolac is rapid after oral ingestion or injection. After oral administration, the average time to peak plasma concentration is 48 minutes, and, after intramuscular injection, 54 minutes (65,66). The bioavailability of oral ketorolac is very high, with little presystemic metabolism, and like other NSAIDs it is extensively, 99%, protein bound (67,57). The volume of distribution at steady state is 0.1 litre kg^{-1} (65,66). In pregnancy, ketorolac crosses the placenta, but transfer is low in comparison with the opioids (68). Elimination is mainly by glucuronic conjugation and urinary excretion, although parahydroxylation also occurs (66). The elimination half-life of ketorolac is around four to six hours (66,67) but this may be prolonged in the elderly (69) or by renal impairment (70), necessitating a reduction in dose.

As well as oral and parenteral systemic injections, ketorolac has been studied as a local gel for ankle sprains (71), and an opthalmic preparation for inflammatory eye disorders (72,73).

Oral ketorolac has been investigated as an analgesic after various forms of surgery. 10 mg ketorolac was as effective as 650 mg of aspirin in relieving postpartum uterine pain (74). After gynaecological surgery, ketorolac 10 mg was as effective as paracetamol 1000mg and codeine 60 mg (75). A number of studies have used ketorolac after orthopaedic surgery when opioids are no longer required and have found that ketorolac is as effective as paracetamol, diflunisal,and dihydrocodeine (76,77,78).

Intramuscular ketorolac has been shown to be an effective analgesic after minor surgery. Ketorolac 30 and 90 mg was more effective than pethidine 50 or 100 mg after oral surgery (79), and 30 mg was superior to pentazocine 30 mg in treating postoperative pain (80). When given as an intramuscular premedication before minor

surgery, ketorolac was as effective as morphine in reducing postoperative pain, effective blood levels were attained, but the opioid gave more sedation (81).

Ketorolac given by injection has also been found to be equipotent with opioids after major surgery. In single dose intramuscular studies performed on the first or second day after operation, ketorolac 10, 30 and 90 mg were compared with morphine 6 and 12 mg after major surgery. In the presence of moderate to severe postoperative pain, ketorolac 30 or 90 mg was as effective as morphine 12mg with a longer duration of action. Ketorolac 30 or 90 mg was a better analgesic than morphine 6 mg, and ketorolac 10 mg was as effective as morphine 6 mg (82,83).

The effect of combining ketorolac and opioid therapy has been studied after upper abdominal surgery. Continuous intramuscular infusions of ketorolac (1.5 and 3 mg/hr) reduced patient opioid (morphine) requirements by 30% over twenty-four hours. The ketorolac group had lower pain scores and those patients given the higher dose of ketorolac had lower postoperative increases in $PaCO_2$ than the control group (84). Ketorolac administration may therefore have a morphine sparing effect which also minimises the respiratory side-effects of the opioid.

1.7.6 Other NSAIDs Ibuprofen, given by suppository, significantly reduced patient opioid requirements after lower abdominal surgery (85). Intravenous ketoprofen was associated with better recovery, lower pain scores, and a reduced requirement for further analgesia than pethidine following nasal surgery (86).

1.8 NSAID side-effects

Unfortunately, the NSAIDs do have side-effects as a consequence of their mechanism of action, and they are a major cause of serious adverse drug reactions reported to the regulatory authorities (87,88). Because prostaglandins act as local tissue regulators, inhibition of their synthesis and release may produce unfortunate adverse effects (5). Essentially these effects are well known and recognised as a consequence of long term aspirin or NSAID therapy (89,87). In surgical patients, the main concerns are the platelet, renal, and peptic ulceration side-effects (30). As yet few studies have investigated the side-effects produced when NSAIDS are given for a short period after surgery, and most reports and investigations of toxicity concern long term administration. In certain respects the surgical patient may be more at risk from NSAID induced side-effects and this led one reviewer to comment:-

> " NSAID therapy should also be withheld from patients who are about to undergo surgery because of the risk of acute renal failure, as well as of impaired hemostasis due to the effects of these agents on platelet function" (90).

There have been many studies on the analgesic effect of NSAIDs after surgery, but there is a definite paucity of information about the safety aspects of these agents, especially with regard to the platelet and renal effects.

1.8.1 Platelet function and haemostasis Platelet cyclo-oxygenase is essential for the production of cyclic endoperoxides and thromboxane A_2, important mediators of aggregation and

vasoconstriction, processes which constitute the primary haemostatic response to vessel injury (91). Glycoprotein receptors for TxA_2 and cyclic endoperoxides have been isolated in the membranes of human platelets using radiolabelled ligands (92,93). While it is clear that NSAIDs and aspirin, which has a similar inhibitory effect on cyclo-oxygenase, inhibit aggregation and prolong bleeding time in volunteers (94,95,96), there is little information on the perioperative situation where the haemostatic response may be altered by the stress of surgery.

Aspirin ingestion is well recognised as a factor in increasing blood loss after surgery (97), a problem also encountered with NSAIDs (38,39,48). Aspirin ingestion in the seven days before cardiac surgery increases the risk of reoperation for rebleeding, the requirement for blood products including platelets and prolongs the patients stay in intensive care and in hospital (98). The haemostatic problem after aspirin may last up to 14 days because it inhibits platelet cyclo-oxygenase irreversibly by acetylation (99,6,14). Haemostasis returns to normal after aspirin only when new platelets have been synthesised because, once formed, they are incapable of making new enzymes. In comparison, other NSAIDs are reversible cyclo-oxygenase inhibitors and only affect platelets while there are effective circulating concentrations of the drug present (99,100,101). It is likely therefore, that the duration of the anti-platelet effect of NSAIDs will be shorter than aspirin, although the magnitude of effect may be the same.

Ketorolac is known to inhibit platelet function in volunteers (102,103), as does diclofenac (45), which has produced severe spontaneous bruising in a patient (104). There is little information

about the importance of the anti-platelet effects of these drugs in surgical patients, although concern has been expressed about using diclofenac when extensive surgical dissection is required (48).

Surgical patients also receive other agents which can affect bleeding and could interact with a NSAID to produce increased operative loss. Postoperative pulmonary embolus is an important cause of death for which heparin, dextran, and warfarin may be used as prophylaxis (105,106). The problem is that these agents could interact with NSAIDs and lead to increased bleeding at operation.

The combination of heparin and ketorolac has been studied in volunteers (103) and suggests that any interaction is probably clinically insignificant. Few studies have examined the effect on haemostasis and operative blood loss of giving a NSAID and subcutaneous heparin together to patients having surgery.

Dextran is also used during surgery in certain circumstances as prophylaxis against venous thrombosis, especially after major orthopaedic procedures (105). There has been no investigation of the combined effect on haemostasis of giving dextran and a NSAID simultaneously. The consequences of any interaction between NSAIDs and dextran may be severe during surgery and should be investigated before the combination is given to patients.

Surgical patients may be on long term warfarin therapy, but this is usually discontinued for the time of surgery. Warfarin may be useful in low doses as prophylaxis against pulmonary emboli (105), although this is not common practice. Volunteer studies have shown that simultaneous administration of ketorolac with warfarin produced no interaction, although close monitoring of patients on such combination therapy was advised (107).

1.8.2 Renal function The adverse renal effects of NSAIDs are serious and have been well described, representing a significant problem in the use of these drugs (90,108,109,110,111,112). Most studies have concerned the effect of long term oral NSAID intake for medical conditions, and have found that regular consumption of non-narcotic analgesics should be routinely considered as a risk factor for any non-congenital cause of chronic renal failure (113). As yet, little work has been done on the acute effects on renal function of short term parenteral administration of NSAIDs in the perioperative period (19).

Renal prostaglandin physiology The kidney has enzymes for the metabolism and catabolism of most prostaglandins (114) where they seem to act as local tissue hormones (115). Renal prostaglandins have various physiological roles, including the maintenance of blood flow and glomerular filtration rate (GFR) in the presence of vasoconstrictor hormones, regulation of tubular handling of electrolytes, and modulation of the effects of other renal hormones (116,90,108,115).

Prostacyclin (PGI_2) and PGE_2 are the prostaglandins produced in greatest abundance in the kidney. There is a degree of specialisation of function and these two prostaglandins are produced in different sites and have different actions (117,112,114). PGI_2 is produced mainly in the cortex in renal vessels and glomeruli, and acts as a vasodilator and maintains GFR. PGE_2 is a medullary hormone synthesised in the collecting tubules where it enhances sodium, chloride and water excretion, in the medullary interstitial cells producing vasodilatation and natriuresis, and in the glomeruli maintaining glomerular filtration rate.

Other prostaglandins are produced in the kidney, including $PGF_{2\alpha}$ which increases NaCl and water excretion in the collecting tubules, and thromboxane (TxA_2), which may reduce GFR after renal transplantation (118).

Prevention of renal prostaglandin synthesis by NSAIDs can interrupt these physiological processes and lead to clinically significant adverse effects in certain circumstances, even after only a few doses (90,108,109).

Renal blood flow Prostaglandins E_2 D_2 and I_2 (prostacyclin) are potent renal vasodilators which have a protective role during acute renal hypoperfusion (119). Normally, renal prostaglandins are thought to have little effect on the regulation of blood flow, but in certain clinical states their importance is increased greatly.

Renal vasoconstrictor hormones such as renin, angiotensin, noradrenaline, and vasopressin produce a compensatory increase in renal vasodilator prostaglandins by induction of the enzyme phospholipase (115). This enzyme breaks down membrane phospholipids to produce arachidonic acid, the basic metabolic requirement for prostaglandin synthesis by cyclo-oxygenases (figure 1). The resultant increase in prostaglandin production tends to maintain renal perfusion, counteracting the effect of the vasoconstrictor hormones.

In clinical conditions where there are high concentrations of circulating vasoconstrictors, blood flow to the kidney may become dependent on renal prostaglandin synthesis. NSAID administration can then lead to impaired renal function and failure by removing the protective vasodilator effect of prostaglandins and allowing the unopposed action of circulating vasoconstrictor hormones

(90,108,109,110,115,120). Medical conditions characteristic of this include cardiac failure, cirrhosis with ascites, and hypovolaemia and hypotension.

During and after anaesthesia and surgery there is an increase in the level of hormones including catecholamines, angiotensin, vasopressin, and renin described as part of the metabolic response to stress (121,122). Such hormonal changes can impair renal function during anaesthesia (123,124,125). In the face of such increased vasoconstrictor hormonal activity, it has been postulated that there is a compensatory increase in the production of local renal prostaglandin vasodilators and that the anaesthetised patient is particularly susceptible to the adverse renal effects of NSAIDs (90,120,109). It is indeed known that the anaesthetised, laparotomised, dog is much more sensitive to the adverse renal effects of indomethacin than the awake animal (126).

The risk of unexpected sudden blood loss occurring leading to acute hypotension during surgery may further increase the risks associated with NSAID administration. During experimental haemorrhage and hypotension, renal prostaglandins oppose the vasoconstrictor action of angiotensin II and maintain blood flow (127). During hypotension renal prostaglandins activate specific R2 chemoreceptors which excite afferent nerves and thus contribute to autoregulation of renal blood flow (128). Administration of NSAIDs could also impair this protective mechanism of prostaglandins during episodes of hypotension, which can occur unexpectedly during surgery.

Renal tubular function Prostaglandins are also important in determining the renal tubular handling of electrolytes (115,90). Prostaglandins are thought to inhibit reuptake of chloride ions from the ascending limb of the loop of henle, resulting in increased

excretion of salt and water. Animal experiments have shown that normal tubular excretion of sodium and water is dependent on prostaglandins which act by suppression of renal medullary sodium-potassium-ATPase (129). PGE_1 stimulates chloride ion secretion in renal epithelial cells (130). Infusions of iloprost, a synthetic prostacyclin analogue, reduces the reabsorption of sodium in the loop of Henle in humans, increasing salt and water excretion (131).

Interaction with renin and vasopressin Renal prostaglandins increase renin release and inhibit the effect of vasopressin on the collecting ducts (115,116,108).

Prostacyclin infusions increase renin release in man (132). Because renin is one the main factors in controlling aldosterone, renal prostaglandins can increase aldosterone release and potassium excretion. Excessive renal prostaglandin production has been implicated in the hypokalaemic alkalosis associated with the high renin, aldosterone, and angiotensin II concentrations of Bartter's Syndrome in which platelet defects are also present (133).

NSAIDs are known to potentiate vasopressin (108,115,116). There is an interaction between vasopressin and renal prostaglandins so that each modulate the effect of the other (134). Vasopressin increases the production of cyclic AMP by renal tubular cells thus increasing permeability and water reabsorption. This effect is opposed by renal prostaglandins, and it has been demonstrated that PGE_2 blocks the effect of vasopressin hormone on the collecting tubule increasing water excretion (108,134). Indeed, indomethacin has been used to treat nephrogenic diabetes insipidus (135).

NSAIDs and renal function In physiological terms, renal prostaglandins are therefore important in the control of renal blood flow, renal tubular function, renin and aldosterone release, and the action of vasopressin. By inhibiting prostaglandin production, NSAIDs may reduce renal blood flow and impair excretion of water and electrolytes (90,108,115,120). The clinical significance of this will depend on the patients general condition before the drug is administered (111).

There have been few studies on the renal effect of short term NSAID administration, but adverse effects can occur after only a few oral doses in susceptible individuals. In patients with asymptomatic renal failure a brief course of ibuprofen can precipitate acute renal failure (110). In susceptible patients, short acting NSAIDs may affect renal function even after a very short exposure (109,110). Risk factors for NSAID nephrotoxicity include age (greater than sixty years), atherosclerosis, diuretic therapy, existing renal impairment, and states of renal hypoperfusion including cardiac failure, hepatic cirrhosis, and hypovolaemia (111). Many of these risk factors are present in patients having surgery, and general anaesthesia and surgery may produce an additional tendency towards NSAID nephrotoxicity. Therefore, many surgical patients may be susceptible to the adverse renal effects of NSAIDs, and clinical studies are required to investigate this.

Chronic renal failure A common cause of drug induced chronic renal failure is "analgesic nephropathy" involving interstitial nephritis and papillary necrosis. This is most often associated with phenacetin, but has been reported after other NSAIDs (90).

Renal flank pain syndrome A sudden onset renal failure with haematuria and flank pain has been reported with various NSAIDs (136), and has occurred in a healthy volunteer after short term ketorolac therapy (data on file, Syntex Laboratories).

Before the routine use of NSAIDs in surgical patients can be recommended, detailed investigation of the renal effects is required.

1.8.3 Gastrointestinal effects The association of NSAIDs with gastric and duodenal ulcers is well recognised, but it is now becoming apparent that the large and small intestines are also affected.

Peptic ulcers Aspirin has been known to damage the human gastric mucosa for a considerable time (137), and many investigations have suggested that NSAIDs have a similar effect. The role of NSAIDs in peptic ulceration was recently reviewed, and the conclusion made that:-

> "Non-steroidal anti-inflammatory drugs cause gastric ulcers and probably duodenal ulcers. The size of this risk is not clear, but the increased chance of involuntary presentation with haematemesis and melaena or perforation probably lies between a 50% and a fivefold increase." (138)

The gastric and duodenal epithelia have various protective mechanisms against acid attack. These include the mucus layer, bicarbonate secretion, mucosal hydrophobic properties, rapid cellular regeneration after damage, and an abundant blood supply (139). Many of these factors involve prostaglandins and can be adversely affected by aspirin and NSAIDs (140,141), although the relationship between

ulceration and these drugs continues to be questioned (142). The anti-platelet effect of NSAIDs may increase the risk of bleeding from ulcers, and the risk of upper gastrointestinal haemorrhage is significantly increased by these drugs (143). Gastric microvascular endothelium is a major target for aspirin injury, and damage and deep necrosis can be significantly reduced by arachidonic acid pretreatment (144). Such work indicates that prostaglandin production may be important at various and multiple sites in maintaining mucosal integrity. Attempts have been made to prevent NSAID induced ulcers using prostaglandin analogues and H_2 receptor anatagonists. Misoprostol, a PGE_1 analogue, specifically reduces NSAID related gastric ulceration (145), but in contrast ranitidine prevents duodenal ulceration (146). NSAIDs have been shown to inhibit regenerative cell proliferation at the edge of ulcers, a critical mechanism for mucosal repair, and misoprostol reduces this harmful effect (147).

The clinical implication of this is unclear, as it is not known whether such effects will be produced by administering parenteral NSAIDs for a few days after surgery. Indeed, it could be that surgical patients are at increased risk of mucosal damage from NSAIDs, as they may be fasted for a period of days with deranged gastro-intestinal function, because of surgical manipulation and opioid administration, in addition to being stressed. Near-fatal peptic ulceration and bleeding can occur in post-partum patients with no previous history of problems after relatively short oral administration of NSAIDs, even after only ten days treatment (148). NSAIDs should be avoided after surgery if the patient has a history of peptic ulceration as this increases the chance of problems developing (146).

Little is known of parenteral diclofenac and ketorolac in this respect. Early animal experimentation suggested ketorolac had a favourable therapeutic ratio for gastrointestinal erosion (58), but studies in humans have been less reassuring. In a controlled endoscopic study, invasive gastric antral ulceration was present in four of five volunteers who had been given ketorolac 90 mg intramuscularly four times daily for five days, with evidence of a dose related effect (149). In the same study, the clinically recommended intramuscular dose (56,67) of 10 to 30 mg four times daily was found to produce some mucosal injury, but this was less than oral aspirin 650 mg four times daily (149). Oral ketorolac produces mild gastrointestinal symptoms in some patients within a few days, although no more than other NSAIDs (67,77).

Enteropathy NSAIDs can also have adverse effects on the lower gut, producing an enteropathy (150). It has been estimated that 10% of cases of newly diagnosed colitis may be related to NSAID ingestion (151). Animal work has shown that single large doses of indomethacin given to rats produce intestinal as well as gastric lesions and that these changes are temporally related to inhibition of prostacyclin synthesis (152). NSAID induced enteropathy in rats is associated with an increase in bowel permeabilty and resembles inflammatory bowel disease (153). The production of protective intestinal mucin is reduced by aspirin and increased by prostaglandins (154). Patients receiving long term NSAID therapy for arthritis have an abnormal increase in bowel permeability, affecting both the large and small intestine (155,156). NSAID therapy is associated with an enteropathy similar to that of Crohn's disease, and that this may persist for up to 16 months after ingestion (157). It is thought that by decreasing mucosal prostaglandin synthesis NSAIDs may impair bowel wall

integrity and allow bacterial invasion and damage. Recent enteroscopic studies have shown that small bowel ulceration is also associated with NSAIDs (158).

1.8.4 Aspirin sensitive asthma This is common in patients who have asthma and chronic rhinitis or nasal polyps (159). Bronchospasm occurs soon after aspirin ingestion, and patients can also be sensitive to other NSAIDs (160). The incidence is around 10% of asthmatics (estimates being from 3 to 20%), usually in middle age (159).

The mechanism is unclear, but the cyclo-oxygenase inhibitory activity of a drug is important (160). Cyclo-oxygenase inhibitors may divert more arachidonic acid to lipoxygenase metabolic pathways, producing substances which can precipitate bronchospasm, including leukotrienes and slow reacting substance (159). There may be an interaction here with the peptide endothelin-1 which may be involved in the exaggerated bronchial muscle tone in asthmatics (161), and which increases lipoxygenase products of arachidonic acid metabolism (162). Other factors could be involved as patients with this disorder have an abnormal in vitro response to aspirin of platelets, releasing cytotoxic mediators, a mechanism dependent on inhibition of prostaglandin synthesis and prevented by inhalation of nedocromil sodium, a new drug which stabilizes mast cells (163). The importance of this syndrome has been emphasised by reports of fatal bronchospasm in asthmatic patients after NSAID ingestion (164). Interestingly NSAIDs do not produce problems when given to patients with bronchial hyperresponsiveness from cigarette smoking (165). The ability of a NSAID to produce this syndrome is directly related to potency as a

prostaglandin synthesis inhibitor (160). Ketorolac and diclofenac are very powerful inhibitors of cyclo-oxygenase, and it may be prudent to avoid them in all asthmatic patients.

1.8.5 Hepatotoxicity Aspirin and NSAIDs have hepatotoxic effects, normally after prolonged, excessive, exposure (166,167). Diclofenac has been associated with fatal hepatitis (168) which can develop within a few weeks of commencing therapy (169). Again the risk of precipitating hepatotoxicity as a consequence of a short course of NSAIDs is not known, although borderline increases in serum aminotransferase concentrations may occur in 15% of patients (57).

1.8.6 Injection site damage Intramuscular diclofenac can produce appreciable pain on injection, and is associated with muscle damage and increases in serum creatinine phosphokinase (CPK) (64). Preliminary studies have shown that intramuscular ketorolac does not produce muscle pain or rises in serum CPK (64,59), but further studies are required in patients receiving multiple injections. The irritant nature of the injectable preparation of diclofenac is emphasised by the observation that, when given intravenously, diclofenac results in venous thrombosis (170), although this may be reduced by diluting the drug in volumes of dextrose solution for infusion (52). Injection site pain is a significant problem with diclofenac, and has led to the widespread use of alternative routes of administration, including suppository.

1.8.7 Other side-effects Mild adverse nervous system effects have been reported after ketorolac, including somnolence, headache, and dizziness (57,67). Blood dyscrasias, erythema multiforme,

anaphylaxis, urticaria, erythema multiforme, and pancreatitis have all been reported to be associated with NSAIDs, although they are uncommon (89,171).

In very preterm infants, indomethacin reduces cerebral blood flow and oxygen delivery, and could increase the risk of hypoxic brain injury (172). It is not known whether NSAIDs have this effect in older children or adults.

Some myocardial protection against coronary vessel occlusion can be conferred in animals by preconditioning episodes of ischaemia, an effect blocked by cyclo-oxygenase inhibitors, suggesting a protective role for prostaglandins, probably prostacyclin (173). It is unclear whether NSAIDs can increase the consequences of acute myocardial ischaemia in humans.

1.9 Aims of studies comprising the thesis

The aims of this thesis were to assess the efficacy of the new NSAID, ketorolac, and to evaluate the safety of ketorolac and diclofenac when given after surgery. Any potential respiratory benefits of using NSAIDs after surgery were examined. The acute effects of ketorolac and diclofenac on platelet function and haemostasis were investigated. Changes in renal function associated with ketorolac and diclofenac were observed.

1.9.1 Ketorolac as a postoperative analgesic

Cholecystectomy study Ketorolac, 30 mg by intramuscular injection, was compared with morphine 10 mg. Initially a single dose pilot study was performed, and then a large study was completed of

the effects of the drug over two days after upper abdominal surgery. The analgesic effect of ketorolac was compared with morphine and any side-effects noted.

Thoracotomy study In this study, ketorolac, 10 or 30 mg, with a placebo group, was given by regular intramuscular injection for two days to patients after thoracotomy, who also had free access to intravenous morphine by patient controlled analgesia (PCA, Abbott PCA plus infuser). Previous work had indicated that, when given in this manner, ketorolac had a clinically significant morphine-sparing effect (84,85) after abdominal surgery. Such an effect, if confirmed, would be very desirable after thoracotomy when the analgesic effect of opioids is often associated with depression of respiration and inhibition of expectoration. Analgesia and morphine usage was assessed, and arterial blood sampling performed to detect any respiratory benefits of ketorolac administration.

1.9.2 Platelet function

Ketorolac In the cholecystectomy study described above, platelet function was measured in a group of twenty patients. Platelet function was investigated *in vivo* (skin bleeding time) and *in vitro* (platelet aggregation in whole blood), and changes from control values observed after ketorolac or morphine. Surgical blood loss was also noted for all one hundred patients in the cholecystectomy study, and so the effect of ketorolac on platelet function and surgical blood loss was investigated. The effect of ketorolac on surgical blood loss was also examined in the thoracotomy study.

Ketorolac and dextran In a volunteer study, the haemostatic consequences of giving intramuscular ketorolac with intravenous dextran was investigated. Platelet function was assessed as before,

and any interaction between ketorolac and dextran examined. Venous blood thromboxane, coagulation factors, and fibrinolysis were also measured. The incidence of injection site pain after ketorolac was also noted.

Diclofenac The effect of diclofenac on platelet function was investigated, in a similar fashion to ketorolac, in a group of twenty patients having thoracotomy.

1.9.3 Renal function

Ketorolac In the cholecystectomy and thoracotomy studies, plasma urea, creatinine, and electrolyte concentrations were measured before and after the investigation. Any changes were examined and compared with the control groups.

Unfortunately it was not possible to make further studies of the renal effect of ketorolac because the manufacturers (Syntex) were unwilling to release supplies of this unlicensed drug for such an investigation.

Diclofenac The effect of diclofenac 75 mg b.d. on renal function and renal prostacyclin generation was examined in patients having oesophagogastrectomy, and compared with a control group receiving morphine analgesia. Plasma creatinine and electrolytes, creatinine and free water clearances, and urinary sodium and potassium excretion rates were measured before and for two days after surgery. Perioperative renal prostacyclin generation was examined by measuring the production of the stable urinary metabolite, 6-keto-$PGF_{1\alpha}$, on each study day. Changes in prostacyclin production and renal function were then examined for any effect of diclofenac.

1.9.4 Other adverse effects Many of the recognised side-effects of NSAIDs have been described after chronic administration. In this thesis, the incidence of gastrointestinal, respiratory, and hepatic side-effects was observed after short-term drug administration of ketorolac in the postoperative period. All other adverse events, including pain on injection, were recorded.

CHAPTER 2

METHODS USED IN THIS THESIS

2.1 Introduction

In this thesis, the efficacy and safety of using ketorolac and diclofenac after surgery is assessed. The efficacy of ketorolac was assessed by measurements of pain intensity and pain relief, and safety by the platelet and renal effects of the two NSAIDs and by the incidence and severity of any other adverse effects.

2.2 The assessment of pain and analgesia after surgery

A considerable part of this thesis concerns appraisal of ketorolac as an analgesic and involves measurement of pain after surgery. Pain is difficult to assess and quantify at any time (174,175,176), but the postoperative period presents distinct problems (177,178,179,180).

Pain has been defined by the International Association for the Study of Pain as:

> "an unpleasant sensory and emotional experience with actual or potential tissue damage or described in terms of such damage" (181).

Postoperative pain is related to the tissue damage of the surgical incision, and should diminish as wound healing occurs. It is therefore an acute pain which can be further defined as being:

> "associated with a specific injury and which would be expected to resolve with the healing of that injury" (182).

The degree of pain observed after an operation will therefore depend not only on the patient's own sensory and emotional response to injury, but additionally on the incision performed and the time elapsed since surgery. The assessment of an analgesic in the postoperative period must therefore take account of these factors.

Patients may also be less able to comply with pain assessments in the immediate postoperative period because of the residual sedative effects of anaesthesia. This produces a tendency for analgesic studies to be performed later in the postoperative period when pain may have diminished significantly and patients can cooperate. The disadvantage of this is that analgesics found to be effective by such studies may nevertheless be unsuitable for use immediately after operation when pain intensity is greater and the quality of pain may be different. Ideally, methods of pain and analgesia assessment should be used which can be applied at any time after surgery.

2.2.1 Methodology of studies Postoperative pain studies should be designed to minimize the effect of the factors described above.

Surgery Pain intensity and duration will depend on the surgery performed, and investigations should ideally use a standard operation. The choice of operation is important as analgesic studies tend to more discriminating and productive when performed after major surgery, than after less painful procedures (177,178). The anaesthetic technique should also be standardized as this can affect postoperative pain and analgesic requirements. Subject and observer bias and other confounding variables should be minimized by ensuring that the study is double-blind and that treatment is allocated randomly (183). In particular, study groups should be balanced for age and sex as these affect analgesic requirements (184).

Time of assessment Postoperative pain is transient and will vary depending when observations are made. Assessments should therefore be made at set times after surgery, preferably beginning soon after emergence from anaesthesia.

2.2.2 The subjective assessment of pain

Patient or observer The patient's own impression is the most important, but at times this may not be available, especially immediately after operation, and the assessment of an experienced observer may then provide valuable information. Ideally, one trained observer should assess all the patients in a study to reduce the variability of results.

Verbal rating scales (VRS) Both the patient and the observer can complete these for pain intensity. Commonly four point scores are used:

0 = no pain

1 = mild pain

2 = moderate pain

3 = severe pain

An alternative, simpler, score has been suggested for use by observers immediately after surgery when patients find it difficult to complete any scores (185):

0 = no pain

1 = pain which is not bad enough to need medication

2 = pain which needs relief

The advantage of these verbal rating scales is that they are easily performed, but their disadvantage is a relative lack of sensitivity.

Numerical rating scales Pain is scored numerically, for example from 0 to 100. This may represent a compromise between simple verbal rating scales and visual analogue scales which patients sometimes find confusing.

Visual analogue scales (VAS) These are horizontal 10 cm lines marked 'no pain' (at 0cm) and 'worst possible pain' (at 10 cm). The line should be a least 10 cm to reduce variability (186). Patients mark the line at the point they feel is appropriate, and the distance from zero, in millimetres, gives a non-verbal measurement of pain. VAS may be more discriminating than a VRS (187,188), although both may be reliable in the postoperative period and produce equivalent results (174).

Compared with simple rating scales more patient compliance is required for VAS, often preventing their use immediately after surgery. Some patients find it difficult to relate their pain to a horizontal line on paper at any time. Variations of the VAS have been used to overcome these problems including a pain slide rule which is marked 'no pain' and 'worst pain imaginable' at either end, and the score can be read directly from the back (189).

The McGill Pain Questionnaire (MPQ) This represents a more detailed, 'multidimensional' approach to pain assessment than the simple VRS and VAS rating scales (190). The MPQ consists of a number of adjectives from which the patient chooses those most appropriate to their pain state. It is designed to reflect three dimensions of pain; sensory, affective, and evaluative. Sensory word descriptions relate to the temporal, spatial, pressure, and thermal properties of pain. Affective words refer to tension, fear, and autonomic functions. Pain intensity is reflected by evaluative word descriptions. This multidimensional approach to pain has proven to be

successful, although it is of limited use after surgery when patients may be unable to complete such a complicated test which takes 10 to 20 minutes to do.

2.2.3 The objective assessment of pain

Modification of the stress response to surgery After surgery there are rises in blood pituitary adrenal, renal and sympathetic hormones, and metabolic factors including (122):

Pituitary - ACTH, ß-endorphin, prolactin, growth hormone.
Adrenal/renal/sympathetic - cortisol, aldosterone, adrenaline, renin, noradrenaline.
Metabolic - blood glucose, lipolysis, muscle amino acids.

These changes represent the stress response to surgery which can be modified by analgesia, although even total pain relief may not decrease it significantly after major operation (122). A new analgesic can be assessed by the effect it has on this response, although such studies are of less use when comparing individual doses of different drugs.

Respiratory parameters Painful incisions in the chest and abdomen inhibit respiratory activity leading to changes in arterial blood gases and respiratory function tests. Measurement of respiratory function by spirometry after operation may give useful information about pain intensity (191), and peak expiratory flow rate is often used for this purpose.

Arterial blood carbon dioxide tension Pain may lead to hyperventilation which may be prevented by effective analgesia. Opioids given after surgery, as a consequence of their respiratory depressant effect, may increase $PaCO_2$, and this may be avoided by using alternative analgesics (37,38,84).

Autonomic responses Heart rate, blood pressure, skin conductance and temperature have been correlated with painful stimuli, but these responses habituate rapidly and are affected by many factors other than pain, including anxiety.

Electrophysiological methods Measurements of cortical evoked potentials can be used to assess experimentally applied pain stimuli, but such techniques are difficult to apply after surgery (192).

2.2.4 The assessment of pain relief

Verbal rating scales These can be completed by the patient and the observer using the four point scale:

0 = no pain relief

1 = mild pain relief

2 = moderate pain relief

3 = complete relief

Visual analogue scales As with pain intensity, pain relief can be assessed using VAS marked 'no relief' and 'complete relief' at either end.

Additional analgesia The effect of a study drug can be assessed by the patient's additional requirements for analgesia. Patient controlled analgesia (PCA) allows access to intravenous opioids on demand, while the study drug is given by a different route. PCA demands and opioid usage then reflect the efficacy of the study drug.

This method has been used successfully to assess intramuscular NSAIDs after surgery (84). Alternatively the requirement for additional analgesia administered by nursing staff may be recorded (41).

2.2.5 Derived scores These are used when the effect of an analgesic is observed over a timed period, typically of 6 hours. If pain intensity scores are performed before (baseline) and at times after analgesic administration then pain intensity difference (PID) can be calculated as baseline pain minus the timed score. Over an assessment period PIDs can be added giving the summed pain intensity difference (SPID) for both VRS and VAS scores. Similarly timed pain relief scores can be summed over an assessment period to give a total pain relief score (TOTPAR). SPID and TOTPAR and the visual analogue equivalents are often used to compare analgesics after surgery (82,83).

2.2.6 The placebo effect There can be a significant placebo effect in pain studies (193), but it is not ethically acceptable to administer placebo injections in the presence of severe postoperative pain. It is possible to include placebo groups after surgery if alternative analgesia is provided by other means, for example by PCA (84,85).

2.3 Methods used in this thesis to assess pain and analgesia

In this thesis, the assessment of analgesic efficacy is based on the use of subjective rating scales for pain intensity and pain relief. In each study only one operation was used and the anaesthetic

technique standardized. Patients were randomly allocated to treatments and studies were double-blind. To reduce variability one nurse-observer scored all the patients.

2.3.1. Observer assessment The observer scored pain intensity and relief using the four point scales:

0 = no pain	0 = no pain relief
1 = mild pain	1 = mild relief
2 = moderate pain	2 = moderate relief
3 = severe pain	3 = complete relief

In making these assessments, the observer took account of the patient's demeanour and spontaneous comments. The observer scored pain and analgesia before the patient made any assessments.

In the pilot study of the effect of ketorolac after cholecystectomy (Chapter 3.1), the simpler three point scale was used:

0 = no pain

1 = pain which is not bad enough to need medication

2 = pain which needs relief

2.3.2 Patient assessments The patients used the same four point VRS, and also completed VAS for pain intensity and pain relief. Both forms of rating scale were used to allow for the difficulty patients experience in completing VAS immediately after operation.

In the study of ketorolac as an adjunct to morphine after thoracotomy (Chapter 4), the patients scored pain both at rest and upon taking a deep breath.

2.3.3 Derived scores When repeated assessments were made of individual doses of study medication (Chapter 3.2), SPID and TOTPAR and the visual analogue equivalents were calculated and used for comparison.

2.3.4 Demand analgesia When PCA was used (Chapter 4) patient morphine consumption was analysed and used to compare the study groups. In the other studies requirements for rescue analgesia and the time between doses of study medication were used as indicators of analgesic efficacy (Chapter 3.2).

2.3.5 Overall assessments The patients and the observer gave their overall assessments of analgesia as poor/fair/good/very good.

2.3.6 Instruction of patients On the day before surgery, each patient was carefully shown how to use the VRS and VAS for pain intensity and pain relief, and sample scorecards were left by the bedside so that they could become fully accustomed to them before the study began. The subjects were also told that they should make their own assessments, without any influence from the observer or other staff.

2.3.7 Patient pain intensity and pain relief scorecards Booklets of cards were used for patient assessments. At the beginning of the study each patient was given a booklet for pain intensity and one for pain relief, coloured pink and yellow, respectively. On each card there was a VAS and a VRS for pain or pain relief. After each assessment, the completed card was torn out of the booklet so that the patient could not see the previous scores made.

2.3.8 Other assessments used The rate and reason of premature withdrawal from study groups was examined.

2.4 Methods used to assess platelet function and haemostasis

2.4.1 Introduction The effect of ketorolac and diclofenac on platelet function was assessed in patients using skin bleeding time, whole blood *in vitro* platelet aggregation, and surgical blood loss. In a volunteer study of the possible haemostatic interaction between ketorolac and dextran-70, additional tests were done, including thromboxane production, coagulation factors, and tissue plasminogen activity.

Platelet aggregation It has recently become possible to study *in vitro* platelet aggregation in whole blood (194,195). This may be more physiological than traditional turbidometric methods using platelet-rich plasma, as the platelets are left in their natural milieu surrounded by red and white cells that can influence the aggregatory response (196,197). Aggregation induced by collagen and arachidonic acid is dependent mainly upon platelet thromboxane production, and can be inhibited NSAIDs.

Platelet thromboxane production Thromboxane A_2 is produced by platelet cyclo-oxygenase and promotes aggregation and adhesion, which are necessary for primary haemostasis. Thromboxane A_2 is rapidly metabolized in the blood and measurement of the stable product thromboxane B_2 is a more reliable indicator of production (4,8).

Dextran The mechanism of action of dextran is not completely known, but it may involve haemodilution and improved blood flow, impairment of haemostasis including an anti-platelet effect, a fall in factor VIII and increased tissue plasminogen activity (198,199). Unlike NSAIDs, dextran is not thought to affect thromboxane synthesis

but rather reduces platelet adhesiveness by a mechanism which may involve the endothelial response to injury. The effect of dextran, alone and in combination with ketorolac, was investigated using whole blood thromboxane B_2, von Willebrand antigen, factor VIII activity, and tissue plasminogen activator activity.

Von Willebrand factor is important in primary haemostasis and is produced in the endothelium and the liver. Endothelial damage leads to release of von Willebrand factor, and platelets adhere to it, producing primary haemostasis. Von Willebrand factor is a good measure of endothelial injury or stimulation. Dextran may stimulate the endothelium in a nonspecific manner, and in this thesis von Willebrand antigen was measured to assess that effect. Von Willebrand factor also has a separate role as a carrier protein for factor VIII, and was previously termed factor VIII related antigen (91).

Factor VIII is produced in the liver and is important in coagulation, and may be affected by dextran (198). Stimulation of the endothelium by dextran could also affect factor VIII by increasing the release of the carrier protein, von Willebrand factor. To assess these actions of dextran, factor VIII coagulant activity was measured.

Tissue plasminogen activator increases fibrinolysis by promoting the conversion of the precursor plasminogen to active plasmin (91). In this thesis, tissue plasminogen activator antigen was measured to investigate the possibility that dextran may increase the activity of this substance (198).

2.4.2 Skin bleeding time This *in vivo* test of platelet function was performed on the forearm by the modified method of Ivy (200,201) using a Simplate-II bleeding time device (Organon Teknika) to

standardize the length and depth of incision. The Simplate-II is a sterile, disposable, device used to make uniform incisions for the bleeding time test. The spring-loaded blades are contained in a plastic casing, and, when triggered on the forearm, make two incisions in line, 5mm long by 1 mm deep.

The subject was seated comfortably and the arm supported with the volar aspect of the forearm exposed. The incision site was selected and cleaned with an alcohol swab. A sphygmomanometer cuff was applied to the upper arm and inflated to 40 mmHg, and maintained at that pressure. The Simplate-II device was placed firmly on the forearm, without pressing, perpendicular and distal to the antecubital fossa. The device was triggered, and a stopwatch timer simultaneously activated. Each 30 seconds the flow of blood was observed by blotting with a Whatman No.1 filter paper disc, taking care not to disturb the platelet plug. The timer was stopped when blood no longer stained the filter paper. A butterfly bandage was applied to the wound to approximate the skin edges. The bleeding time was measured for each incision and the mean recorded. The upper limit of normal for skin bleeding time using this technique is 10 minutes (201).

In this thesis skin bleeding time was measured before and one hour after intramuscular injection of ketorolac or diclofenac, and any change observed. Most of the skin bleeding times were performed by the author, and in every case the same observer did all the tests in any one subject.

2.4.3 Platelet aggregation This was studied in vitro using a Clay-Adams Ultra-Flo 100 whole blood platelet counter (195,202). Spontaneous, collagen induced ($2\mu g\ ml^{-1}$, Semmelweiss), and arachidonic acid (0.5 mmol $litre^{-1}$, Sigma) induced aggregation was

observed. A venous blood sample was taken, anti-coagulated with 3.8% trisodium citrate, and taken directly to the laboratory so that it could be studied within one hour. From each sample a red cell count was first determined and dialled into the whole blood platelet counter. A 10 μlitre aliquot was withdrawn and the baseline platelet count determined (100%). The aggregating agent, if used, was then added and the sample stirred at a constant 1000 rpm and 37^{o}C. Further aliquots were taken at five and ten minutes for spontaneous aggregation, and one, three, and five minutes for collagen and arachidonic acid induced aggregation. The platelet count at each sample time was determined as a percentage of the baseline count. Collagen and arachidonic acid induced aggregation depend to a large extent on thromboxane production, but spontaneous aggregation does not.

Using this technique, aggregation is measured by the percentage fall in the number of free platelets from baseline during the observation period. These studies were performed before and one hour after the administration of ketorolac or diclofenac, and any change in aggregation noted.

2.4.4 Blood loss Surgical blood loss was estimated by weighing of swabs and suction loss at operation. When surgical drains were positioned, as after thoracotomy, any continuing postoperative bleeding was recorded.

2.4.5 Whole blood thromboxane B_2 (TxB_2) generation Aliquots of 1 ml of fresh venous blood were left to clot spontaneously at 37^{o}C for 30 minutes. The specimen was centrifuged at 3,000 rpm for 15 minutes at 4^{o}C, and the serum then analysed for TxB_2 by radioimmunoassay

(203). To increase yield, TxB_2 was first converted to the methyl oxime form by incubation with methoxyamine hydrochloride. Tritiated thromboxane B_2 was obtained from Amersham International, and antisera to thromboxane B_2 was raised in the University of Edinburgh (203).

2.4.6 von Willebrand Factor antigen (vWF:Ag) An aliquot of venous blood was anticoagulated with 3.2% trisodium citrate and vWF:Ag measured by the Laurell "rocket" electroimmunoassay (204), a method used for quantitative analysis of charged proteins. The sample containing the protein (vWF:Ag) is placed in a well in an agarose gel containing antibody, and an electrophoretic field induces migration of antigen which reacts with the antibodies to form precipitation zones like ascending rockets, hence the name. The final position of the precipitation zone depends on the amount of antigen present in the sample.

2.4.7 Factor VIII coagulant activity (FVIIIc) The activity of FVIII was measured by a modification of the kaolin clotting time using anticoagulated venous blood (205). An aliquot of the plasma to be tested is mixed with haemophilic plasma preincubated with kaolin, calcium is added, and the specimen tilted continually until clot appears. The correction of the clotting time of the haemophilic plasma measures the FVIIIc of the test sample.

2.4.8 Tissue plasminogen activator antigen (tPA antigen) A double monoclonal antibody enzyme linked immunosorbent assay (ELISA) was used to measure total plasma tPA antigen (206). The mouse antibodies to tPA antigen were raised in the University of Edinburgh.

Horseradish peroxidase (Sigma) was conjugated with one antibody, and the reaction of this with tetramethylbenzidine substrate (Sigma), measured by absorption of light, forms the basis of the assay.

2.5 Methods used to assess renal function

2.5.1 Plasma urea, creatinine and electrolytes This was performed by routine analysis in the clinical chemistry laboratory of the Royal Infirmary of Edinburgh. Normal ranges for this laboratory are: sodium 132-144 mmol/litre; potassium 3.3-4.7 mmol/litre; urea 2.5-6.6 mmol/litre; creatinine 55-150 μmol/litre.

2.5.2 Urine flow rate and electrolyte excretion When patients were catheterised, urine flow rate and sodium and potassium excretion were calculated, by normal laboratory methods.

Urinary clinical chemistry was performed as a batch at the end of the study. Aliquots of the urine collection were frozen at -20^{o}C until the analysis was performed.

2.5.3 Creatinine and free water clearances Creatinine clearance and free water clearance (urine flow rate - osmolar clearance) were also calculated.

2.5.4 Renal prostaglandin generation The renal production of prostacyclin, PGI_2, can be assessed by measuring the urinary concentration of the stable metabolite 6-keto-$PGF_{1\alpha}$ (207,208). PGI_2 produced in tissues normally breaks down spontaneously to 6-keto-$PGF_{1\alpha}$, which is then rapidly metabolised in the systemic circulation to the main urinary product 2,3 dinor-6-keto-$PGF_{1\alpha}$ (4,8,207). 6-keto-$PGF_{1\alpha}$ can be used to investigate renal production of PGI_2 since it is

not further metabolised in the urine (207). It is accepted that measurement of 6-keto-$PGF_{1\alpha}$ and 2,3 dinor 6-keto-$PGF_{1\alpha}$ reflect renal and systemic prostacyclin production respectively (209). Urinary 6-keto-$PGF_{1\alpha}$ concentration was measured from samples collected and stored as described above. Knowing the urinary volume produced in a given time, the production per minute of 6-keto-$PGF_{1\alpha}$ was calculated.

Measurement of urinary 6-keto-$PGF_{1\alpha}$ concentration was by radioimmunoassay (210). Aliquots of urine were collected and frozen at -20°C until the analysis was performed in a batch. Urine was acidified and the prostaglandin extracted into ethyl acetate. The assay used a double-antibody technique as the separation method. The specific antibody for 6-keto-$PGF_{1\alpha}$ was raised in the Department of Pharmacology of the University of Edinburgh, and tritiated 6-keto-$PGF_{1\alpha}$ was obtained from Amersham International Ltd. The inter- and intra- assay coefficients of variation for the assay were 15% and 11% respectively.

2.6 Study details

2.6.1 Ethics committee approval and consent The studies comprising this thesis were assessed and approved by the Lothian Health Board anaesthetics ethics committee. Informed, written, consent was requested from patients and volunteers before they were enrolled. In each case consent was witnessed by the author.

2.6.2 Patient enrolment and exclusion criteria Patients were enrolled from the surgical lists of the Royal Infirmary, the Western General Hospital, and the Thoracic Unit of the City Hospital, Edinburgh. Exclusion criteria were a history of ulcer disease,

bleeding tendency, asthma, allergy, aspirin intolerance, age less than eighteen years, recent analgesic administration, and alcohol or narcotic abuse.

2.6.3 Study blinding and randomization All the studies were performed in a double-blind randomized manner so that neither the patient nor the observer knew which drug had been given. Randomization was by means of tables of random numbers used to allocate treatments. Upon enrolment, each patient was allocated a study number and corresponding treatment. Numbered envelopes containing the treatment given to each patient was held by the hospital pharmacy in the form of a randomization code, and were only referred to if an adverse event occurred. At the end of each study the code was broken and the data analysed.

2.6.4 Data collection and recording Subject record books were used for each study in the thesis, and all data were written in these for later analysis. When patient controlled analgesia was used a printout was made each 24 hours from the Abbott PCA plus machine using a hand-held printer (Epson P-40) and the hourly morphine usage was then transcribed into the study record book. Pain and pain relief scores were made in separate record books which were arranged so that the subject and observer could not see the last score they had made.

2.7 Statistical design, data analysis, and presentation

2.7.1 Statistical power In the design of the efficacy studies, an assessment of statistical power was made so that an adequate number of patients were included. A nomogram was used which related power,

total study size, the standarized difference, and the significance level (211). The standarized difference is the smallest difference which would be clinically relevant, divided by the estimated standard deviation of the sample. A discussion of the estimation of statistical power is included in each chapter where appropriate.

2.7.2 Statistical tests (212,211,183) All tests were two-tailed and the significance level was set at 5%.

Categorical data were analysed by Fisher's exact or Pearson's Chi-square test where appropriate.

Comparisons of nonparametric data from two groups were made using the Mann-Whitney U test, for unpaired samples. When there were more than two groups the Kruskal-Wallis test was used.

Paired and unpaired t-tests were used to compare parametric data from two treatment groups. Analysis of variance was used when there more than two groups, or when repeat observations were made on the same subjects. In Chapter 4, one-way analysis of variance was used to analyse data from different groups. In Chapter 5.4, two-way analysis of variance was used when different treatment effects were obtained from the same volunteers. When appropriate, 95% confidence intervals were calculated (95% CI).

All VRS, and derived scores including SPID, TOTPAR and visual analogue SPID and TOTPAR were analysed by nonparametric methods. In chapter 4.1, VAS were analysed using analysis of variance.

2.7.3 Calculation All statistical calculations were performed by the author using the programme 'Minitab' (version 6.2) (213) on an IBM-compatible personal computer.

2.7.4 Presentation of results Demographic data are summarized by mean (SD), and other parametric data by mean (SE). Nonparametric data are represented by median (range).

2.7.5 Construction of figures The data were entered into the graphics programme 'Slidewrite plus' (Advanced graphics software). Figures were then produced on a Hewlett-Packard LaserJet II printer.

2.8 Classification of adverse events

An adverse event was taken to mean any undesirable occurrence during the study, and was not necessarily drug related.

An adverse drug reaction was defined as any effect of the drug not of therapeutic, diagnostic, or prophylactic value (88).

A 'serious' reaction was a fatal, life-threatening, disabling, or incapacitating adverse event (88). Other adverse reactions were described as 'minor', and included reactions leading to premature withdrawal from the study.

CHAPTER 3

KETOROLAC COMPARED WITH MORPHINE

3.1 A single dose pilot study of ketorolac 30 mg and morphine 10 mg after cholecystectomy

3.1.1 Introduction Although ketorolac had been studied as a postoperative analgesic, little work had been done concerning the efficacy of the drug when used immediately after surgery. In this investigation the analgesic effect of ketorolac was assessed in the immediate postoperative period after upper abdominal surgery (cholecystectomy). Ketorolac is a relatively new analgesic, and, before a large study was embarked upon, a single dose pilot study of twenty patients was first performed to assess the efficacy and safety of intramuscular ketorolac.

3.1.2 Methods

Twenty patients undergoing elective cholecystectomy for gallstones were studied.

Anaesthesia After premedication with oral temazepam 20 mg, anaesthesia was induced with intravenous thiopentone and maintained with halothane, enflurane, or isoflurane in an oxygen, nitrous oxide mixture. Tracheal intubation was facilitated with intravenous suxamethonium. The lungs were ventilated artificially and vecuronium or atracurium given intravenously to achieve muscle paralysis. Neostigmine with atropine was given to antagonise the neuromuscular block. No analgesics were used other than study medication. Subcutaneous heparin (5,000 iu with premedication) was given electively at the time of premedication to all patients as prophylaxis against deep venous thrombosis.

Study design This was a double-blind, single dose, comparison of two treatment groups: ketorolac tromethamine 30mg and morphine 10 mg. Patients were allocated randomly to receive a single intramuscular dose of ketorolac or morphine. Upon enrolment, the patient was allocated a study number and a numbered ampoule containing either ketorolac 30 mg or morphine 10 mg. The anaesthetist in charge of the patient gave the injection to the vastus lateralis muscle using a 23 gauge needle, thirty minutes after induction of anaesthesia.

Efficacy

Pain Two observers independently scored the patient's pain each thirty minutes for up to four hours from the time of study drug administration. Scores were:

0 = no pain

1 = pain which is not bad enough to need analgesia

2 = pain which needs relief.

If the patient was still anaesthetised at an observation time a score of 0 was recorded. If a score of 2 was given then morphine rescue analgesia was administered. If the patient required rescue analgesia before the end of the four hour study period then a score of 2 was recorded for each of the remaining observation times.

Each patient was therefore assessed eight times by two observers over a four hour period producing a total pain score which ranged from 0 (no pain) to 32 (required rescue analgesia within thirty minutes of the study drug).

Time to next analgesia The time from administration of the study drug to the next analgesic was recorded to the nearest half hour.

Overall pain score Each observer and each subject (next day) assessed the overall quality of analgesia as very good; good; fair; poor.

Side-effects All side-effects were noted including nausea, vomiting, and injection site discomfort. Operative blood loss was measured by weighing swabs and measuring the suction loss.

Statistical Analysis Patient details are summarized as mean (SD), for other parametric data mean (SE) are given and between group comparisons made using unpaired t tests. For the pain scores median (range) are given, and the Mann Whitney U test used to compare the groups.

3.1.3 Pilot study results

Patient data 20 patients entered the study. The groups did not differ significantly with respect to age 52.4(9.7) year ketorolac, 54.7(8.9); weight 66.1(16.7) kg ketorolac, 73.6(15.6) morphine; height 165 (8.8)cm ketorolac, 164(8.2) morphine; and sex distribution, male/female 4/6 and 3/7 respectively.

Pain Scores There was no statistical difference between the observer pain scores from the two groups (P=0.63). The median score in the ketorolac group was 19.5 (range 8-28), and in the morphine group 22 (0-32).

Time to next analgesia The mean time in minutes to next analgesia in the ketorolac group was 156, and 138 in the morphine group (P= 0.62).

Observers' overall assessments The two observers agreed in each case in their overall assessments. In the ketorolac group the assessment of analgesia was very good 2, good 2, fair 4, and poor 2. The assessment in the morphine group was very good 1, good 4, fair 0, and poor 5. The ketorolac group received better overall assessments than the morphine group (five of whom were classed as having poor analgesia).

Patients' overall assessment The patients classed ketorolac as very good 2, good 4, fair 3, and poor 1. Morphine was assessed as very good 0, good 3, fair 3, and poor 4.The observers and the subjects agreed in their assessments apart from one subject in the ketorolac group who felt that his analgesia was very good whilst the observers felt it was poor.

Blood loss The mean loss in the ketorolac group was 231(55) ml, and in the morphine group 213(47), (P=0.86). One patient in each treatment group had a higher than normal blood loss (ketorolac 695 and morphine 595 ml). The patient in the ketorolac group had a very inflamed gall bladder bed, and the patient receiving morphine had adhesions due to previous surgery.

Adverse events There was no report of continuing injection site pain. One patient in each group required treatment with cyclizine for nausea. One subject who had morphine became heavily sedated, although this did not require specific treatment.

3.1.4 Discussion In this pilot study, a single intramuscular dose of ketorolac 30 mg given during surgery gave analgesia which did not differ from that of morphine 10 mg. Pain scores, time to next analgesia, and patient and observer overall assessments did not differ for ketorolac and morphine. Operative blood loss was not significantly increased by the NSAID. However, there was a marked variation between patients in pain intensity and in requirements for additional analgesia, even after the same operation. This meant that any further study comparing ketorolac with morphine would have to be large enough to take account of the interindividual differences seen in this pilot study.

On the basis of this pilot study, it was felt appropriate to proceed with a larger investigation comparing ketorolac with morphine after cholecystectomy.

3.2 A multiple dose study of ketorolac 30 mg versus morphine 10 mg intramuscularly after cholecystectomy

3.2.1 Introduction This study was designed to pursue the promising results of the pilot study and examine in greater depth the efficacy and safety of multiple doses of intramuscular ketorolac 30mg compared with morphine 10mg after cholecystectomy. Previous studies, giving good results, had not examined the effect of ketorolac immediately after surgery, but had been performed up to a day afterwards (82,83). The timing of an analgesic study after operation may be important, since investigations using intravenous lysine salicylate had found that it was unsuitable for use in the presence of severe pain present immediately after operation (36), although it was effective later (35). The aim of this study was to examine the efficacy of intramuscular ketorolac in comparison with morphine both immediately after surgery and also later in the postoperative period.

3.2.2 Methods

Patient selection and exclusion criteria One hundred male and female patients undergoing elective cholecystectomy were studied. The exclusion criteria and anaesthetic technique were the same as the pilot study.

Study design A double-blind, multiple dose, parallel group comparison of two treatments; ketorolac tromethamine 30mg and morphine 10 mg. Patients were randomly allocated to receive ketorolac

or morphine (fifty in each group) in blocks of ten. The two analgesics were supplied in identical 1 ml amber coloured ampoules in boxes of eight, numbered 1 to 100. Each patient was allocated a study number, and received all eight doses from that box.

Administration of analgesia The first dose was given to the vastus lateralis muscle at induction of anaesthesia by the anaesthetist, using a 23 gauge needle. Doses were then given by the ward staff on patient demand, up to two hourly with a maximum of six doses in twenty four hours. Each patient could receive eight doses of study medication and the study lasted up to forty-eight hours. If analgesia was inadequate then rescue medication (morphine) was given at the discretion of the nurse, and the patient continued in the study.

Efficacy Assessments were made on the second dose of study medication (ie immediately after surgery, day 1) and on a dose on the morning of the next day (day 2). The patient and an independent nurse-observer scored pain intensity separately before injection, and pain intensity and pain relief at 0.5, 1, 2, 3, 4, 5, and 6 hours. If the patient required further analgesia, or fell asleep in the six hour study period, then the last score recorded was used for the remaining observation times.

Pain scores Scores were made by the same nurse-observer. The patients gave assessments by verbal rating scales and visual analogue scales.

Pain intensity scores Pain intensity was scored by the nurse and the patient on a four point VRS:

0 = no pain

1 = mild pain

2 = moderate pain

3 = severe pain

The patient also completed 10cm VAS for pain, (0-no pain to 10cm-worst possible pain).

Pain relief scores The observer and the patient scored pain relief on a four point VRS:

0 = no relief

1 = slight

2 = moderate

3 = complete relief

The patient also completed VAS for pain relief (0-no relief to 10cm-complete relief).

Derived scores Pain intensity differences (PID) were calculated by subtracting the scores from the baseline score. The seven PID from the six hour observation periods were added together to give summed pain intensity differences (SPID). SPID were derived for the observer and patient for days 1 and 2. The visual analogue equivalent of SPID from the patient was calculated (visual analogue SPID). Total pain relief scores (TOTPAR) and the visual analogue equivalent were calculated (visual analogue TOTPAR) by adding the scores from each observation time together.

Intervals between injections We recorded the time in minutes between the second dose (ie immediately after surgery) and the next analgesic injection as a further measure of efficacy.

Morning assessments. On the morning after surgery (day 2) and the next morning (day 3) the patient was asked if he or she had slept well, if the pain control was satisfactory, and about any unpleasant dreams. Oral temperature was noted at this point.

Final assessment. At the end of the study both patient and observer independently gave an overall opinion of analgesia as very good/ good/ fair/ poor.

Oral intake and intravenous fluids The time in hours was recorded from the end of surgery to established oral intake and to removal of the intravenous infusion.

Completion rates and early withdrawal Each subject completed the study if all eight doses of medication over days 1 and 2 were received. Completion rates were compared between the groups, and reasons for withdrawal noted.

Injection site discomfort The subject rated pain on injection as none/ minimal/ moderate/ severe.

Adverse events All were recorded, and venous blood was sampled for haematological and biochemical analysis before and after the study period.

3.2.3 Statistical design and analysis The pilot study had indicated that there could be a wide variation between patients in pain experience after cholecystectomy, and this study was designed to be large enough to compensate for that.

In comparing the two analgesics, the most important measurement of efficacy was the SPID. As the pain scores were on an ordered four point scale, pain intensity difference at each assessment could be -3 to 3. SPID over six hours (seven assessments) could range from -21 to 21, with a mean of zero and standard deviation of approximately 7.

Taking a significance level α of 5%, a difference between the analgesics in SPID of 4 (approximately 10%) could be detected with a power of 80% if the total sample size was one hundred patients (211).

For demographic data mean (SD) are given. For other data median and range are given, and nonparametric statistical tests used. Categorical data were analysed using Fisher's exact or Pearson's Chi-square test. Ordinal and interval data were analysed using the Mann-Whitney U test.

3.2.4 Enrolment rate and exclusions (table 1) To enrol one hundred patients into this study, an attempt was made to recruit every person having elective cholecystectomy in the Royal Infirmary and the Western General Hospital of Edinburgh over a period of time, although it proved impossible to study all patients available to us at a given time. Of the patients contacted, a large number, 113 were found to be unsuitable on the basis of exclusion criteria (table 1), meaning that 213 patients had to be approached before the study could be completed. The main reasons for exclusion were peptic ulcer disease, asthma and chronic obstructive airways disease, involvement in other clinical studies (perhaps to be expected in teaching hospitals), and poor general medical condition (most often due to ischaemic heart disease). Of all the patients approached, only four declined to participate after the nature of the study had been explained to them. It took fourteen months to complete the study.

Reason	Number
Peptic ulcer disease	16
Asthma	9
Severe COAD	12
Aspirin sensitivity	3
Opiate sensitivity	1
Concomitant medication	14
Recent opiate intake	4
Alcohol abuse	2
Psychiatric illness	5
Involved in other clinical studies	13
Patient declined	4
Unsuitable for medical reasons	30
Total	113

Table 1 Reasons for exclusions from the cholecystectomy study.

3.2.5 Results

Patient details (table 2) The two treatment groups did not differ significantly with respect to sex, age, height, weight, position of incision, and duration of surgery.

Efficacy (table 3)

Baseline pain intensity Pain intensity did not differ significantly for the two groups on days 1 and 2. The patients tended to score pain as "severe" on day 1 and "moderate" on day 2.

Performance of assessments On day 1, only 70% and 40% of the patients could complete the VRS and VAS assessments respectively. On day 2, all the patients remaining in the study could do both VRS and VAS assessments.

Pain intensity scores Observer and patient SPID were significantly less for ketorolac than for morphine on day 1. On day 2 ketorolac and morphine results did not differ.

Visual analogue SPID was less for ketorolac on day 1, but the difference was not statistically significant. On day 2 there was no difference.

Pain relief scores Observer and patient TOTPAR were significantly lower for ketorolac on day 1, but on day 2 there was no difference.

Visual analogue TOTPAR showed no difference between the drugs on either day.

Intervals between injections, and rescue morphine (table 4) After the second dose of study medication, patients receiving ketorolac required repeat analgesia much sooner than those receiving morphine. In the first 24h of the study, the ketorolac group required more rescue medication than the morphine group. In the second 24h there was no difference between the groups.

	KETOROLAC	MORPHINE
M/F	17/33	13/37
Age(yr)	53.5(14.2)	52.3(14.9)
Height(cm)	166.2(9.9)	164(7.8)
Weight(kg)	69.4(12.1)	67.3(12.8)
Subcostal incision	39	37
Midline incision	11	13
Duration(min)	86(3.9)	91(5.1)

Table 2 Details of the patients in the cholecystectomy study (mean, SD), incision site, and duration of surgery (mean, SE).

	KETOROLAC	MORPHINE	P
BASELINE PAIN			
Observer			
Day 1	2 (1,3)	2 (2,3)	0.48
Day 2	2 (1,3)	2 (1,3)	0.18
Patient			
Day 1	3 (2,3)	3 (2,3)	0.99
Day 2	2 (1,3)	2 (1,3)	0.2
Patient visual analogue			
Day 1	81 (52,100)	80 (63,100)	0.42
Day 2	52 (10,100)	64 (9,99)	0.13
SPID			
Observer			
Day 1	0 (-7,12)	7 (0,14)	0.0001
n	48	45	
Day 2	7 (0,10)	6 (-5,13)	0.9
n	37	38	
Patient			
Day 1	0 (-7,11)	6 (0,13)	0.003
n	32	30	
Day 2	1 (-5,13)	5 (-11,13)	0.21
n	37	38	
Patient visual analogue			
Day 1	7 (-81,427)	109 (-112,420)	0.11
n	19	18	
Day 2	112 (-136,470)	132 (-339,522)	0.41
n	37	38	
TOTPAR			
Observer			
Day 1	1.5 (0,14)	13 (0,20)	0.0001
n	48	45	
Day 2	13.5 (0,21)	12.5 (2,20)	0.79
n	37	38	
Patient			
Day 1	0 (0,14)	6 (0,20)	0.029
n	32	30	
Day 2	12 (0,21)	12 (2,16)	0.62
n	37	38	
Patient visual analogue			
Day 1	46 (0,532)	86 (0,458)	0.24
n	19	18	
Day 2	320 (0,70)	373 (58,630)	0.61
n	37	38	

Table 3 Ketorolac after cholecystectomy. Baseline pain, and SPID and TOTPAR over 6 hours, by the nurse observer and the patient. Visual analogue scale in mm. Median (range). P: Mann-Whitney U test. For the observer, n is the number of patients studied at each time. For patients, n is the number able to perform each assessment at each point in the study.

	KETOROLAC	MORPHINE	P
Time (min)	72.5 (15,1125)	207.5 (20,915)	0.0001
Morphine(mg)			
Day 1	10 (0,36)	0 (0,55)	0.003
Day 2	0 (0,10)	0 (0,10)	0.9

Table 4 Ketorolac after cholecystectomy. Time from the second intramuscular dose to the next injection and daily requirements for rescue morphine. Median (range). P: Mann-Whitney U test.

Morning assessments (table 5) The patients in the two groups reported similar satisfaction with overnight sleep and pain relief. There was no difference in the incidence of psychological disturbances or pyrexia.

Final Assessment (table 6) There was no statistical difference in the overall opinion of the patients or observers of the study medication. Nevertheless six patients who received ketorolac described their analgesia as poor.

Oral intake and intravenous fluids (table 6) The time until oral intake recommenced was not different between the groups, but the morphine group received intravenous fluids for longer.

Completion rates and early withdrawal (table 6) The completion rate did not differ significantly for the two groups, although more patients did withdraw in the ketorolac group. The most common reason for early withdrawal was that parenteral analgesia was no longer required and oral therapy was started. Failure of analgesia accounted for seven and two withdrawals from the ketorolac and morphine groups respectively.

Injection site abnormalities and pain (table 6) There was no difference in the incidence of injection site abnormality or pain on injection between the groups.

Adverse events Ketorolac produced more nausea (P=0.005) and vomiting (P=0.05) on the day of operation, but not on the day after (P=0.73, and 0.85 respectively). Morphine was associated with a higher incidence of drowsiness on days 1 (P=0.0001) and 2 (P=0.007). Mild dyspepsia was more common with ketorolac (7 patients) than morphine (2 patients), although this did not reach statistical significance (P=0.1, Fisher's Exact test).

	KETOROLAC	MORPHINE	P
Day 2			
Satisfactory sleep?			
Y/N	26/20	25/22	0.74
Satisfactory analgesia?			
Y/N	36/10	38/9	0.76
Psychological disturbances?			
Y/N	8/38	8/39	0.96
Temperature>38°C?			
Y/N	2/44	4/43	0.41
Day 3			
Satisfactory sleep?			
Y/N	19/7	26/7	0.61
Satisfactory analgesia?			
Y/N	24/2	32/1	0.42
Psychological disturbances?			
Y/N	2/24	2/31	0.80
Temperature>38°C?			
Y/N	0/26	2/31	0.20

Table 5 Ketorolac after cholecystectomy. Morning assessments on the second and third study days.

	KETOROLAC	MORPHINE	P
Patient			
Very good	21	23	0.22
Good	17	16	
Fair	3	4	
Poor	6	0	
Observer			
Very good	22	21	0.91
Good	13	13	
Fair	7	8	
Poor	6	4	
Oral intake (hr)	27.5 (18,50)	30 (20,112)	0.16
Infusion (hr)	48.5 (25,108)	51.5(26,200)	0.04
Completion rate			
completed	19	27	0.16
withdrew	31	23	
Injection site abnormality			
Y/N	10/39	7/41	0.59
Pain on injection			
None	35	36	0.65
Minimal	11	7	
Moderate	3	4	
Severe	0	0	

Table 6 Ketorolac after cholecystectomy. Overall opinion of study medication, time to oral intake, duration of intravenous infusion, completion rates, and injection site abnormality and pain. Median (range).

Two patients from the ketorolac group and four from the morphine group were withdrawn because of adverse events. In the ketorolac group one patient was returned to theatre because of continuing blood loss; an obvious source was controlled. Another of the ketorolac group developed a chest infection. Two of the morphine group had excessive postoperative blood loss. One was returned to theatre, but no obvious bleeding vessel was found; the other required a blood transfusion only. Two of the morphine group developed chest infections; one also experienced excessive drowsiness which was treated with naloxone. No severe adverse events were reported.

Venous blood was sent for biochemical and haematological analysis before and after the study. No abnormal liver function tests or changes in haematology values were detected. Changes in urea, creatinine and electrolyte concentrations levels are presented in Chapter 6.

3.2.6 Discussion After cholecystectomy, ketorolac 30 mg gave significantly worse analgesia in the immediate postoperative period when compared with morphine 10 mg, but on the next day the effect of the two drugs did not differ. This was demonstrated by observations of pain intensity, pain relief, time to next injection, and overall assessment of analgesia. The baseline pain intensity in the immediate postoperative period was severe, and the next day it was moderate. Our findings suggest that an intramuscular dose of ketorolac 30 mg is sufficient for the relief of moderate, but not severe pain.

The encouraging result of the pilot study was therefore not confirmed by this study. Whereas the pilot study indicated that ketorolac was safe to use and had an appreciable analgesic effect, it it was not sufficiently large or detailed to explore fully the

difference between ketorolac and morphine analgesia. It was necessary to study a much larger number of patients to ensure that any differences between morphine and ketorolac could be detected.

Other observers found that ketorolac 30 mg was at least as effective as 12 mg of morphine in relieving moderate to severe pain after various operations, including major surgery (82,83). As these were single dose studies performed up to two days after surgery they should be compared with, and are similar to, our day 2 results.

Recently ketorolac 10 mg has been compared favourably with morphine 10 mg after gynaecological laparotomy (214). A 30 mg loading dose of ketorolac followed by 10 mg four hourly resulted in pain scores similar to those seen after morphine, although pain-relief scores were better with the opioid. Differences between that study and the one described here may account for the better performance of ketorolac after gynaecological surgery. These include the less painful surgical incision and the administration of an opioid premedication in the study of Powell and others (214). It is therefore possible that ketorolac could be used alone for less painful operations than cholecystectomy, especially if an opioid has already been given in theatre.

Our conclusion that ketorolac is unsuitable for the relief of severe pain is similar to that from studies on the analgesic effect of a parenteral formulation of aspirin. Lysine acetyl salicylate is a poor analgesic when compared with morphine as a bolus in the immediate postoperative period (36), but equivalent to morphine when given as an infusion over a period of time (35).

Although ketorolac was a poor analgesic in the immediate postoperative period, the ketorolac group expressed overall satisfaction with their analgesia, and only required a small dose of

rescue morphine (10 mg) in the first twenty four hours and none the next day. Such results may indicate that the quality of ketorolac analgesia became similar to that of morphine after the initial postoperative period. A morphine sparing effect of ketorolac, after abdominal surgery, has been documented before (84), and is further investigated in this thesis (Chapter 4).

Patients found it difficult to do VRS and, particularly, VAS assessments in the immediate postoperative period, confirming the value of an observer at that time (table 3). On the day after surgery the patients found it easy to perform the scores. Observers are therefore very useful in studies performed soon after surgery when much information could be lost if only patient scores were collected. The use of VAS immediately after surgery may be of limited value.

Ketorolac does not inhibit gut motility (62), and in this study the patients receiving ketorolac required intravenous fluids for a significantly shorter time, although the time to oral intake did not differ between groups. This may be important because ketorolac may also be available as tablets which could be used when the patient can take fluids. It was noted that many patients in this study required parenteral analgesia for only a short time after cholecystectomy.

Intramuscular ketorolac did not produce more injection site pain or abnormalities than morphine. Ketorolac given as repeated intramuscular injections does not increase serum creatinine phosphokinase levels, but diclofenac does (64). The muscular discomfort produced by injections of diclofenac may not be a problem with ketorolac.

Adverse reactions were minor. Although opioids are recognised to have an emetic effect, ketorolac was associated with more nausea and vomiting on the day of operation than morphine. Other

gastrointestinal side-effects were minor, ketorolac 30 mg intramuscularly resulted only in mild, transient, dyspepsia in 7 out of 50 subjects. Ketorolac 30 mg may not produce peptic ulceration when given for a short time after abdominal surgery. In view of the results of volunteer studies concerning the effect of ketorolac on gastric mucosa (149), this drug should not be given if there is a history of peptic ulceration. Drowsiness and sedation were persistent problems with morphine as could be predicted from work done on the psychomotor effects of ketorolac and opioids (64). There were no clinically relevant changes in liver function or haematology tests after repeated administration of ketorolac over two days.

Of all the patients approached for this study, more than 10% were excluded because of a history of peptic ulceration and asthma (table 1), and this may be a reflection of the fact that a considerable proportion of general surgical patients will have absolute contraindications to the use of NSAIDs.

3.2.7 Conclusion Although ketorolac was a useful parenteral analgesic after upper abdominal surgery, 30 mg intramuscularly was adequate only for the relief of pain of moderate intensity. Immediately after upper abdominal surgery when pain was severe, ketorolac alone was not sufficient and was inferior to morphine 10 mg. The administration of ketorolac intramuscularly for two days after surgery did not produce any serious adverse effects.

CHAPTER 4

KETOROLAC AS AN ADJUNCT TO MORPHINE

4.1 Intramuscular ketorolac in combination with intravenous patient controlled analgesia after thoracotomy

4.1.1 Introduction The cholecystectomy study indicated that ketorolac may not be sufficient to relieve severe pain when used alone, but previous work has suggested that NSAIDs may still be a useful component of analgesia when treating severe pain when combined with relatively low doses of opioids. That is, NSAIDs may act as adjuncts and have an opioid sparing effect. After upper abdominal surgery continuous intramuscular infusions of ketorolac (1.5 or 3 mg/hr) improve analgesia, reduce patient controlled opioid requirements, and are associated with less postoperative respiratory depression (84). Indomethacin has a morphine sparing effect after surgery also (38), and, when given by suppository, reduces pain scores and opioid requirements after thoracotomy when pain and opioids often impair respiratory function (41). The possible morphine sparing effect of NSAIDs is worthy of further study because not all investigations have had this result (49,50).

In this study carried out after thoracotomy, the potential benefits of giving regular intramuscular ketorolac in combination with intravenous patient controlled analgesia (morphine) were investigated.

4.1.2 Methods

Patient selection and exclusion criteria The subjects were elective admissions to the thoracic unit in the City Hospital, Edinburgh, for thoracotomy and resection of lung tumours. 75 patients (aged 18 to 75y) were enrolled after giving written informed consent.

Anaesthesia and surgery Premedication was with intramuscular papaveretum and atropine (prophylactic subcutaneous heparin, 5000 iu, was given at the time of premedication). Anaesthesia was induced with intravenous thiopentone, and maintained with oxygen in nitrous oxide and enflurane. Tracheal intubation was facilitated with intravenous suxamethonium and muscle paralysis maintained with alcuronium. At the end of the operation, neostigmine with atropine was used to antagonise residual neuromuscular blockade. Intercostal nerve blocks were performed after induction of anaesthesia using bupivacaine 0.5% with adrenaline 1/200,0000. If opioid analgesia was required during surgery intravenous fentanyl was given. All patients had an intercostal incision for thoracotomy and lung resection.

Study design This was a double-blind randomized study of six hourly intramuscular injections of ketorolac 30 mg, ketorolac 10 mg, or placebo.

Upon enrolment, subjects were allocated a study number (1 to 75) and a corresponding box of study medication containing nine ampoules for intramuscular injection. The ampoules were identical (amber coloured, 1ml) and contained ketorolac 30mg, 10 mg, or placebo according to the randomization schedule.

Drug administration The first dose of study drug was given intramuscularly to the vastus lateralis muscle, using a 23 gauge needle, at the end of the surgical procedure before anaesthesia was reversed, and the remaining eight doses were given six-hourly thereafter. Administration of the study drug was delayed until the end of surgery because of concern about the effect of ketorolac on platelet function and haemostasis. The study ended two hours after the last injection, 50 hours after the first dose of study medication was given.

Patient controlled analgesia In the postoperative period the subjects had access to intravenous morphine from a patient controlled analgesia (PCA) machine (Abbott Lifecare PCA plus). The pump was set to deliver a bolus of morphine 2mg on demand, with a lockout time of 15 minutes. No background infusion was used. The use of patient controlled analgesia allowed the inclusion of an intramuscular placebo group in the study. If analgesia was inadequate then the PCA bolus dose of morphine was increased. During the two day study period the subjects were nursed and monitored in a high dependency unit.

Efficacy

Morphine usage The patient's requirements for morphine from the PCA machine were recorded hourly during the two day study period.

Pain scores Both the patient and one nurse observer independently assessed pain at set times during the study. Pain at rest and pain on deep breathing were recorded two hours after the first (day 1), fifth (day 2) and ninth (day 3) intramuscular injections of study drug. The intramuscular injections were given at six hourly intervals, meaning that pain assessments were performed at 2, 26, and 50 hours into the study which ended at the last assessment.

Each patient assessed pain at rest and during deep breathing by a four point VRS (0 = no pain, 1 = mild, 2 = moderate, 3 = severe pain), and by a 10 cm VAS (0 no pain to 100 mm worst possible pain).

One nurse observer independently scored the patients pain using the four point score described.

Overall score On the day after surgery (day 2) and the last day of the study (day 3) the observer and the patient gave an overall assessment of pain relief as 'excellent/good/fair/poor'. At the same time the patients reported whether they had slept well the previous night and whether their pain control had been satisfactory.

Physiotherapist's score After thoracotomy, physiotherapy is an important part of the overall management of the patient. An unfortunate effect of opioids is that the sedation they produce together with their anti-tussive effect can impair the patient's compliance with physiotherapy. During this study the unit physiotherapist scored the ability of the subjects to comply as poor, fair, good, or excellent.

Withdrawal rate Patients were classed as withdrawing from the study if they did not receive all nine intramuscular injections of study drug. The time and reason for withdrawal were recorded.

Sedation score The observer assessed the subjects level of sedation using a four point score (0 awake and alert, 1 awake but drowsy, 2 asleep and easily rousable, 3 asleep and rousable only by physical stimuli). These assessments were done at the same time as the pain scores.

Respiratory rate and arterial blood gas analysis The patient's respiratory rate was recorded, and a sample of arterial blood taken (from an indwelling catheter) for analysis of oxygen and carbon dioxide partial pressures and hydrogen ion concentration. If the patient was receiving supplementary oxygen then this was noted, together with the concentration delivered. These assessments were made at the same times as the pain scores (2, 26, and 50 hours from the beginning of the study). Respiratory rates and arterial blood carbon dioxide tensions ($PaCO_2$) were compared between the groups as a measure of respiratory effects.

Blood loss from chest drains The blood loss, if any, from the chest drain left at operation was measured on each study day.

Return of gastrointestinal function In order to assess the recovery of bowel function the time in hours to the return of bowel sounds and the resumption of oral (fluid) intake was recorded.

Haematology, Biochemistry Venous blood was sampled and sent for haematological and biochemical analysis before surgery and on each study day.

4.1.3 Statistical design and analysis The primary variable under analysis in this study was the subject's morphine usage. From preliminary observations, we predicted that the expected mean value of this in the first twenty four hours would be around 60 mg with a standard deviation of 20 mg. A difference of morphine usage between groups of about one third (20mg) would be clinically significant and has been found in similar studies after abdominal surgery with ketorolac (84) and after thoracotomy and abdominal surgery with indomethacin (41,38). A difference of morphine consumption between groups of 20 mg could be detected with a statistical power of 75% if there were 25 patients per treatment group (211).

Analysis of variance and the Kruskal-Wallis test were used to test for differences between the three treatment groups (placebo, ketorolac 10 mg, and ketorolac 30 mg), as described in chapter 2.7.3. One way analysis of variance was used to analyse morphine consumption and VAS results. The Kruskal-Wallis test was used for other scores.

4.1.4 Results

Patient details and surgical procedure (table 7) 75 patients were enrolled, 25 to each group. The treatment groups did not differ significantly in age, height, or weight. The majority of patients were male, and the sexes were similarly distributed between the

	PLACEBO	K10mg	K30mg
M/F	19/6	20/5	23/2
Age(yr)	60(9.5)	59.2(10.3)	56.5(13.5)
Height(cm)	172(11.9)	170(7.5)	170(9.3)
Weight(kg)	69.4(13.1)	68.5(13)	70(14.7)
Pneumonectomy or lobectomy	21	19	17
Segmental resection	2	2	2
Removal of thoracic cyst	1	-	2
Thoracotomy, no resection	1	4	4

Table 7 Details of the patients in the thoracotomy study and the surgical procedure. Mean (SD). K10mg and K30mg are ketorolac 10 and 30 mg respectively.

groups. All operations were performed via an intercostal incision. Surgery was most commonly pneumonectomy or lobectomy for carcinoma of the lung, in a few cases partial tumour resection was performed, but in 9 of the patients it was impossible to remove any lesion and only thoracotomy was carried out.

Efficacy

Morphine usage (table 8, figure 2) The rate of morphine usage was consistent with the predictions of the statistical design of the study. The mean morphine consumption by the placebo group was 61 mg (SD 18.4) in the first 24 hours.

There was no significant difference in the amount of morphine used by the three drug groups at any time during the study period, although the placebo group tended to require more on average than the ketorolac groups. At 24 hours, the placebo group had used an average of 8.4 mg more morphine than the ketorolac 10 mg group (95% CI -8 to 25 mg, P=0.12), and 6 mg more than the ketorolac 30 mg group (95% CI -11 to 23 mg, P=0.42). At 48 hours, the placebo group had used an average of 15 mg more morphine than the ketorolac 10 mg group (95% CI -14 to 43 mg, P=0.18) and the ketorolac 30 mg group (95% CI -12 to 42 mg, P=0.32), differences which were not statistically significant. Morphine usage was similar in the two ketorolac groups (P=0.6, and P=0.87 at 24 and 48 hours).

Patient pain assessment (table 9) There was no statistically significant difference between the drug groups for pain at rest or on taking a deep breath at any of the three observation times when measured by a VRS or VAS. Pain intensity tended to be mild at all times when the patient was resting, and increased with deep breathing in all treatment groups. On the third day, VAS for pain at rest

	PLACEBO	K10mg	K30mg
24 hours	61(3.9)	52(6.4)	55(6.7)
48 hours	97(6.7)	82(10)	82(10)

Table 8 Ketorolac after thoracotomy. PCA morphine consumption at 24 and 48 hours. Mean (SE).

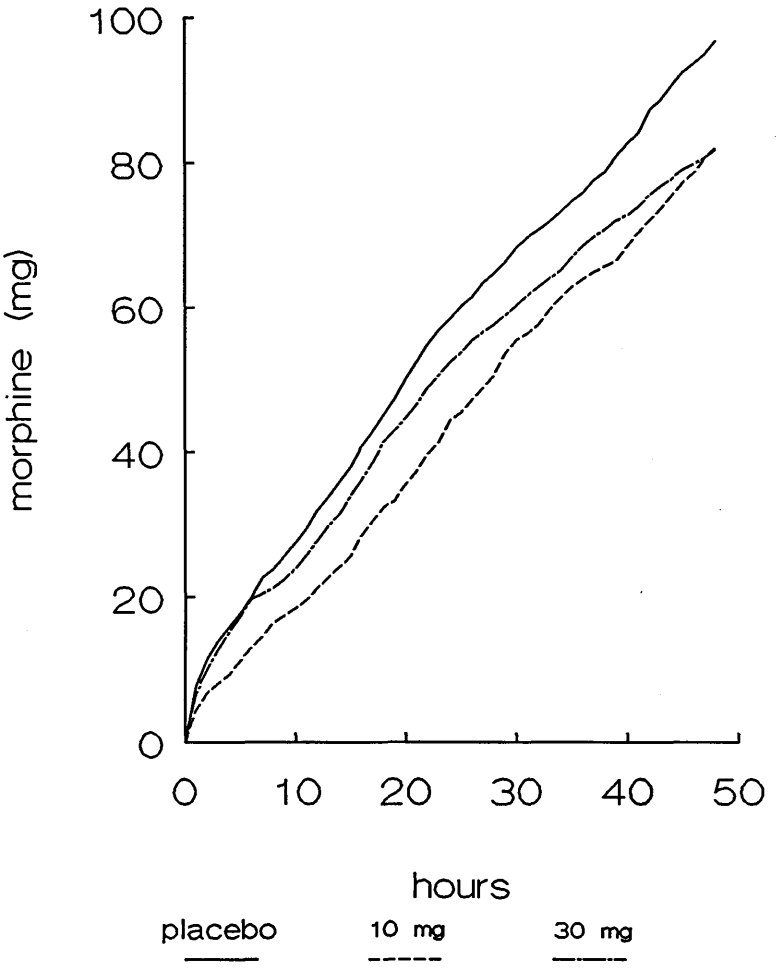

Figure 2 Mean cumulative morphine requirements after thoracotomy. Placebo, ketorolac 10 mg, and ketorolac 30 mg.

	PLACEBO	K10mg	K30mg
PAIN AT REST			
Visual Analogue Scale			
Study day			
1	26(4.5)	20(4.6)	27(4.7)
2	23(6)	29(5)	19(4.8)
3	19(5.4)	20(4.8)	11(2.7)
Verbal Rating Scale			
Study day			
1	1(0-3)	1(0-3)	1(0-2)
2	1(0-2)	1(0-2)	1(0-2)
3	1(0-2)	1(0-2)	1(0-2)
PAIN ON DEEP BREATHING			
Visual Analogue Scale			
Study day			
1	31(4.7)	26(4.5)	36(5.5)
2	37(6.5)	39(5)	32(5)
3	26(5.6)	28(6.3)	18(4)
Verbal Rating Scale			
Study day			
1	1(0-3)	1(0-3)	1(0-2)
2	1(0-3)	2(0-2)	1(0-2)
3	1(0-2)	1(0-3)	1(0-2)

Table 9 Ketorolac after thoracotomy. Pain assessments by patients at rest and upon taking a deep breath. Visual analogue score in mm, mean (SE). Verbal rating score median (range).

tended to be higher for the placebo group than ketorolac 30 mg, but this was not statistically significant (P=0.2, mean difference 8 mm, 95% CI -2 to 20).

Observer pain assessment (table 10) The observer scored pain as being absent or mild when the patient was at rest. There was no difference between the groups at any of the observation times.

Patient and observer overall score (table 11) The patients in all groups indicated a high degree of satisfaction with their analgesia, usually scoring it as good or excellent, and there was no difference between the treatment groups. The observer score indicated that the ketorolac group had better analgesia, although this only approached statistical significance (P=0.1, and P=0.06, Kruskal-Wallis, days 2 and 3 respectively).

Physiotherapy assessment (table 12) There was no difference in the ability of the patients to comply with physiotherapy, although the ketorolac 30 mg group tended to have higher scores.

Sedation (table 12) There was no difference between the groups on days 1 and 2. On day 3, 8 of 13 patients in the placebo group, 15 of 17 in the ketorolac 10 mg group, and 21 of 22 in the ketorolac 30 mg group were completely awake with a sedation score of 0. The difference in the sedation scores of placebo and ketorolac 30 mg was statistically significant (P=0.01, Kruskal-Wallis). There was no statistically significant difference between placebo and ketorolac 10 mg (P=0.1), or the two ketorolac groups (P=0.43).

Withdrawal rate (table 13) More patients in the ketorolac 30 mg group completed the study than in the placebo group (P=0.005, Fisher's exact test). There was no difference between the placebo and

	PLACEBO	K10mg	K30mg
APPARENT PAIN			
Verbal Rating Scale			
Study day			
1	0(0-2)	0(0-2)	0(0-1)
2	1(0-2)	1(0-2)	1(0-2)
3	0(0-2)	0(0-2)	0(0-2)

Table 10 Ketorolac after thoracotomy. Pain assessment by the observer. Median (range).

	PLACEBO	K10mg	K30mg
PATIENT			
Day 2			
Poor	1/16	0/18	0/23
Fair	2/16	2/18	2/23
Good	7/16	7/18	6/23
Excellent	6/16	9/18	15/23
Day 3			
Poor	0/13	0/16	0/22
Fair	0/13	0/16	2/22
Good	5/13	8/16	7/22
Excellent	8/13	8/16	13/22
OBSERVER			
Day 2			
Poor	0/16	0/18	0/23
Fair	3/16	2/18	1/23
Good	8/16	4/18	9/23
Excellent	5/16	12/18	13/23
Day 3			
Poor	0/13	0/16	0/22
Fair	4/13	3/16	1/22
Good	4/13	6/16	5/22
Excellent	5/13	7/16	16/22

Table 11 Ketorolac after thoracotomy. Patient and observer overall assessment of analgesia.

	PLACEBO	K10mg	K30mg
Physiotherapy			
Day 2			
Poor	0/16	0/18	0/23
Fair	4/16	3/18	2/23
Good	11/16	8/18	11/23
Excellent	1/16	7/18	10/23
Day 3			
Poor	0/13	0/16	0/22
Fair	5/13	2/16	0/22
Good	5/13	7/16	10/22
Excellent	3/13	7/16	12/22
Sedation			
Day 1	2(0-3)	2(0-3)	1(0-3)
Day 2	0(0-1)	0(0-2)	0(0-2)
Day 3	0(0-2)	0(0-2)	0(0-2)

Table 12 Ketorolac after thoracotomy. Physiotherapy and sedation scores, median (range).

	PLACEBO	K10mg	K30mg
n	25	25	25
Day 1	4	2	2
Day 2	6	6	0
Day 3	3	2	1
Completed study	12*	15	22

Table 13 Withdrawals and completion rates in the thoracotomy study.
*Significantly less than K30mg.

ketorolac 10 mg (P=0.4), or ketorolac 10 and 30 mg (P=0.1). The majority of patients who withdrew were in the placebo group, and the most common reason for withdrawal was poor pain relief.

Of the 13 subjects in the placebo group who withdrew early, 11 did so because of inadequate analgesia, 1 had a postoperative bleed, and 1 was not given a dose of study drug in error.

In the ketorolac 10 mg group, 5 withdrew because of poor analgesia. 1 each stopped early because of pronounced respiratory depression, lobar collapse of the lung requiring bronchoscopy, dyspepsia with respiratory depression and a low renal output, and 2 were not given doses of study drug by mistake.

In the ketorolac 30 mg group, only 2 withdrew because of inadequate analgesia, and 1 patient had a postoperative bleed.

Respiratory rate and arterial blood analysis (table 14, figure 3)

There was no difference between the three groups in respiratory rate or arterial blood carbon dioxide tension ($PaCO_2$, kPa)at 2, 26 and 50 hours after the end of the operation and the beginning of the study.

Consideration of the change in $PaCO_2$ in individual patients after operation did, however, suggest a difference between the placebo and ketorolac groups (figure 3). From the two hour arterial blood sample to 26 hours all three groups showed a fall in $PaCO_2$. This trend continued in the ketorolac groups, but was not sustained in the placebo group so that there was no difference in $PaCO_2$ in these subjects at the 2 and 50 hour samples (P=0.96). Mean $PaCO_2$ was higher at 50 hours in the placebo group 6.14(0.42)kPa compared with the ketorolac 10 mg group 5.35(0.2) (P=0.1, 95%CI -0.3 to 1.9 kPa), and the ketorolac 30 mg group 5.5(0.26) (P=0.2, 95%CI -0.8 to 0.5kPa).

	PLACEBO	K10mg	K30mg
RESPIRATORY RATE			
Day 1	17(0.8)	16(1)	16(0.7)
Day 2	18(0.7)	18(0.8)	18(0.4)
Day 3	19(0.5)	20(0.9)	19(0.4)
PaCO2(kPa)			
Day 1	6.24(0.14)	6.43(0.16)	6.19(0.17)
Day 2	5.9(0.14)	5.78(0.15)	5.84(0.1)
Day 3	5.82(0.18)	5.28(0.16)	5.5(0.23)

Table 14 Respiratory rate and arterial blood carbon dioxide tension after thoracotomy. Mean (SE).

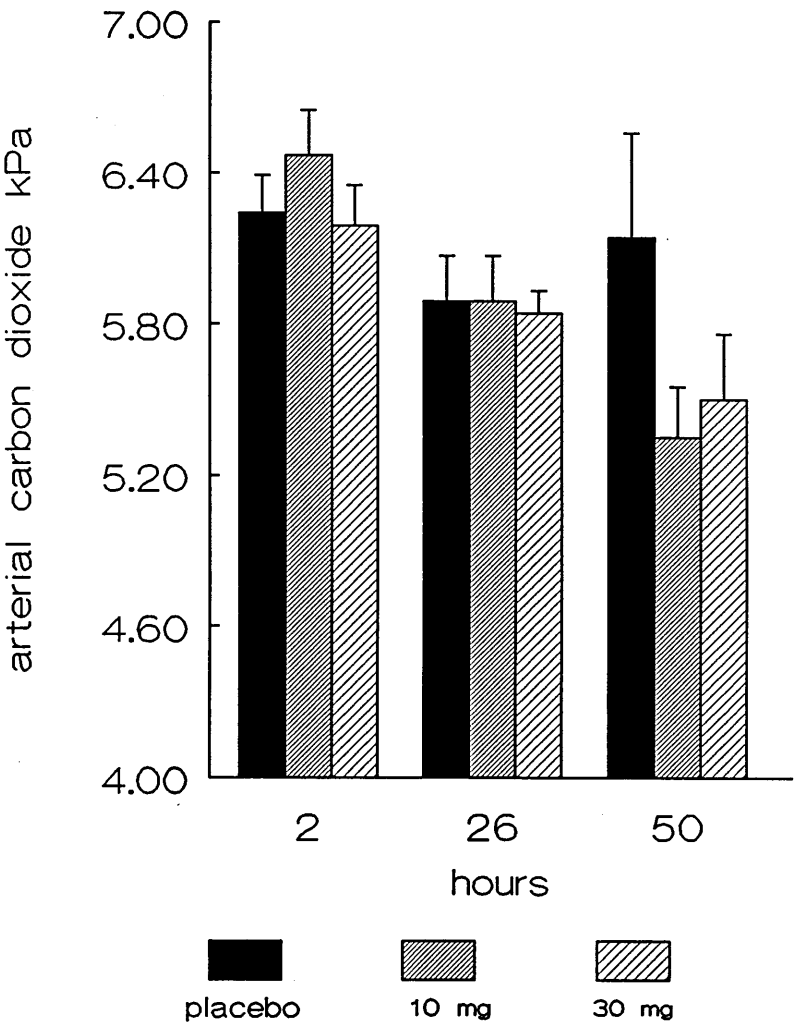

Figure 3 Arterial blood CO_2 tension after thoracotomy. Mean (SE).

These mean differences were not statistically significant (P=0.23, analysis of variance), perhaps because only 12 subjects continued in the placebo group to this point in the study.

Blood loss from chest drains and gastrointestinal function (table 15) Ketorolac did not increase blood loss from wound drains. Gastrointestinal function, assessed by the time to return of bowel sounds and return to oral intake, did not differ between the groups.

Haematology and biochemistry There were no abnormal changes found on laboratory analysis of blood over the three study days. Specifically, no abnormal liver function tests were found with ketorolac. Changes in blood urea and electrolytes are discussed in chapter 6 of this thesis.

Adverse events Although five patients were withdrawn because of adverse events, these were not thought to be 'serious' (see chapter 2.8).

One patient in the placebo group had a severe postoperative haemorrhage, and was returned to theatre where a bleeding bronchial artery was successfully ligated.

Three patients were withdrawn from the low dose ketorolac group. Two had respiratory depression, thought to be related to opioids, and one also had dyspepsia and a poor urine output. Both of these patients were given naloxone to antagonise the depressant effect of morphine. One subject required suction bronchoscopy to treat collapse of a lobe of the lung.

One patient in the ketorolac 30 mg group had a large and rapid blood loss from the intercostal chest drain and lobectomy and was withdrawn in the immediate postoperative period. The blood loss was

	PLACEBO	K10mg	K30mg
BLOOD LOSS (ml)			
Day 2	576(68)	581(51)	653(78)
Day 3	308(80)	364(66)	420(89)
GASTROINTESTINAL			
Bowel sounds (h)	24.2(1)	25.4(1.1)	28.7(1.8)
Oral intake (h)	27.5(1.5)	26.9(1.5)	27(1.5)

Table 15 Blood loss from surgical drains, and time to return of gastrointestinal function after thoracotomy. Mean (SE).

expected as there were many pleural adhesions and it had been a difficult surgical dissection. Skin bleeding time was normal (200), and only a blood transfusion was needed.

All of these patients made a full recovery and required no further treatment.

Other adverse events are listed (table 16). Nausea and vomiting were common complaints, although relatively less so in the ketorolac 10mg group. The placebo group tended to have more chest infections postoperatively. Urinary retention and poor urine output were complaints associated with ketorolac. One other patient from the ketorolac 10 mg group had mild dyspepsia. Muscle pain after injection of ketorolac was not a problem.

4.1.5 Discussion This investigation did not find any clear benefit in administering regular intramuscular injections of ketorolac after thoracotomy to patients receiving morphine by patient controlled analgesia. Morphine use, patient and observer pain assessments, and compliance with physiotherapy were very similar in all the treatment groups (although the ketorolac groups tended to score slightly better). There was some evidence from the observer's overall score that ketorolac improved analgesia. High dose ketorolac was associated with less sedation on day 3 (table 12) and a higher study completion rate (table 13), which may be subtle indicators of beneficial actions of the NSAID.

There was evidence that ketorolac reduced morphine requirements by about 15 mg over 48 hours (table 8, figure 2), a difference which was not statistically significant in this study. Such a reduction in opioid requirement may be also considered clinically insignificant.

	PLACEBO	K10mg	K30mg
Nausea, vomiting	11	4	15
Chest infection	4	1	2
Urinary retention	1	3	8
Low urine output	0	3	1
Bronchospasm	0	1	1
Dyspepsia	0	1	0
Flatulence	2	1	1
Headache	0	1	0

Table 16 Numbers of patients with adverse events after thoracotomy.

Previous studies using similar numbers of patients, found that administration of ketorolac (84) and indomethacin (41,38) significantly improved postoperative analgesia whilst reducing opioid requirements by around one third. Such an effect was not found in this study, and it may be reasonable to make comparisons with these earlier investigations to discern why there should be such different results from the present study. It should be noted that not all studies have found that NSAIDs improve analgesia or reduce opioid requirements (49,50).

Gillies and others (84) studied 61 patients after upper abdominal surgery who were given continuous intramuscular infusions of saline, ketorolac 1.5 mg/hr, or ketorolac 3 mg/hr, for 24 hours. In a similar fashion to this study, morphine requirements were measured using a patient-controlled analgesia system. Patients who were given ketorolac required on average 25 mg less morphine in twenty-four hours, had better pain relief, and less postoperative increase in arterial carbon dioxide tensions than controls. Doses of ketorolac were slightly lower than in this study at 36 mg (low dose) or 72 mg (high dose) over 24 hours. It may be that continuous infusions of ketorolac are more effective than intermittent injections, and there is some evidence to that effect (215,216). Ketorolac has a relatively short half-life (65,66,67) and six-hourly intramuscular administration may not be frequent enough; perhaps a continuous low dose infusion would have been better. Also the severity of pain experienced by the patients may have differed between the studies; upper abdominal surgery may be more painful than thoracotomy allowing patients to derive more benefit from addition of an NSAID. Indeed the pain scores reported by Gillies and others were appreciably higher than those recorded after thoracotomy in this study. Also,

intercostal nerve blockade was performed in this study using bupivacaine, a long acting local anaesthetic, which may also reduce postoperative pain. There is evidence that patients are better able to compare between analgesics in the presence of severe pain (83). An additional factor is that the patients enrolled in this study were older than in Gillies and others, and age is an important determinant of analgesic requirement (184).

In comparison with the work of Gillies and others (84), the identifiable reasons for the different result in this study are that ketorolac was given intermittently (not continuously), pain severity may have been less (operative site, local anaesthetic block), and analgesic requirements may have differed in the more elderly patients in this study.

Pavy and others (41) studied the effect of indomethacin on pain relief after thoracotomy, confirming the beneficial results reported by Reasbeck and colleagues after abdominal surgery (38). 60 patients were given either indomethacin (200mg at the end of surgery then 100mg twice daily) or placebo suppositories. Postoperatively patients were given papaveretum by continuous infusion which was adjusted by the nursing staff to give adequate pain relief. Indomethacin resulted in improved pain relief and a significant reduction of papaveretum requirements (about 40 mg over 48 hours). In comparison with the study described in this thesis, the obvious differences are that Pavy and colleagues used a different NSAID by suppository, with continuous infusions of opioid adjusted to analgesic effect by staff, and did not use intercostal nerve blockade. Indomethacin could be more effective than ketorolac, but there have been no comparative studies. Suppository may deliver the drug at more constant rates providing more stable blood concentrations than intermittent injections, like

the intramuscular infusions of Gillies and others (84). PCA should be more sensitive to the needs of the patient than continuous infusions altered by nursing staff. The pain scores reported by Pavy and colleagues for their control group were again appreciably higher than in the study presented in this thesis (41). It is possible that pain relief given by continuous infusion of papaveretum gave poorer analgesia than morphine by PCA, and paradoxically allowed the benefits of indomethacin to be more obvious. It should be noted that Pavy and others did not use intercostal nerve block during surgery, which would be expected to increase pain severity, again perhaps allowing the benefit of NSAID administration to be more obvious.

In this study, there was some indication that ketorolac administration was associated with lower $PaCO_2$ values on the second postoperative day (figure 3), although statistical significance was not reached. This may be evidence of continuing respiratory depression in the patients in the placebo group, who were also more sedated at this time (table 12). The high $PaCO_2$ values two hours after operation (table 14) may result from the residual effects of anaesthesia and it could have been expected that tensions would fall thereafter towards preoperative values. Unfortunately the present study did not investigate this fully, as arterial blood was not sampled in the preoperative period, but earlier studies have shown that ketorolac does reduce postoperative changes in $PaCO_2$ (84), and indomethacin minimises postoperative respiratory depression (38). This may be an important beneficial effect of ketorolac, even in the late postoperative period when respiratory side-effects are known still to occur (33) and when oxygen supplementation is normally stopped. This effect of ketorolac administration may be worthy of further study.

The adverse events seen were unlikely to result from ketorolac administration. One individual did have a brisk blood loss after ketorolac 30 mg, but the dissection had been difficult and platelet function as assessed clinically by the skin bleeding time was normal. As in the cholecystectomy study (Chapter 3.2), gastrointestinal problems with ketorolac were uncommon. Two patients in the low dose ketorolac group had dyspepsia, but none complained of this with the higher dose of the NSAID. Liver function was not impaired by ketorolac. Urinary retention and low urine output (which were not clearly distinguished in this investigation) may have been associated with ketorolac administration.

4.1.6 Conclusion There was no clear benefit in giving ketorolac intramuscularly to patients after thoracotomy who had had intercostal nerve block and were receiving morphine by PCA. In comparison with previous studies, the absence of any benefit of ketorolac could have resulted from the intermittent method of administration, the low pain state associated with intercostal nerve block and the use of PCA, as well as the age of the patients.

CHAPTER 5

THE EFFECT OF KETOROLAC AND DICLOFENAC ON PLATELET FUNCTION

5.1 Introduction

If the use of NSAIDs as postoperative analgesia becomes accepted practice, ketorolac may be used during and after surgery, just as diclofenac has become popular (45,47). There is some concern over the perioperative use of NSAIDs as they prevent thromboxane A_2 (TxA_2) production by inhibition of cyclo-oxygenase (13). TxA_2 and cyclic endoperoxides are important mediators of platelet aggregation and vasoconstriction, processes involved in the primary haemostatic response to vessel injury (91). Specific receptors for TxA_2 and cyclic endoperoxides have been isolated in human platelets (92). The possibility exists therefore, that NSAID administration during surgery could affect platelet function, impair haemostasis, and increase blood loss. Indeed concern has been expressed about the use of diclofenac during major surgery, until detailed studies of the platelet effects have been performed (48).

NSAIDs and aspirin, which has a similar inhibitory effect on cyclo-oxygenase, inhibit platelet aggregation and prolong bleeding time in volunteers (94,95,100). There is insufficient information on the perioperative situation where the haemostatic response may be altered by the stress of surgery, although aspirin is well recognised to be a cause of postoperative bleeding (97,98).

Patients undergoing surgery may be given heparin or dextran as prophylaxis against deep venous thrombosis (105,106), and these could interact with NSAIDs. The effect of ketorolac with heparin has been studied in volunteers (103), but there is little information on the effect in patients. It is known that the combination of aspirin and heparin, an effective prophylaxis against deep venous thrombosis (217), can be associated with severe bleeding problems (218). Dextrans are used intravenously during surgery for volume expansion

as well as prophylaxis against venous thrombosis, and have some anti-platelet effects. There have been no investigations of the potential interaction between NSAIDs and dextran on haemostasis.

The methods described in Chapter 2.4 were used to investigate the effect of ketorolac and diclofenac on skin bleeding time, whole blood platelet aggregation and operative blood loss, and also to assess combinations of ketorolac and dextran-70.

5.2 The effect of ketorolac 30 mg on platelet function and blood loss during cholecystectomy

5.2.1 Introduction The effect of ketorolac on platelet function was observed in patients enrolled into the cholecystectomy study, described in Chapter 3.2 of this thesis. Operative blood loss (100 patients), skin bleeding time (20 patients), and whole blood platelet aggregation (10 patients) were observed in a double-blind randomized study of ketorolac 30 mg and morphine 10 mg. All patients were given subcutaneous heparin (5000 iu) one hour before surgery.

5.2.2 Methods The study protocol for the cholecystectomy study is described in Chapter 3.2.2. Patients were given either ketorolac 30 mg or morphine 10 mg by intramuscular injection after induction of anaesthesia. In all 100 patients in the cholecystectomy study operative blood loss was estimated by weighing swabs in theatre. Within the randomization schedule, in 10 subjects from each of the ketorolac and morphine groups the skin bleeding time was recorded before surgery and one hour after the first dose of study medication. In 10 of these 20 subjects *in vitro* platelet aggregation studies were also performed at the same time. None of the 20 subjects was a

cigarette smoker. In this way, changes in skin bleeding time and platelet aggregation were observed after ketorolac and morphine. The methods used for skin bleeding time and *in vitro* platelet aggregation studies are described in full in Chapter 2.4. In this study, spontaneous, collagen induced, and arachodonic acid induced *in vitro* platelet aggregation was examined.

Statistical analysis Between group comparisons (operative blood loss) were made using unpaired t-tests, and changes within individual patients after drug administration (skin bleeding time, platelet aggregation) were analysed using paired t-tests.

5.2.3 Results

Patient details These have previously been summarized in this thesis (table 2).

Operative blood loss (Figure 4) There was no statistical difference in the blood loss of the two groups (P=0.71); the mean loss of the ketorolac group was 218 ml (SE 19, range 20-580 ml), and the morphine group 231 ml (SE 30, range 25-950 ml).

Skin bleeding time (Table 17) This was significantly prolonged by ketorolac from a mean of 223 to 297 s (P=0.007, 95% CI 26 to 123 s). After ketorolac the longest bleeding time was 369 s, an increase of 214 over the control value, but still within the upper limit of normal of 600 s. The morphine group showed no change in bleeding time (P=0.33, 95% CI -14 to 5 s).

Platelet aggregation (Table 17, figures 5, 6 and 7) Spontaneous platelet aggregation was unchanged after ketorolac. Collagen and arachidonic acid induced aggregation were reduced after ketorolac, but statistical significance was approached only for collagen induced aggregation, perhaps due to the small number of patients studied.

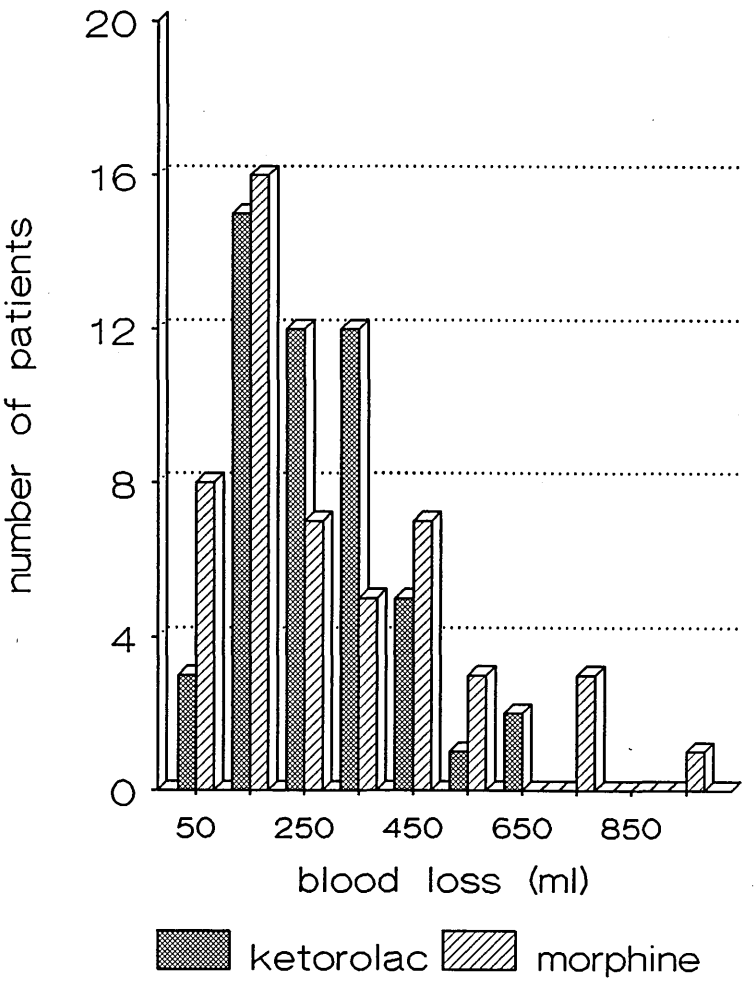

Figure 4 Operative blood loss during cholecystectomy.

	Before	After	P
Skin bleeding time (s)			
ketorolac	223(16)	297(14)	0.007
morphine	242(14)	237(14)	0.33
Platelet aggregation			
Spontaneous			
5 min:			
ketorolac	59 (4)	62 (6)	0.13
morphine	57 (5)	57 (7)	0.79
10 min:			
ketorolac	44 (6)	45 (4)	0.9
morphine	42 (3)	44 (5)	0.51
Collagen			
1 min:			
ketorolac	26 (7)	56 (16)	0.2
morphine	18 (5)	15 (3)	0.52
3 min:			
ketorolac	14 (2)	37 (13)	0.1
morphine	11 (3)	8 (2)	0.26
5 min:			
ketorolac	15 (2)	35 (11)	0.16
morphine	12 (2)	9 (2)	0.48
Arachidonic acid			
1 min:			
ketorolac	39 (14)	59 (9)	0.45
morphine	23 (11)	13 (4)	0.24
3 min:			
ketorolac	27 (10)	49 (7)	0.25
morphine	16 (7)	9 (1)	0.38
5 min:			
ketorolac	24 (6)	49 (7)	0.26
morphine	13 (2)	10 (2)	0.11

Table 17 The effect of ketorolac 30 mg on skin bleeding time and whole blood platelet aggregation. Values before and one hour after intramuscular injection of ketorolac or morphine. Whole blood platelet aggregation is expressed by the percentage of platelets present in the sample at each time (baseline count = 100%). Mean (SE), P: paired t-test.

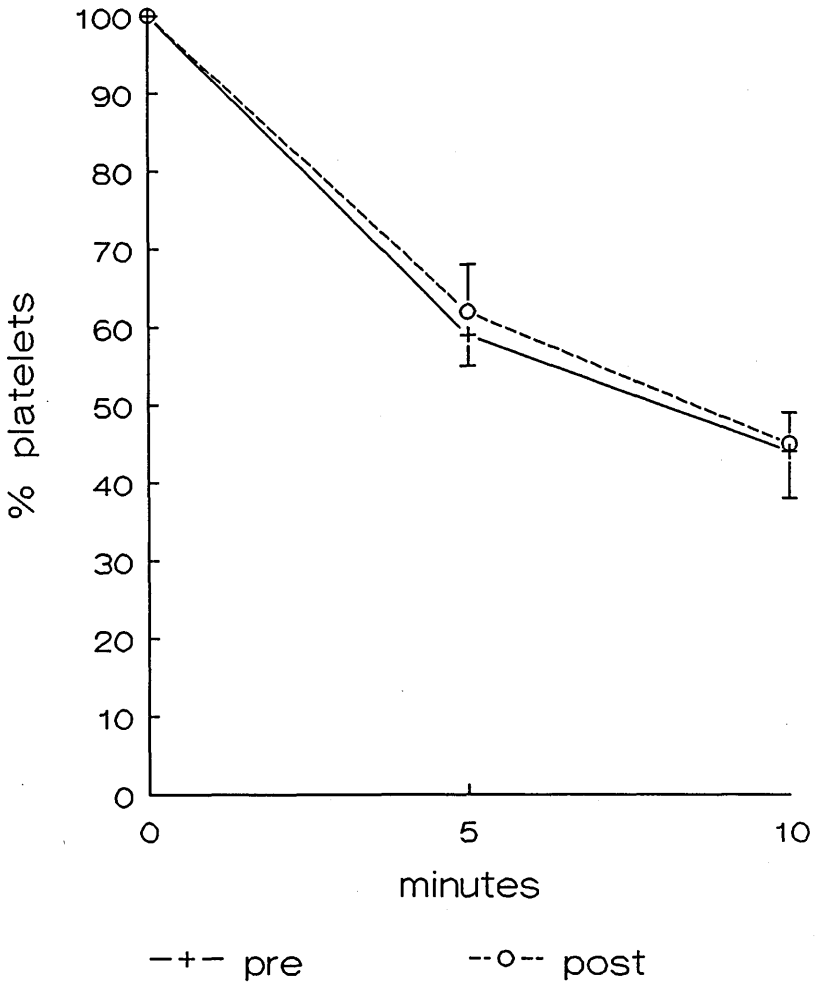

Figure 5 Spontaneous platelet aggregation (ketorolac). The percentage of unaggregated platelets in the sample is plotted against time. Mean (SE).

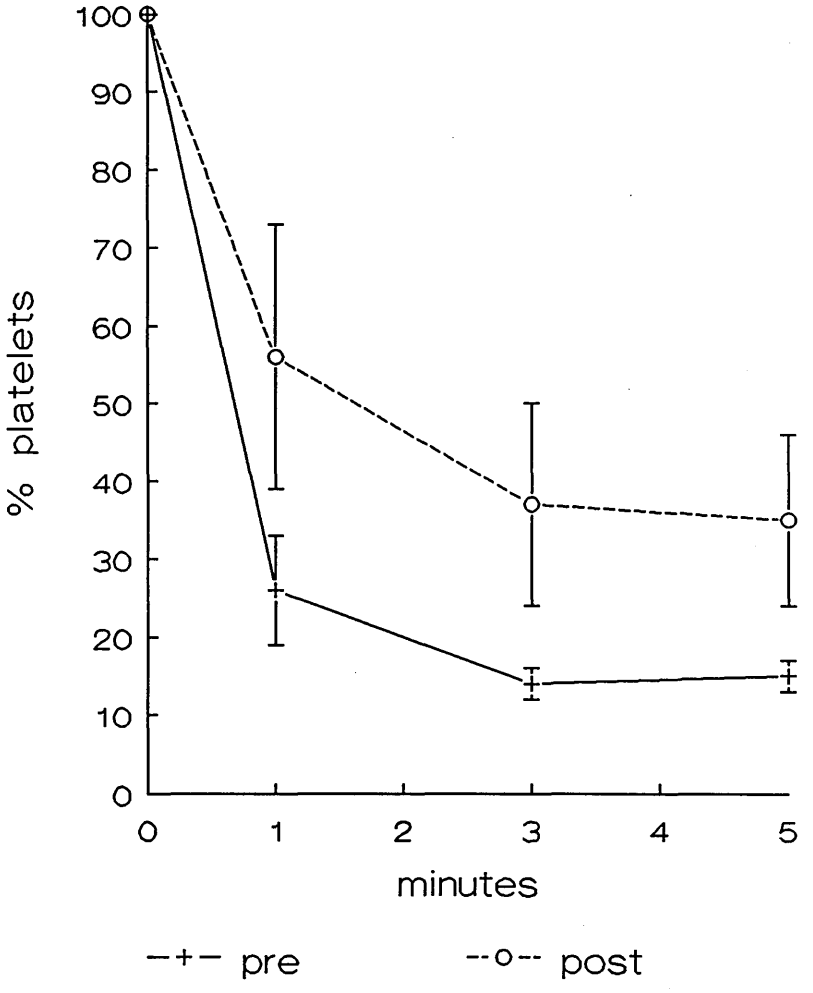

Figure 6 Collagen induced platelet aggregation (ketorolac). Mean (SE).

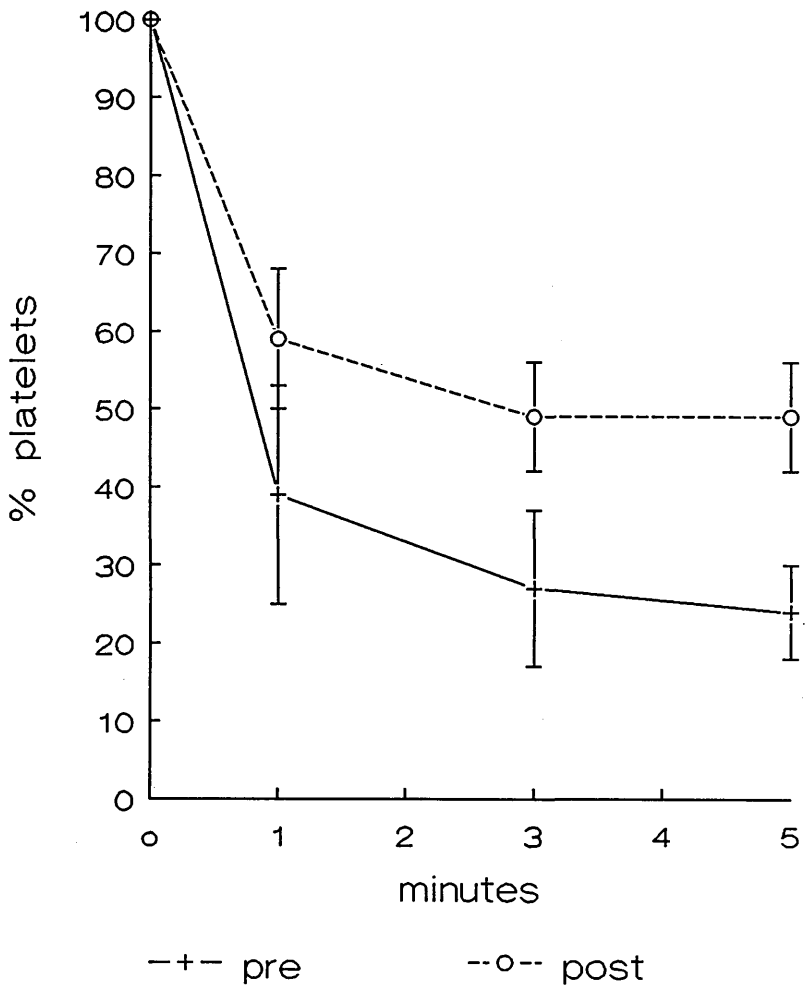

Figure 7 Arachidonic acid induced platelet aggregation (ketorolac). Mean (SE).

Collagen and arachidonic acid aggregation depend on thromboxane production, spontaneous aggregation does not. There was no change in platelet aggregation in the morphine control group under any condition.

5.2.4 Discussion A single intramuscular dose of ketorolac 30 mg given at induction of anaesthesia did not increase the operative blood loss of cholecystectomy, even in the presence of heparin. However, platelet function was affected, and ketorolac prolonged skin bleeding time and tended to inhibit platelet aggregation as observed in volunteer studies (102,103). The effect was similar to that of a single dose of aspirin, and may be clinically insignificant because none of the bleeding times after ketorolac were abnormal (94).

5.3 The effect of diclofenac 75 mg on platelet function during thoracotomy

5.3.1 Introduction The effect on platelet function and haemostasis of diclofenac 75 mg intramuscularly given at induction of anaesthesia was investigated in patients having thoracotomy for lung resection. The patients were also given subcutaneous heparin before surgery.

5.3.2 Methods Twenty patients undergoing thoracotomy were studied, aged 27 to 79 years. The anaesthetic technique was as described in this thesis for the thoracotomy study using ketorolac (Chapter 4). Subcutaneous heparin (2500 iu subcutaneously, one hour preoperatively) was given as prophylaxis against deep venous thrombosis. All patients had intercostal nerve blocks before surgery

(bupivacaine 0.5%). The subjects were randomly allocated so that ten of them were given 75 mg diclofenac intramuscularly at induction of anaesthesia. The clinician administering the injection was not otherwise involved in the study.

Skin bleeding times (all subjects) and platelet function tests (ten subjects) were done on the day before surgery, and repeated one hour after induction of anaesthesia. Surgical blood loss was estimated by the weighing of swabs at operation and collection of suction blood. In five subjects in each group, whole blood platelet aggregation was studied in vitro as described in Chapter 2.4. In this study, because of cost, only collagen (2 μg ml^{-1}, Semmelweiss) was used as an aggregating agent for the in vitro platelet studies.

20 patients entered and completed the trial. No adverse events were encountered.

Statistical analysis As in the previous study, unpaired and paired t-tests were used to analyse blood loss and changes in skin bleeding time and platelet aggregation.

5.3.3 Results

Patient details and blood loss (table 18) The diclofenac and control groups were similar in age, height, weight, smoking history, and sex distribution. Surgical procedures performed were lobectomy (5 diclofenac; 4 control), pneumonectomy (2 diclofenac; 2 control), open lung biopsy (2 each group), pleurectomy (1 diclofenac), and thoracotomy with no resection (2 control). Blood loss did not differ between the groups (P=0.80), although there was a wide range within each group (diclofenac 20 to 1200 ml; control 20 to 1700ml).

	Diclofenac	Control	P
Age (years)	61.2 (13.9)	61.1 (13)	
Height (cm)	163.1(4.4)	164.9(5.4)	
Weight (kg)	62.5 (10.1)	67.7 (9.8)	
Smoker (Y/N)	4/6	2/8	
Sex (M/F)	4/6	4/6	
Blood loss (ml)	352 (125)	300 (165)	0.8

Table 18 Diclofenac and platelet function. Patient details (mean, SD) and blood loss (mean, SE). P: unpaired t-test.

Skin bleeding time (table 19) This was significantly prolonged one hour after diclofenac 75 mg im from a mean of 250 s to 330 s (P=0.0001, 95%CI 47 to 115 s). There was no change in the control group (P=0.66, 95%CI -24 to 16). After diclofenac the range of bleeding times was from 247 to 480 s. The longest prolongation of bleeding time in a subject was from 350 s before diclofenac to 480 s after, but this is still within the normal upper limit of 600 s.

Whole blood platelet aggregation (table 19, figures 8 and 9) Diclofenac significantly reduced collagen induced *in vitro* platelet aggregation at the three and five minute sample times, but not at one minute. At five minutes, the 95% CI for the reduction in platelet aggregation with diclofenac was from -35.5 to -1.7%. The control group showed a tendency towards reduced aggregation one hour after induction of anaesthesia, but this was not statistically significant (at five minutes P=0.09, 95% CI -13 to 1.4%).

5.3.4 Discussion This study has demonstrated that one hour after an intramuscular dose of diclofenac 75 mg skin bleeding time is prolonged and whole blood platelet aggregation is inhibited. As already noted, skin bleeding time is a useful clinical test of platelet function, and collagen induced aggregation depends largely on thromboxane production by platelet cyclo-oxygenase. In the relatively small number of patients studied, blood loss was not increased by diclofenac.

Previous work found no change in skin bleeding time in patients twenty four hours after an intramuscular dose of diclofenac 33.6 mg followed by an intravenous infusion of 6.7mg/hr (40). This was a surprising observation in view of the known effect of cyclo-oxygenase inhibitors on thromboxane production. The present study has

	Before	After	P
Skin bleeding time (s)			
Diclofenac	250(16.9)	330(19.7)	0.0001
Control	226(18.7)	222(15.5)	0.66
Diclofenac platelet aggregation			
1 minute	34(11)	48(14)	0.077
3 minutes	17(6)	26(6)	0.024
5 minutes	17(5)	36(9)	0.038
Control platelet aggregation			
1 minute	30(16)	40(11)	0.38
3 minutes	14(3)	18(4.4)	0.1
5 minutes	16(4)	22(4)	0.1

Table 19 The effect of diclofenac 75 mg on skin bleeding time and collagen induced whole blood platelet aggregation. Bleeding times are shown for each group of ten subjects before and one hour after diclofenac injection. For platelet aggregation the values shown are the percentage of free platelets present at each time in the presence of a collagen aggregator. Mean (SE). P: paired t-test.

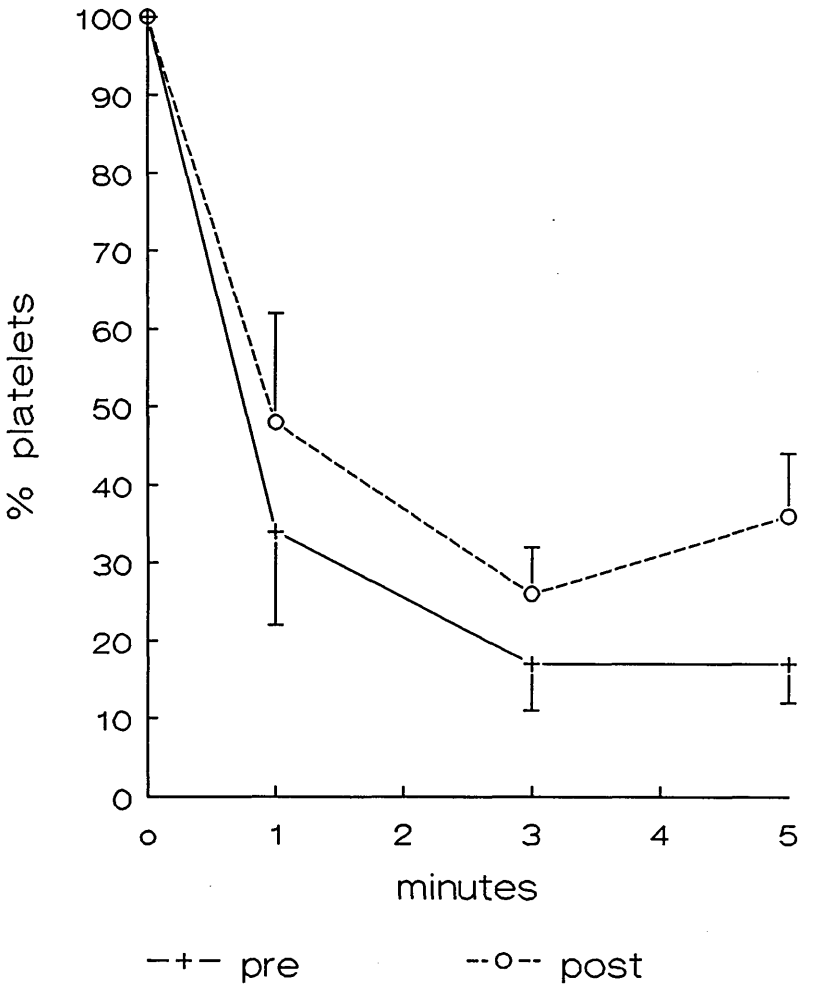

Figure 8 Collagen induced platelet aggregation (diclofenac). Mean (SE).

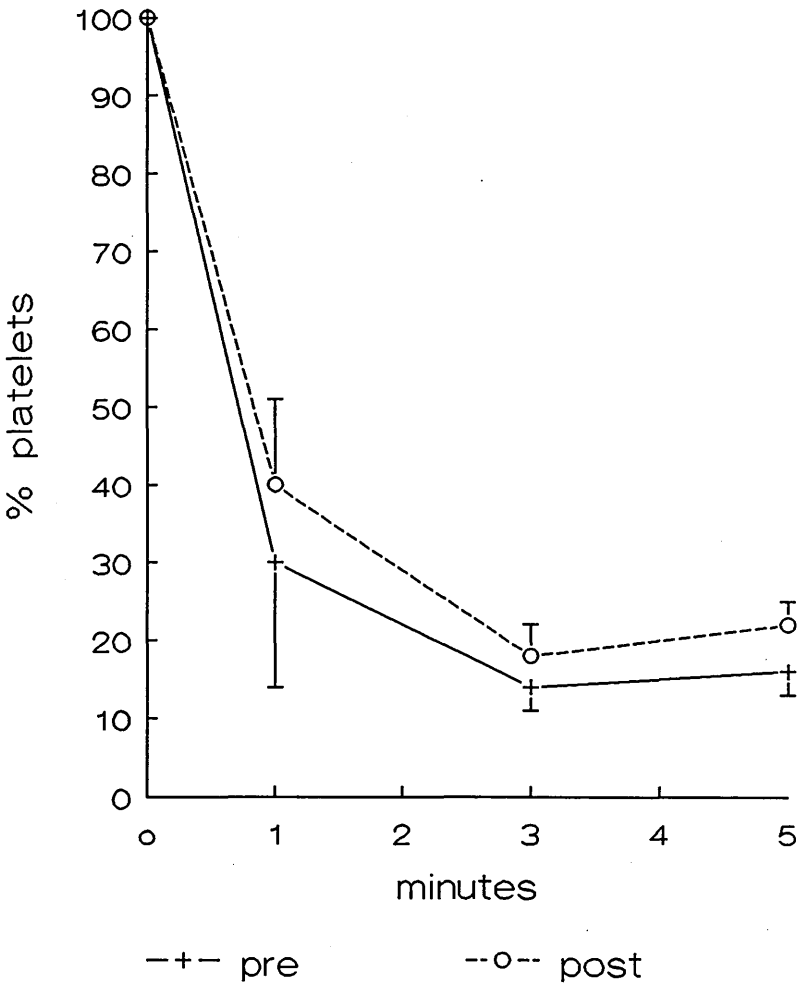

Figure 9 Collagen induced platelet aggregation (control). Mean (SE).

demonstrated that the clinically recommended adult diclofenac intramuscular dose, 75mg, affects skin bleeding time within one hour of administration in patients having surgery.

The mean increase in skin bleeding time seen with diclofenac 75 mg was 80 seconds (95%CI 47 to 115 seconds, table 19). This is comparable with the change of 74 seconds (95% CI 26 to 123 seconds, table 17) produced by ketorolac 30 mg, reported in section 2 of this chapter, and is similar to the effect of aspirin (94). Whole blood platelet aggregation was inhibited similarly by ketorolac and diclofenac. As with ketorolac, skin bleeding time was prolonged by diclofenac, but not above the upper limit of 600 seconds. Indeed the longest bleeding time after diclofenac was only 480 seconds. Therefore, although ketorolac and diclofenac affect platelets, they may not produce an abnormal haemostatic state in previously normal individuals. However, it has been shown that certain members of the population are more sensitive to the haemostatic effects of aspirin than others (201,219) and so some patients could have a greater effect from ketorolac or diclofenac than reported here.

In contrast to the ketorolac study, this investigation was not large enough to investigate properly the effect of diclofenac 75 mg on operative blood loss after thoracotomy. Previous studies have found that preoperative administration of lower doses of diclofenac do not increase blood loss after gynaecological laparotomy (33.6 mg intravenously; 40) or transurethral prostatectomy (50 mg orally; 220). Experience with other NSAIDs suggests that the dose used is important in determining whether blood loss is increased or not. For example, in gynaecological laparotomy preoperative intravenous indomethacin 0.8 mg/kg increased intraoperative blood loss (39), but 25 mg did not (40). The clinically used intramuscular dose of

diclofenac is 75 mg, and further studies are required to ascertain whether the platelet dysfunction produced by this is associated with increased blood loss.

There was a tendency towards reduced platelet aggregation in the control group which was statistically insignificant (table 19) but as it could reflect the effects of anaesthesia and surgery on platelet function it may merit further study.

5.3.5 Conclusion Ketorolac 30 mg and diclofenac 75 mg when given intramuscularly impair platelet function within one hour. The magnitude of this effect is similar to a single dose of aspirin. This effect should be considered if blood loss seems excessive when they have been given intraoperatively, although blood loss was not increased by ketorolac after cholecystectomy, or by diclofenac after thoracotomy, even in the presence of heparin. It may be prudent to avoid the use of ketorolac, diclofenac or another NSAID in the presence of other defects of haemostasis or coagulation. Indeed the administration of an NSAID could reveal a subclinical haemostatic problem, and if this was suspected the skin bleeding time would be a useful clinical test to perform (219).

5.4 Haemostatic effects of ketorolac with and without concomitant dextran in normal volunteers

5.4.1 Introduction Ketorolac is therefore a potent inhibitor of platelet aggregation and haemostasis, and is active within one hour of intramuscular administration. The possible interaction between dextran, given for prophylaxis of venous thrombosis especially during hip surgery (105), and NSAID administration has not been

investigated. Other NSAIDs have been recommended for the relief of pain after hip operations (46,47). As ketorolac will be used during, as well as after, surgery, it would seem important to demonstrate that there is no adverse haemostatic interaction with dextran.

As discussed in Chapter 2.4.1, the precise mode of action of dextran is unclear, but may involve a beneficial effect due to haemodilution and improved blood flow, as well as haemostatic effects which include anti-platelet effects, a fall in factor VIII and increased tissue plasminogen activity (198). Dextran increases skin bleeding time by reducing platelet adhesiveness, but is not thought to have any effect on thromboxane synthesis. A disadvantage of the use of dextran is the risk of anaphylactoid reaction, but this can be significantly reduced by pretreatment with the low molecular weight hapten dextran (dextran-1) (198), although this is not freely available in this country. Of the various molecular weights of dextran available, dextran-70 is used most often during surgery for volume expansion and prophylaxis of venous thrombosis, and this preparation was used in this study (Macrodex, Pharmacia).

The object of this volunteer study was to determine if there was any risk of impairing haemostasis by giving ketorolac with dextran-70. Platelet function was investigated by measuring skin bleeding time, whole blood platelet aggregation, and thromboxane production. To investigate possible effects of dextran on coagulation and fibrinolysis, von Willebrand Factor antigen (vWF:AG), factor VIII coagulant activity (FVIIIc), and tissue plasminogen activator antigen (tPA antigen) were measured (Chapter 2.4).

5.4.2 Methods

Volunteers Twelve healthy male volunteers were enrolled with no history of atopy, asthma, bleeding disorders, or previous exposure to dextran. If a subject withdrew for any reason then provision was made for a replacement volunteer to be recruited.

Subjects avoided aspirin intake for at least two weeks before and also during the study. Similarly caffeine ingestion and cigarette smoking were forbidden for a day before each study period.

Study design A double-blind, randomized, crossover study of healthy male volunteers. On four separate study days the volunteer was given one of the following combinations:

ketorolac placebo/dextran placebo

ketorolac active/dextran placebo

ketorolac placebo/dextran active

ketorolac active/dextran active

At the end of the study period each volunteer had been given each of the four combinations. Allocation of the volunteers to treatment order was randomized by a four by four latin square design.

Ketorolac was supplied as 30 mg in 1ml amber coloured ampoules, and dextran as dextran 70 in sterile 5% dextrose solution. Matching placebos were supplied so that all four combinations were identical in appearance.

Drug administration On each study day an intravenous infusion was commenced at 10 am containing 500 ml of dextran-70 or dextrose 5% placebo. At 2 pm the intramuscular injection of ketorolac 30mg or placebo was given to the deltoid muscle using a 23G needle. One hour later skin bleeding time was performed and blood taken for analysis.

The peak effect of dextran is thought to occur 4 to 6 hours after administration, and peak blood levels of ketorolac are seen one hour after intramuscular injection. Observations and measurements were therefore made when both dextran and ketorolac should have been active.

Because anaphylactoid reactions to intravenous dextrans occur once in 400 exposures, and this may be reduced by pretreatment with dextran-1 (hapten dextran, Pharmacia), each subject was given dextran-1 intravenously at the beginning of every study day before the dextran-70/placebo infusion.

Platelet function, skin bleeding time, and fibrinolysis On the first and last study days control tests were performed before any drugs were given to check that there were no baseline changes. On each day testing was repeated at the end of the study period one hour after the intramuscular injection (3pm).

Investigations The methods and techniques used in this study are described in detail in Chapter 2.4. Platelet function was assessed by skin bleeding time and *in vitro* platelet aggregation (using collagen and arachidonic acid aggregators). Venous blood thromboxane B_2 (TxB_2) generation was also measured. To investigate dextran effects on coagulation and fibrinolysis, von Willebrand Factor antigen (vWF:Ag), factor VIII coagulant activity (FVIIIc), and tissue plasminogen activator antigen (tPA antigen) were measured.

Injection site abnormalities At the end of each study day the site of the intramuscular injection was examined by the observer for evidence of bruising, and this was recorded as none, mild, moderate, or severe. The subject was asked to comment whether the intramuscular injection had produced no, mild, moderate, or severe pain.

Adverse events All adverse events were recorded. During the intravenous infusion arterial blood pressure was monitored because of the incidence of anaphylactoid reactions to dextran, and the study was performed in a ward setting where resuscitation drugs and equipment were readily available.

Statistical analysis The variables used were skin bleeding times, whole blood platelet aggregation, venous blood TxB_2, vWF:Ag, FVIIIc, and tPA antigen. Because of the skewed nature of venous blood TxB_2 values the analysis was performed on logged data, and results given in the tables as mean (range).

To examine whether the baseline variables changed during the course of the study control measurements were performed on days 1 and 4 before drugs were given, and were compared using a paired t-test.

Analysis of values after drug treatment was by analysis of variance which fitted subjects, period (order of drug combination administration), and treatment effects. Only the treatment effect was found to be significant so the others were omitted from further analysis. The treatment effect was then divided into a 'ketorolac' effect, a 'dextran' effect, and their interaction.

5.4.3 Results

Volunteers All subjects were healthy males, mean age 31(9) year, mean weight 76.6 (8.8) kg, mean height 179 (6.1) cm. Eleven volunteers completed four study days. One subject completed only two days and was withdrawn because of an allergic reaction to dextran, and unfortunately his replacement also withdrew after completing two study days when he was involved in a road traffic accident. These two

subjects, who attended for prestudy screening and two study days each (covering all four treatment combinations), were included in the analysis.

Baseline tests On day 1, the baseline mean skin bleeding time was 340 (29)s, range 169-538s. On day 4, the baseline bleeding time was 376 (32)s, range 285-565s. This change was not statistically significant (P=0.3).

Skin bleeding time (table 20) The mean increase in skin bleeding time with ketorolac was 69s, although this was not statistically significant (P=0.19, 95% CI -37 to 175s). Dextran produced a mean increase of 50s, but again this was not statistically significant (P=0.33, 95% CI -52 to 151 s). There was no evidence of an interaction between ketorolac and dextran (P=0.90), although bleeding times tended to be higher when both active treatments had been given.

Platelet functions tests (table 20) In the presence of a collagen aggregator, ketorolac significantly increased the number of unaggregated platelets by a mean of 23% of the baseline count over five minutes (P=0.0001, 95% CI 15 to 31%). Dextran had no effect (P=0.53) and there was no interaction between ketorolac and dextran (P=0.38).

With arachidonic acid, ketorolac again had a significant effect, increasing the number of unaggregated platelets present at five minutes by 39% of the baseline count (P=0.0001, 95% CI 30 to 48%). Dextran had little effect (P=0.25), and there was no interaction between ketorolac and dextran (P=0.24).

Whole blood thromboxane B_2 (TxB_2) generation (table 21) TxB_2 concentrations were lower by a factor of 39.8 after ketorolac (P=0.0001, 95% CI 28.5 to 55.5). Dextran had no effect (P=0.90).

Skin bleeding time (s)

	Dextran placebo	Dextran active
Ketorolac placebo	404(47)	460(47)
Ketorolac active	479(54)	522(54)

Collagen induced platelet aggregation

	Dextran placebo	Dextran active
Ketorolac placebo	13(4)	12(4)
Ketorolac active	32(4)	38(5)

Arachidonic acid induced platelet aggregation

	Dextran placebo	Dextran active
Ketorolac placebo	12(4)	12(4)
Ketorolac active	46(4)	56(5)

Table 20 The effect of ketorolac and dextran on skin bleeding time, and collagen and arachidonic acid induced whole blood platelet aggregation (percentage free platelets at five minutes). Mean (SE).

	Dextran placebo	Dextran active
Ketorolac placebo	236.4(40-817.5)	323.5(87.2-762.5)
Ketorolac active	8.3(3-28.8)	5.8(3-16.4)

Table 21 The effect of ketorolac and dextran on venous blood thromboxane B_2. ng/ml, mean (range).

There was an interaction between ketorolac and dextran which was statistically significant (P=0.04), but this was much smaller than the effect of ketorolac alone.

Von Willebrand Factor antigen (vWF:Ag)(table 22) Dextran produced a statistically insignificant reduction in vWF:Ag of 12.3 iu/dlitre (P=0.15, 95%CI -29.6 to 4.9 iu/dlitre). There was no evidence of an effect of ketorolac (P=0.99), or an interaction (P=0.70).

Factor VIII coagulant activity (FVIIIc) (table 22) Dextran reduced FVIIIc by a mean of 13 iu/dlitre (P=0.04, 95% CI -25 to -1 iu/dl). Ketorolac had no effect (P=0.33), and there was no interaction between the two drugs (P=0.17).

Tissue plasminogen activator antigen (tPA antigen) (table 22) There was no effect of ketorolac (P=0.32), dextran (P=0.81), or any interaction (P=0.73).

Injection site abnormalities and pain No bruising or prolonged tenderness occurred at the intramuscular injection site, but four subjects experienced mild or moderate pain when ketorolac was injected, whereas pain did not occur upon placebo injection.

Adverse events One volunteer was withdrawn after an adverse reaction to intravenous dextran, consisting of pruritis, mild vasodilatation and hypotension. Dextran administration was stopped, no specific treatment was required, and the subject recovered uneventfully. There were no other adverse events, and no clinically significant changes on biochemical and haematological analysis of blood.

vWF:Ag (iu/dlitre)	Dextran placebo	Dextran active
Ketorolac placebo	91(8)	82(8)
Ketorolac active	95(9)	79(9)
FVIIIc (iu/dlitre)	**Dextran placebo**	**Dextran active**
Ketorolac placebo	70(6)	65(6)
Ketorolac active	72(7)	51(7)
tPA (ng/ml)	**Dextran placebo**	**Dextran active**
Ketorolac placebo	12.3(0.8)	12.4(0.8)
Ketorolac active	11.7(0.9)	11.2(0.9)

Table 22 The effect of ketorolac and dextran on von Willebrand factor antigen, factor VIII coagulant activity, and tissue plasminogen activator. Mean (SE).

5.4.4 Discussion There was an increase in skin bleeding time of 69 s after ketorolac, but this was not statistically significant. This result is similar to previous work in volunteers (103) and patients (Chapter 5.2). The potency of ketorolac as a cyclo-oxygenase inhibitor was confirmed by the marked reduction in thromboxane synthesis (revealed by venous blood TxB_2 concentration). Blood TxB_2 is used to investigate the rate of production of thromboxane A_2 which is metabolized rapidly in the circulation (4,8). There was evidence of a small but statistically significant interaction between ketorolac and dextran on TxB_2 concentration. There was a trend for skin bleeding times to be higher when ketorolac was given in combination with dextran, which, although statistically insignificant, may have reflected the interaction seen with TxB_2. There was little change in coagulation factors, but dextran reduced FVIIIc, and this could have resulted from haemodilution. Dextran may enhance fibrinolytic activity by increasing tissue plasminogen activity (198), but using a modern Elisa technique for tPa antigen we could find no evidence of this. There was also no evidence of any effect of dextran-70 on the endothelium from the measurements of vWF:Ag.

Four subjects experienced mild or moderate pain upon ketorolac injection, but this did not result in prolonged discomfort suggesting that muscle damage is not a problem with this drug (64).

5.4.5 Conclusion Ketorolac decreased platelet function probably by inhibiting thromboxane generation, while dextran by itself had no effect. The combination of ketorolac and dextran resulted in a small but significant interaction with respect to TxB_2; there was no significant effect on skin bleeding time or platelet aggregation. The

clinical significance of the combination effect on TxB_2 is unclear as it was much smaller than that of ketorolac alone. FVIII coagulant activity was decreased by dextran.

Although we have seen no gross abnormality of haemostasis in this volunteer study, simultaneous use of ketorolac and dextran-70 should be carefully monitored for any adverse effect.

CHAPTER 6

THE EFFECT OF KETOROLAC AND DICLOFENAC ON RENAL FUNCTION

6.1 Introduction

Renal prostaglandins have many physiological roles (116) and NSAIDs can adversely affect renal function in certain circumstances (61,90,108,110,111,112). Because the use of NSAIDs after surgery is becoming common, it would seem important to assess this problem. This thesis examines the clinical relevance of inhibition of renal prostaglandin production in surgical patients.

It would have been desirable to study in detail the renal effects of the new agent ketorolac, but this was not possible because the manufacturers were unwilling to release supplies of this drug for such a study. The renal effect of ketorolac was therefore assessed by serial blood urea, creatinine, and electrolyte concentrations from patients in the cholecystectomy and thoracotomy studies previously described in this thesis (Chapters 3,4).

A detailed study was performed concerning the effect of giving diclofenac during and after major surgery. Fluid and electrolyte balance, renal function, and renal production of prostacyclin were observed.

All the methods used in these studies to investigate renal function are described in Chapter 2.5.

6.2 The effect of ketorolac on renal function

6.2.1 Methods In the cholecystectomy and thoracotomy studies described earlier in this thesis (Chapters 3,4) renal function was assessed by biochemical analysis of venous blood during the period of study.

In the cholecystectomy study (Chapter 3.2), blood was sampled after 24 hours so that 50 patients given ketorolac could be compared with 50 controls. In the thoracotomy study (Chapter 4), repeat sampling was performed at the end of the study period so that the effect of ketorolac at low and high doses over 48 hours could be examined, and compared with a placebo group.

During these studies intravenous fluid administration was standardized as far as possible. After cholecystectomy, patients were given six hourly dextrose 5% 500 ml alternating with normal saline 500 ml. The results of this study have indicated that there was a tendency for the ketorolac group to require fluids for a shorter time (table 6). In the thoracotomy study, intravenous Hartmann's solution (sodium 131, potassium 5, calcium 2, chloride 111, and lactate 29 mmol/litre approximately) was alternated with dextrose 5% at the rate of 500 ml six hourly. Other fluids, including blood and colloids, were also administered when clinically indicated.

Statistical analysis Plasma urea, creatinine, and electrolyte concentration were measured before and after surgery. Changes within patients were examined using paired t-tests. In addition, the number of patients who had biochemical results outwith the laboratory range of normal during the period of study are listed for each drug treatment (normal values for the laboratory are given in Chapter 2.5.1).

6.2.2 Results

Ketorolac after cholecystectomy (tables 23,24) No clinical problems were encountered with renal function during the cholecystectomy study. Biochemical abnormalities were mild and did not differ between the ketorolac and morphine groups (table 23). No

	Ketorolac	Morphine
Potassium >4.7 mmol/litre	0	1
Sodium <132 mmol/litre	2	3
Urea >6.6 mmol/litre	4	4
Creatinine >150 μmol/litre	0	0

Table 23 Ketorolac and renal function. The number of patients with abnormal clinical chemistry results after cholecystectomy.

	Preoperative	24 h	P
Ketorolac			
Sodium	140(0.3)	138(0.4)	0.002
Potassium	3.9(0.1)	3.8(0.1)	0.25
Urea	4.8(0.2)	4.1(0.2)	0.003
Creatinine	82(3)	85(3)	0.5
Morphine			
Sodium	140(0.2)	136(0.4)	0.000
Potassium	4.1(0.1)	3.9(0.1)	0.02
Urea	5(0.2)	3.6(0.3)	0.000
Creatinine	85(2)	79(3)	0.02

Table 24 The effect of ketorolac on renal function after cholecystectomy. Plasma urea, creatinine, and electrolytes before, and after 24 hours. Mean (SE), P: paired t-test. Sodium, potassium, urea in mmol/litre and creatinine in μmol/litre.

patient developed severe hyperkalaemia, the highest postoperative potassium concentrations being 4.5 mmol/l and 4.9 mmol/l in the ketorolac and morphine groups respectively.

The two groups differed in the changes seen within individual patients in plasma urea, creatinine and electrolytes over the 24 hour study period (table 24). In the morphine control group there was a significant fall in urea, creatinine, sodium, and potassium one day after operation from baseline values. In the ketorolac group only urea and sodium concentrations fell (but to a lesser extent) and there was no fall in plasma potassium or creatinine.

Ketorolac after thoracotomy (tables 25,26) In comparison with the previous study, abnormal urea and electrolyte concentrations were not uncommon after thoracotomy (table 25). One patient was withdrawn from the study with some concern about renal function, preoperative values were normal, and no specific treatment was required.

A high blood urea was commonly present after surgery, and the incidence of this was significantly greater in the ketorolac groups compared with the placebo group ($P<0.05$, Chi-square). In the high dose ketorolac group, the majority (17 out of 25) had high blood ureas 48 hours after operation, although only 2 also had high creatinine concentrations.

Hyperkalaemia occurred in 12 out of 75 patients, although this was not severe and did not require specific treatment. Of these 12 patients, 4 were from the placebo group, and so high potassium concentrations did not appear to be associated only with ketorolac. The highest potassium was 5.7 mmol/litre, in a patient in the high dose ketorolac group.

	Placebo	10 mg	30 mg
Potassium >4.7 mmol/litre	4	2	6
Sodium <132 mmol/litre	1	3	3
Urea >6.6 mmol/litre	8	14	17
Creatinine >150 μmol/litre	1	1	2

Table 25 Ketorolac and renal function. The number of patients with abnormal clinical chemistry results after thoracotomy. Placebo, ketorolac 10 mg, and ketorolac 30 mg groups.

	Preoperative	48 h	P
Placebo			
Sodium	140(0.5)	136(0.7)	0.0000
Potassium	4.2(0.1)	4.4(0.1)	0.2
Urea	4.9(0.3)	6.1(0.4)	0.002
Creatinine	86(4)	100(7)	0.03
Ketorolac 10 mg			
Sodium	139(0.6)	136(0.6)	0.001
Potassium	4.1(0.1)	4.4(0.1)	0.03
Urea	5(0.4)	7.1(0.6)	0.001
Creatinine	87(3)	95(6)	0.15
Ketorolac 30 mg			
Sodium	140(0.6)	136(0.6)	0.0000
Potassium	4.1(0.1)	4.4(0.1)	0.01
Urea	5(0.2)	7.9(0.5)	0.0000
Creatinine	87(3)	110(7)	0.002

Table 26 The effect of ketorolac on renal function after thoracotomy. Plasma urea, creatinine, and electrolytes before, and after 48 hours. Mean (SE), P: paired t-test.

Analysis of the changes in individual patient's values (table 26) demonstrates some differences between the placebo and the ketorolac groups. In the placebo group there was a significant fall in blood sodium, and a rise in urea and creatinine. Potassium concentrations rose, but this was not statistically significant (mean increase 0.2 mmol/litre, 95%CI -0.1 to 0.5 mmol/litre). With ketorolac, sodium fell, and urea and creatinine were elevated, although the change in the latter was not statistically significant with ketorolac 10 mg. The most notable difference with ketorolac was that there was a statistically significant increase in blood potassium, at 48 hours, in the low (0.2 mmol/litre, 95%CI 0.02 to 0.4 mmol/litre) and high (0.3 mmol/litre, 95%CI 0.1 to 0.6 mmol/litre) dose ketorolac groups.

6.2.3 Discussion Consideration of the results from the placebo groups involved in these two studies suggests that the patients having thoracotomy were more at risk of postoperative renal impairment. There was little apparent upset in blood values after cholecystectomy (tables 23, 24), but after thoracotomy urea, creatinine, and potassium rose (tables 25, 26). These differences could have been due to the different pathologies, age of the patients, and the extent of surgery. Cholecystectomy is performed in a relatively young population for a benign disorder. In contrast the patients in the thoracotomy group were older and having a more invasive operation for a malignant, wasting, disease. Another difference is that after thoracotomy intravenous fluids tend to be restricted to avoid pulmonary oedema which often occurs after manipulation of the lungs, and patients may be relatively dehydrated.

After cholecystectomy, ketorolac 30 mg did not produce abnormal changes in plasma urea, creatinine, or electrolytes. There was

therefore no evidence of any adverse renal effect of giving intramuscular ketorolac after this operation. There was some evidence from the cholecystectomy study that renal function may have been affected in some way by ketorolac. The ketorolac group differed from the consistent postoperative fall in urea, creatinine, and electrolytes seen in the control group, in that potassium and creatinine concentrations did not fall with ketorolac, and the falls in urea and sodium were much smaller. Without more detailed studies it is impossible to identify the reason for these differences. Fluid intake was not strictly controlled in this study and there was indeed evidence that ketorolac was associated with a shorter period of intravenous fluid supplementation (table 6). In the postoperative period renin, angiotensin, aldosterone, and vasopressin concentrations are elevated as part of the stress response to anaesthesia and surgery (121,123,124,125). Ketorolac could have interfered with these processes as renal prostaglandins are known to affect renin (132) and vasopressin (134).

After thoracotomy, ketorolac was associated with high urea concentrations and a rise in plasma potassium. Although these changes were present they did not produce any clinical problems, and hyperkalaemia occurred almost as often in the placebo group. NSAIDs may block the rise in renin produced by prostaglandins (132) and this could have impaired renal tubular potassium excretion in the ketorolac group. An initial report of unpublished observations of the effect of ketorolac on renal function after upper abdominal surgery has indicated that potassium excretion is impaired (216).

6.2.4 Conclusion These observations suggest that ketorolac produces no renal impairment after cholecystectomy, but is associated with increased urea and rises in plasma potassium after thoracotomy for lung resection. Further studies of the effect of NSAIDs on renal function after major surgery are merited.

6.3 The effect of diclofenac on renal function and prostacyclin production after oesophagogastrectomy

6.3.1 Introduction In order to investigate further the effects of NSAIDs on renal function after surgery, diclofenac was used as ketorolac was not available for this purpose. It was our established practice to give intramuscular diclofenac in combination with local anaesthetics to provide analgesia after oesophagogastrectomies, performed via a thoracoabdominal approach. Maintenance of correct fluid balance is important in these cases, because fluid overload can precipitate pulmonary oedema after thoracotomy in these often malnutritioned patients. This was thought to be an appropriate clinical situation to investigate the effect of diclofenac on postoperative renal function, especially since fluid balance is routinely closely monitored after oesophagogastrectomy using central venous and urinary catheters. The effect of intramuscular diclofenac 75 mg twelve hourly on fluid balance, renal function, and renal prostacyclin production was studied in patients having oesophagogastrectomy.

6.3.2 Methods

Patient enrolment Twenty patients were enrolled. Exclusion criteria were as described in earlier studies in this thesis, and patients were also excluded if there was any evidence of renal insufficiency preoperatively on venous blood sampling and biochemical analysis, or a history of diuretic therapy or hypertension. All patients had oesophagogastrectomy for carcinoma, via a thoracoabdominal incision, and were operated on by the same thoracic surgeon.

Study Design A double-blind, randomized study of the effect of diclofenac administration after major surgery. A control group was included for comparison. Renal function and prostacyclin production was measured on the preoperative day, the day of surgery (day 1), and the following day (day 2). Patients were randomly allocated to be given five intramuscular injections of either diclofenac 75 mg (Voltarol, Geigy) or identical placebo, given twelve-hourly over forty-eight hours. The first intramuscular injection was given at induction of anaesthesia.

Anaesthetic technique and monitoring The general anaesthetic technique was standardized. Premedication was intramuscular papaveretum and atropine. Induction was with intravenous thiopentone or propofol, suxamethonium was used to facilitate tracheal intubation, the lungs were ventilated with nitrous oxide in oxygen with enflurane, and neuromuscular blockade maintained with atracurium. Fentanyl was given if indicated during surgery. At the end of the procedure the neuromuscular block was antagonised with neostigmine and atropine.

Intercostal nerve blocks were performed on each patient before surgery (bupivacaine 0.5% with adrenaline). Postoperatively, all patients were given morphine by continuous intravenous infusion at a rate of 1 mg/hour, and supplementary opioid was available if pain relief was inadequate. During the study the patients were nursed in a high dependency unit.

In the operating theatre, central venous, arterial, and urinary catheters were inserted to allow routine monitoring and collection of blood and urine samples in the postoperative period.

Intravenous fluids An attempt was made to ensure that all subjects were given similar volumes of intravenous fluids. Surgical blood loss was replaced in the operating theatre with Hartmann's solution. Postoperatively, Hartmann's solution and dextrose 5% were infused alternately at a rate of 500 ml six hourly. Central venous pressure was maintained between 5 to 10 cm of water by the infusion of aliquots of plasma protein solution.

Measurement of renal function Before operation, venous blood samples were analysed for serum creatinine and electrolyte concentrations. Urine was collected on the day before surgery from the time of enrolment into the study. In the postoperative period, urine output was measured for forty-eight hours from the time of induction of anaesthesia.

Blood samples were taken on the day of surgery (day 1), and the next day (day 2), centrifuged at 2000 rpm, and the plasma removed. Aliquots of the twenty four hour urine collection were stored with the samples of plasma at $-20^{o}C$ for later analysis in a batch when the study was completed.

Plasma and urine creatinine, electrolytes, and osmolality were examined in both groups over the three day study period (preoperative and first and second days after operation). Urine flow rate, urinary excretion of sodium and potassium, creatinine clearance, and free water clearance were calculated.

It was the normal practice of the surgical unit involved in this study to give intravenous frusemide if hourly urine volumes were persistently below 30 ml/hr, in order to avoid fluid overload. After discussion with the clinicians in charge of the unit, it was decided that it would not be possible to discard this practice during the study. In view of this, the prescription of diuretic (intravenous frusemide) in the postoperative period was also recorded as a reflection of physician concern about renal function. For analysis, the number of patients in each group receiving frusemide were compared.

Renal prostaglandin generation Renal production of prostacyclin, PGI_2, was measured before and after surgery using the urinary concentration of the stable metabolite 6-keto-$PGF_{1\alpha}$ (207,208) by the radioimmunoassay method described in Chapter 2.5.4. By measuring changes in prostaglandin levels in a serious of samples from individual patients, many nonspecific factors affecting radioimmunoassays were minimised (221).

Statistical analysis The two treatment groups were compared on the preoperative day and the first (day 1) and second (day 2) days after surgery. Changes in individuals from baseline were examined using paired t-tests, and between group comparisons were made using unpaired t-tests.

6.3.3 Results

Subjects(table 27) Twenty patients were enrolled, and all had oesophagogastrectomy via a thoracoabdominal incision. The diclofenac and control groups were similar with respect to age, height, weight, sex, and surgical blood loss (P=0.6).

Preoperative day There was no statistical difference between the groups for plasma creatinine or electrolytes, urine output, electrolyte excretion, clearances, or 6-keto-$PGF_{1\alpha}$ production.

Plasma sodium, potassium, creatinine, and osmolality (table 28) In the control group, there was a significant fall in plasma sodium concentration on day 1 (P=0.03, 95%CI -7,-0.04 mmol/litre), and plasma osmolality on days 1 and 2 (P=0.07 95% CI -13,0.6 mosm/kg and P=0.03 95% CI -18 to -2 mosm/kg). In the diclofenac group, plasma sodium fell on day 1 (P=0.05, 95% CI -5 to 0 mmol/litre). There was no significant difference between the diclofenac and placebo groups in potassium concentrations at any time, but the diclofenac group did tend to have higher concentrations than the control group on the first postoperative day. On day 1, five of the diclofenac group had potassium concentrations in excess of the laboratory upper limit of normal (4.7 mmol/litre), and three of them were above 5 mmol/litre. By comparison, only two patients in the control group had high potassium concentrations on day 1, and none were above 5 mmol/litre. Potassium concentrations in the diclofenac group returned towards normal by day 2.

Fluid balance (table 29) There was no significant difference in the amount of intravenous fluids given to the two groups on day 1 or day 2 (P=0.9, and 0.5 respectively). After fluid input and output,

	Diclofenac	Control
Age (years)	65.2(9.1)	69.8(9.5)
Height (cm)	169.7(9.9)	167.5(8.4)
Weight (kg)	63(17.2)	68.9(15.7)
Sex (M/F)	9/1	8/2
Blood loss (ml)	500(165)	408(181)

Table 27 Diclofenac and renal function. Patient details (mean, SD) and operative blood loss (mean, SE).

	Diclofenac	Control	P
Sodium (mmol/litre)			
Preoperative	138(1)	138(2)	0.95
Day 1	136(1)	136(2)	0.9
Day 2	135(2)	135(2)	0.9
Potassium (mmol/litre)			
Preoperative	4.4(0.2)	4.1(0.1)	0.2
Day 1	4.6(0.3)	4.2(0.2)	0.2
Day 2	4.3(0.2)	4.3(0.1)	0.8
Creatinine (μmol/litre)			
Preoperative	89(5)	89(7)	0.95
Day 1	99(12)	106(13)	0.69
Day 2	104(16)	98(14)	0.77
Osmolality (mosm/kg)			
Preoperative	282(2)	284(3)	0.7
Day 1	281(3)	278(4)	0.5
Day 2	279(4)	276(4)	0.58

Table 28 Diclofenac and renal function. Plasma sodium, potassium, creatinine, and osmolality. Mean (SE). P: unpaired t-test.

	Diclofenac	Control	P
Fluid balance(ml)			
Day 1	1128(348)	601(127)	0.39
Day 2	1569(275)	1532(233)	0.93
Urine output(ml/min)			
Preoperative	0.75(0.1)	0.89(0.1)	0.27
Day 1	0.62(0.06)	0.88(0.13)	0.02
Day 2	0.9(0.1)	0.98(0.16)	0.65
Sodium excretion(μmol/min)			
Preoperative	63(14)	75(10)	0.51
Day 1	43(9)	78(8)	0.01
Day 2	37(9)	48(11)	0.5
Potassium excretion(μmol/min)			
Preoperative	22(3)	19(4)	0.73
Day 1	49(6)	74(9)	0.04
Day 2	39(3)	41(7)	0.76

Table 29 The effect of diclofenac on fluid balance, urine output, and urinary sodium and potassium excretion. Mean (SE). P: unpaired t-test.

including blood loss, was considered the diclofenac group tended to have a higher positive fluid balance on the first postoperative day, although the difference was not statistically significant.

Urine output (table 29) Urine production was significantly lower in the diclofenac group on the first postoperative day (day 1) compared with the control group (P=0.02, 95%CI -0.5 to -0.06 ml/min). On the next day the two groups had similar urine outputs.

Sodium and potassium excretion (table 29) Urinary excretion of sodium was significantly less in the diclofenac group on day 1 (P=0.01, 95% CI -62 to -8 μmol/min). Potassium excretion increased in both groups in the postoperative period, but the rise was greater in the control group on day 1, so that potassium excretion was lower in the diclofenac group on that day (P=0.04, 95% CI -49 to -1 μmol/min).

Creatinine clearance (table 30) Baseline clearances were similar. In the control group there was a significant increase in creatinine clearance on the first postoperative day (P=0.02, 95% CI 6 to 53 ml/min), but the diclofenac group showed no change in creatinine clearance over the study period.

Free water clearance (table 30) A negative value for free water clearance indicates retention of water. There was a significant difference between the groups on the first postoperative day when the control group retained more free water than the diclofenac group (P=0.04, 95%CI 0.01 to 0.8 ml/min)

Urinary 6-keto-$PGF_{1\alpha}$ (figure 10, table 31) Urinary excretion of 6-keto-$PGF_{1\alpha}$ increased markedly in the control group after surgery, with the highest concentrations on day 1. In contrast, the diclofenac group showed little change in urinary 6-keto-$PGF_{1\alpha}$ over the two days. Consequently urinary 6-keto-$PGF_{1\alpha}$ excretion was significantly higher in the control group on days 1 and 2 (P=0.02 and 0.003 respectively).

	Diclofenac	Control	P
Creatinine clearance (ml/min)			
Preoperative	61(10)	60(7)	0.97
Day 1	62(13)	89(14)	0.17
Day 2	62(11)	77(11)	0.38
Free water clearance (ml/min)			
Preoperative	-0.66(0.2)	-0.07(0.2)	0.15
Day 1	-0.58(0.1)	-0.98(0.2)	0.04
Day 2	-0.3(0.1)	-0.2(0.3)	0.7

Table 30 The effect of diclofenac on creatinine and free water clearances. Mean (SE). P: unpaired t-test.

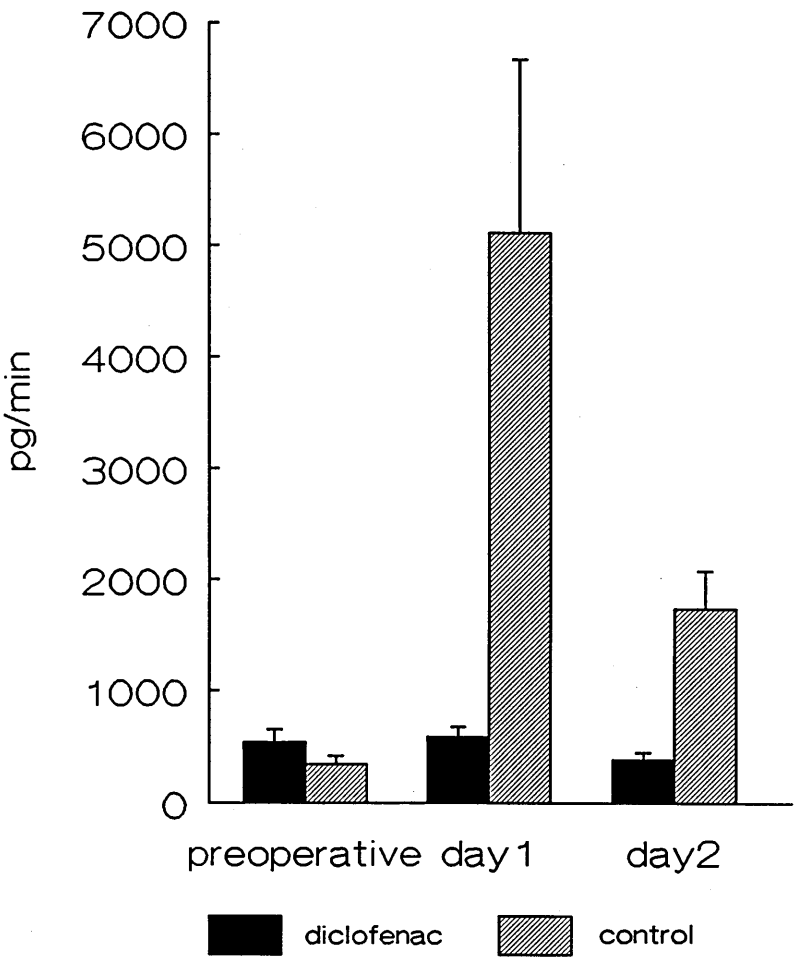

Figure 10 Urinary 6-keto-$PGF_{1\alpha}$ after oesophagogastrectomy. Mean (SE).

	Diclofenac	Control	P
Preoperative	532(120)	338(78)	0.2
Day 1	587(85)	5111(1553)	0.02
Day 2	379(65)	1739(336)	0.003

Table 31 The effect of operation and diclofenac on the urinary excretion of 6-keto-$PGF_{1\alpha}$ (pg/min). Mean (SE). P: unpaired t-test.

Frusemide Diuretic therapy was more often required in the diclofenac group since 9 of them were given frusemide during the study, but only 4 of the control group received the drug (P=0.02).

Adverse events (table 32) One patient in the diclofenac group was withdrawn from the study after eighteen hours because of concern about persistently low urine volumes (averaging 20 ml per hour). Two doses of diclofenac 75 mg had been given before the patient was withdrawn. Despite adequate fluid loading and frusemide administration, intravenous dopamine was required to promote an acceptable urine flow rate. Following withdrawal of diclofenac and commencement of dopamine, renal function improved and the patient recovered completely. Blood analysis revealed a marked rise in creatinine and potassium concentration on day 1. Plasma potassium on day 1 was particularly high at 5.4 mmol/litre (laboratory normal upper limit 4.7 mmol/litre). It should also be noted that, although preoperative creatinine was within normal limits (55 to 150 μmol/litre), this patient had a low preoperative creatinine clearance (45 ml/min) and that this fell by almost half on the first postoperative day. Urinary 6-keto-$PGF_{1\alpha}$ increased in this patient after diclofenac was withdrawn.

6.3.4 Discussion

Renal prostaglandin generation Urinary 6-keto-$PGF_{1\alpha}$ production increased markedly in the postoperative period in the control group, whereas there was no change in the diclofenac group (figure 10, table 31). Urinary 6-keto-$PGF_{1\alpha}$ is an accepted indicator of renal prostacyclin production (207,208,209). To the author's knowledge this is the first report of such a rise in renal prostacyclin production after surgery in humans and of the effect of diclofenac.

	Preoperative	Day 1	Day 2
Sodium (mmol/litre)	138	138	136
Potassium (mmol/litre)	4.6	5.4	4.5
Creatinine (μmol/litre)	101	158	145
Osmolality (mosm/kg)	278	292	289
Creatinine clearance(ml/min)	45	25	26
6-keto-$PGF_{1\alpha}$	262	725	1455

Table 32 Details of the patient withdrawn from the diclofenac group on day 1.

Renal prostaglandins are thought to be act as local vasodilators which maintain function in the presence of high concentrations of circulating vasoconstrictor hormones, when blood flow can become 'prostaglandin dependent' (90,108). On the basis of the results of this study it may be that renal prostaglandins are important after surgery. Renal prostacyclin production peaked on the first postoperative day, perhaps indicating that this effect is most important in the immediate postoperative period.

As there must be significant tissue damage and disruption during and after oesophagogastrectomy, it should be established that the urinary 6-keto-$PGF_{1\alpha}$ measured in this study did indeed represent renal, and not systemic, prostacyclin generation. There is no published work concerning the effect of anaesthesia and surgery on urinary metabolites, but studies have been reported using plasma 6-keto-$PGF_{1\alpha}$ which may give insight into the systemic production of prostacyclin after operation. Minor surgery does not increase plasma 6-keto-$PGF_{1\alpha}$ whether using halothane, enflurane (222), or spinal anaesthesia (223). Plasma 6-keto-$PGF_{1\alpha}$ is elevated upon the surgical incision of laparotomy, but falls again within forty minutes in elderly patients (224). Prostacyclin and TxB_2 release increases during abdominal aortic surgery, an effect prevented by ibuprofen (225). These studies indicate that systemic prostacyclin production is not greatly increased after surgery. The rise in urinary 6-keto-$PGF_{1\alpha}$ observed in this thesis may therefore truly reflect an increase in renal prostacyclin production after major surgery. To further investigate this, it would be useful to observe after surgery both urinary 2,3 dinor 6-keto-$PGF_{1\alpha}$ and 6-keto-$PGF_{1\alpha}$ to represent systemic and renal production of prostacyclin, as performed in other clinical studies (209).

Renal function In this study, diclofenac therapy was associated with a significant reduction in urinary output and sodium and potassium excretion on the first postoperative day when compared with the control group. On the second day, there was no difference between the groups (table 29). Renal prostaglandins increase urinary sodium excretion (129,131), and by inhibiting this diclofenac could produce sodium retention.

Potassium excretion increased in both groups after surgery, but this effect was diminished by diclofenac. Prostacyclin stimulates renin release in man (132), and, by preventing the resultant aldosterone effect, diclofenac could have impaired potassium excretion. Presumably in the postoperative period there is a significant potassium load presented to the kidneys which has to be dealt with to avoid hyperkalaemia. In this study, diclofenac tended to be associated with hyperkalaemia on the first day after surgery, although preoperative values were also slightly higher than in the control group (table 28).

There was no evidence of a fall in GFR after surgery with the NSAID, although the rise in creatinine clearance seen in the control group was not present in the diclofenac group (table 30). Creatinine clearance may not be a reliable estimate of GFR after surgery when plasma creatinine could be changing as a result of muscle damage. Inulin clearance studies may be more useful.

Because NSAIDs potentiate vasopressin (108,115,116,134), it may have been expected that the diclofenac group would retain more water, but in fact the control group conserved more free water on the first postoperative day (table 30). This was reflected in the tendency for plasma osmolality to decrease in the control group (table 28). Other factors, including pain and morphine administration, may be involved

as both are known to increase vasopressin release. The control group did require more morphine 62(5.3) mg, than the diclofenac group 49(7.7) mg, although the difference was not statistically significant (P=0.2, 95% CI -7, 32 mg), but pain assessments were not made. In this respect there is evidence that vasopressin is involved in an non-opioid analgesic system controlled by the hypothalamic paraventricular nucleus (226), although the true role of vasopressin in this system is under scrutiny (227).

Frusemide therapy was required more often in the diclofenac group. Although it would have been desirable to control the administration of diuretics during the study, it was not possible to do so in practice. If diuretics had not been given, the differences between the groups in urine and electrolyte excretion may have been even greater.

The patient withdrawn from the study did appear to have a severe but reversible impairment of renal function, with hyperkalaemia (table 32). This patient, despite having a normal preoperative plasma creatinine of 101 μmol/litre, was subsequently discovered to have a low creatinine clearance of 45 ml/min; an investigation not routinely performed before surgery. The deterioration in renal function observed in this patient may well have resulted from diclofenac, and is similar to the effect of other NSAIDs given to patients with asymptomatic renal failure (110). This emphasises the importance of monitoring renal function when NSAIDs are given to patients at risk of adverse effects.

The patients in this study were elderly and had major surgery for a debilitating disease. It is likely that this group would be susceptible to NSAID induced renal toxicity (111), and this may be less of a problem in other surgical patients.

It would be interesting to pursue these findings in further studies. Para-amino hippuric acid and inulin clearances to measure renal plasma flow and GFR would be useful. Assays of renin and vasopressin would give more information concerning renal potassium and water handling. The effect of opioids and pain on vasopressin should also be addressed, and diuretic therapy controlled more stringently.

6.3.5 Conclusion A postoperative increase in renal prostacyclin production was demonstrated which was suppressed by diclofenac. The reduction of urine output, potassium and sodium excretion, and the tendency to hyperkalaemia observed with diclofenac was present only in the immediate postoperative period when renal prostaglandin production was maximal. One patient given diclofenac had marked renal impairment. This may confirm previous suggestions that renal function is dependent upon prostaglandins immediately after anaesthesia and surgery (90,126), and that this can be adversely affected by NSAID administration. This work emphasises that if NSAIDs are used after major surgery, urinary output and plasma potassium should be monitored. NSAIDs should be avoided in surgical patients when there is a history of pre-existing renal impairment, congestive cardiac failure, liver cirrhosis, or hypovolaemia (90).

CHAPTER 7

NSAIDs AND POSTOPERATIVE PAIN RELIEF

7.1 NSAIDs as postoperative analgesics

Conventional postoperative pain relief based on intramuscular opioids may be unsatisfactory because of under administration resulting from about side-effects and practical difficulties in dispensing controlled drugs (28,30). The potential offered by the NSAIDs was that they were effective and safe analgesics which could be given without concern of side-effects. The studies in this thesis have examined these claims to efficacy and safety.

Potency In common with previous studies of NSAIDs, the investigations performed indicate that ketorolac is not an adequate analgesic for the relief of the severe pain present immediately after abdominal surgery. Later in the postoperative period, when the pain was less, ketorolac was as good as morphine.

This may suggest that ketorolac and diclofenac should not be the sole agents used to treat severe pain. The appropriate use of these drugs may be for the relief of mild to moderate pain either after minor surgery, or on the day after major surgery.

There is a need for clinical studies comparing regimens of ketorolac and diclofenac. Diclofenac 75 mg can only be given twice daily for safety reasons, although it has an elimination half life of only one to two hours (45). The studies presented in this thesis confirm that ketorolac 30 mg, with a longer half life of four to six hours, can be given four times a day with no adverse effects.

Morphine sparing effect After thoracotomy, little benefit was found in combining intramuscular ketorolac with intravenous, patient controlled, morphine. This was in contrast with previous studies where NSAIDs given in this way produced definite benefits (38,84,41). Various reasons for this difference have been discussed in this

thesis, but it may be that the previously reported beneficial, morphine sparing, effect of NSAIDs may not be obvious in every clinical situation.

Route of administration Diclofenac produces muscle damage on injection (64), it is not approved for intravenous use, and as a result rectal administration is becoming popular. Ketorolac will be available initially for intramuscular, and possibly intravenous use, with an oral preparation to follow later. Intramuscular ketorolac has been well tolerated in the studies in this thesis, and it is probable that this will be the main route of administration. The availability of oral preparations of diclofenac and ketorolac means that administration could be continued by tablet once parenteral therapy is no longer required.

Day stay surgery The NSAIDs may be ideal analgesics for day case surgery when patients are discharged home within a few hours of having relatively minor operations. Although only mild to moderate pain should be expected after such surgery, it is often difficult to provide effective relief of this because of the need to avoid opioids with their depressant side-effects and potential for abuse. Ketorolac and diclofenac could safely be given during surgery by injection, and, if necessary, continued afterwards orally when the patient leaves hospital. As ketorolac and diclofenac are not controlled drugs, it is possible to supply them to patients for use at home.

7.2 NSAID side-effects

Administration of NSAIDs should be avoided in certain patients and operations because of potential adverse effects. This may restrict the usefulness of ketorolac and diclofenac.

Platelet function Ketorolac and diclofenac have been shown in this thesis to affect platelet function within one hour of intramuscular administration. Skin bleeding time was prolonged, although values were not above the upper limit of normal. There was no evidence that this increased operative blood loss, even in patients who had also been given subcutaneous heparin. Although these results are reassuring, it may be prudent to avoid or delay NSAID administration when bleeding is expected to be excessive or difficult to control, as abnormal bleeding can occur after aspirin even when skin bleeding time is normal (98). Ketorolac and dextran-70 did not produce any serious interaction in volunteers, but a degree of caution should be exercised in giving this combination to patients until clinical experience of NSAIDs during surgery has expanded.

The anti-platelet effect may also mean that ketorolac and diclofenac should not be given before subarachnoid or extradural blocks are performed as excessive bleeding from trauma to extradural vessels could lead to haematoma formation and have serious consequences (228,106). It may be prudent to delay administration of the NSAID until the block has been performed. If aspirin or an NSAID has already been given, a skin bleeding time estimation may be useful (200), and should be less than 10 minutes (228).

Gastrointestinal system A history of peptic ulceration should be a contraindication to the use of these drugs during surgery. This will mean that a considerable number of surgical patients will be excluded from having these drugs (table 1). The recognition of NSAID induced enteropathy means that a history of inflammatory bowel disease should also be a contraindication, and this should include patients operated on for Crohn's disease and ulcerative colitis.

It is not clear whether a short postoperative course of ketorolac or diclofenac will induce gastrointestinal changes in previously normal patients. In this thesis, dyspepsia was not a common complaint when ketorolac was given for two days after cholecystectomy or thoracotomy. Further studies of the effect of these drugs on the gastrointestinal system, including permeability studies, are required before general administration can be recommended.

Renal function NSAIDs should not be used when there is any pre-existing renal impairment, or in medical conditions where renal perfusion may be dependent upon prostaglandins including congestive cardiac failure, hypovolaemia, or hepatic cirrhosis with ascites (90,31).

This thesis also confirms earlier suggestions that renal function is dependent on prostaglandins after surgery (90,126), and that NSAIDs can have adverse effects even in the absence of pre-existing renal dysfunction. After major surgery, a normal postoperative increase in renal prostacyclin generation was described which was suppressed by diclofenac. Diclofenac was associated with reduced urine flow rate and potassium and sodium excretion and a tendency to hyperkalaemia. One patient had marked renal impairment with diclofenac. It was not possible to study ketorolac in detail, but it did not obviously impair renal function after cholecystectomy, whereas after more major surgery, thoracotomy, there was some evidence of an adverse effect.

If NSAIDs are used after surgery, then renal function should be monitored closely by observing the rate of urine production and serum potassium concentrations. NSAIDs should not be used in surgical patients who have pre-existing renal problems.

Aspirin sensitive asthma NSAIDs should be avoided in patients with asthma and nasal polyps or chronic rhinitis as severe bronchospasm may be precipitated (159). It may indeed be prudent to avoid NSAIDs in any asthmatic patient, as a significant proportion will be affected and severe bronchospasm can be produced (164). The ability of an NSAID to produce bronchospasm is related to potency as a cyclo-oxygenase inhibitor, and ketorolac and diclofenac are much more potent than aspirin. It may therefore be advisable to avoid ketorolac and diclofenac in asthmatics even when there is a history of aspirin ingestion with no effect.

Other side effects No unusual adverse effects, including liver toxicity, blood dyscrasias, or anaphylactic reactions were encountered when ketorolac and diclofenac were given during the studies comprising this thesis. The absence of such problems is not conclusive as the incidence of these problems is known to be low (89,171). There were no nervous system effects, although headache, dizziness, and drowsiness have been reported after ketorolac (57,67). Further clinical experience using these drugs in surgical patients is required to assess the incidence and importance of such adverse effects.

7.3 NSAIDs and the prevention of pain after surgery

Investigations of the pathophysiology of acute pain have suggested that afferent pathways can become sensitised by noxious stimuli (229). Consequently, emphasis is changing to the prevention of pain by pretreatment with analgesics before surgery (230,231). Impressive results have been produced using balanced analgesia of opioids, local anaesthetics and NSAIDs to prevent postoperative pain, even after major surgery (232). With this shift in emphasis from the

treatment to the prevention of pain, it is likely that ketorolac and diclofenac will be increasingly used prophylactically, as part of analgesic techniques also including local anaesthetics and opioids.

7.4 Prostaglandin and thromboxane production after surgery

Little is known of the effect of anaesthesia and surgery on prostaglandin physiology. Recent animal work has found that thiopentone and ether anaesthesia both reduce the density of prostaglandin receptors in the liver, and the comment was made that:

> "...it might be generally acceptable that some prostanoids could play an important role during anaesthesia through their action on the cardiovascular system, or their involvement in haemostasis." (233)

Venous blood TxB_2 production is increased for up to a day after surgery (222,223,40). As thromboxanes are powerful platelet aggregators and vasoconstrictors, this may represent a risk factor for cardiovascular and thromboembolic complications in susceptible patients in the postoperative period (222). By inhibiting thromboxane production and platelet aggregation, ketorolac and diclofenac could have the additional benefit of reducing such cardiovascular complications, including the common problem of thromboembolism (105,106).

Unfortunately, NSAIDs also block the production of prostacyclin (99), which is a vasodilator, prevents platelet aggregation, and may be important in protecting the myocardium against sudden vessel occlusion (173). Aspirin may be more effective at preventing cardiovascular problems after surgery, as it inhibits platelet

thromboxane longer than endothelial prostacyclin (99), which is the basis of low dose therapy in medical practice. Conversely, paracetamol blocks prostacyclin, but not thromboxane (99), an effect which could be considered harmful. Such considerations may be also of importance after vascular surgery when vessel patency may be affected by platelet activity.

If prostaglandins and thromboxanes play an important role after surgery, then NSAIDs could have diverse effects, both beneficial and harmful, which have as yet been disregarded. The effect of anaesthesia and surgery on arachidonic acid metabolism, and of the consequences of NSAID administration, offers a vast and fascinating area for further research.

7.5 Conclusion

NSAIDs may be adequate for the relief of pain of moderate intensity after operation, and it is probable that ketorolac and diclofenac will be commonly used. NSAIDs potentially can have severe adverse actions, and the safe use of ketorolac and diclofenac in surgical patients will be dependent on the proper recognition of their effects and side-effects.

REFERENCES

1. Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of gout. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan Publishing, 1985:674-715.

2. Sunshine A, Olson NZ. Non-narcotic analgesics. In: Wall PD, Melzack R eds. Textbook of pain. 2nd ed. Edinburgh: Churchill Livingstone, 1989:670-685.

3. Von Euler US, Eliasson R. Prostaglandins. London: Academic Press, 1967.

4. Willis AL. The eicosanoids: an introduction and overview. In: Willis AL, ed. Handbook of eicosanoids; prostaglandins and related lipids. Vol I. Boca Raton, Florida: CRC Press, 1987:3-46.

5. Mattie H. Non-opiate analgesics and prostaglandins. In: Feldman SA, Scurr CF, Paton W, eds. Drugs in anaesthesia: mechanisms of action. London: Edward Arnold, 1987:309-320.

6. Smith WL, DeWitt DL, Shimokawa T. Molecular basis for the inhibition of prostanoid biosynthesis by nonsteroidal anti-inflammatory agents. Stroke 1990;21(suppl IV):IV24-IV48.

7. Yokoyama C, Toh H, Miyata A, Tanabe T. Cloning and characterization of human cyclooxygenase gene and primary structure of the enzyme. In: Samuelsson B, Ramwell PW, Paoletti R, Folco G, Granstrom E, eds. Advances in prostaglandin, thromboxane, and leukotriene research. Vol 21A. New York: Raven Press, 1991;61-64.

8. Roberts LJ. Comparative metabolism and fate of the eicosanoids. In: Willis AL, ed. Handbook of eicosanoids, prostaglandins and related lipids. Vol I. Boca Raton, Florida: CRC Press, 1987:233-244.

9. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biology 1971;231:232-235.

10. Ferreira SH, Moncada S, Vane JR. Indomethacin and aspirin abolish prostaglandin release from the spleen. Nature New Biology 1971;231:237-239.

11. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nature New Biology 1971;231:235-237.

12. Ferreira SH. Peripheral analgesia: mechanism of the analgesic action of aspirin like drugs and opiate-antagonists. Br J Clin Pharmacol 1980;10:237S-245S.

13. Vane JR, Flower RJ, Botting RM. History of aspirin and its mechanism of action. Stroke 1990;21(suppl IV):IV12-IV23.

14. Smith WL, DeWitt DL, Shimokawa T. The aspirin and heme binding sites of PGG/H synthase. In: Samuelsson B, Ramwell PW, Paoletti R, Folco G, Granstrom E, eds. Advances in prostaglandin, thromboxane, and leukotriene research. Vol 21A. New York: Raven Press, 1991;77-80.

15. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetaminophenol). Nature 1972;240:410-411.

16. Weissmann G. Aspirin. Sci Am 1991;264(1):58-64.

17. Abramson S, Korchak H, Ludewig R, Edelson H, Haines K, Levin RI, Herman R, Rider L, Kimmel S, Weissmann G. Modes of action of aspirin-like drugs. Proc Natl Acad Sci USA 1985;82:7227-7231.

18. Abramson SB, Weissmann G. The mechanisms of action of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1989;32:1-9.

19. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth 1991;66:703-712.

20. Cousins MJ. Acute pain and the injury response: immediate and prolonged effects. Reg Anesth 1989;14:162-179.

21. Raja SN, Meyer RA, Campbell JN. Peripheral mechanisms of somatic pain. Anesthesiology 1988;68:571-590.

22. Higgs GA. Arachidonic acid metabolism, pain and hyperalgesia: the mode of action of non-steroid mild analgesics. Br J Clin Pharmacol 1980;10:233S-235S.

23. Perl ER. Sensitisation of nociceptors and its relation to sensation. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol I. New York: Raven Press, 1976;17-28.

24. Handwerker HO. Influences of algogenic substances and prostaglandins on the discharges of unmyelinated cutaneous nerve fibres identified as nociceptors. In: Bonica JJ, Albe-Fessard D, eds. Advances in pain research and therapy. Vol I. New York: Raven Press, 1976;41-45.

25. Fink M, Irwin P. Central nervous system effects of aspirin. Clin Pharmacol Ther 1982;32:362-365.

26. Zecca L, Broggini M, Pirola R, Campi R, Bichisao E, Maresca V. The diffusion of pirprofen into the cerebrospinal fluid in man. Eur J Clin Pharmacol 1988;35:81-83.

27. Jurna I, Brune K. Central effect of the non-steroid anti-inflammatory agents, indomethacin, ibuprofen, and diclofenac, determined in C fibre-evoked activity in single neurones of the rat thalamus. Pain 1990;41:71-80.

28. Kuhn S, Cooke K, Collins M, Jones JM, Mucklow JC. Perceptions of pain relief after surgery. Br Med J 1990;300:1687-1690.

29. Harmer M. Postoperative pain relief - time to take our heads out of the sand?. Anaesthesia 1991;46:167-168.

30. Commission on the provision of surgical services. Report of the working party on pain after surgery. London: The Royal College of Surgeons of England, the College of Anaesthetists, 1990.

31. Editorial. Postoperative pain relief and non-opioid analgesics. Lancet 1991;337:524-526.

32. Weis OF, Sriwatanakul K, Alloza JL, Weintraub M, Lasagna L. Attitudes of patients, housestaff, and nurses towards postoperative analgesic care. Anes Analg 1983;62:70-74.

33. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. Br J Anaesth 1990;64:267-275.

34. Cashman JN, Jones RM, Foster JMG, Adams AP. Comparisons of infusions of morphine and lysine acetyl salicylate for the relief of pain after surgery. Br J Anaesth 1985;57:255-258.

35. Jones RM, Cashman JN, Foster JMG, Wedley JR, Adams AP. Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain following thoracic surgery. Br J Anaesth 1985;57:259-263.

36. McAteer E, Dundee JW. Injectable aspirin as a postoperative analgesic. Br J Anaesth 1981;53:1069-1071.

37. Kweekel-De Vries WJ, Spierdijk J, Mattie H, Hermans JMH. A new soluble acetysalicylic acid derivative in the treatment of postoperative pain. Br J Anaesth 1974;46:133-135.

38. Reasbeck PG, Rice ML, Reasbeck JC. Double-blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. Lancet 1982;2:115-118.

39. Engel C, Lund B, Kristensen SS, Axel C, Nielsen JB. Indomethacin as an analgesic after hysterectomy. Acta Anaesthesiol Scand 1989;33:498-501.

40. Rorarius MGF, Baer GA, Metsa-Ketela T, Miralles J, Palomaki E, Vapaatalo H. Effects of peri-operatively administered diclofenac and indomethacin on blood loss, bleeding time and plasma prostanoids in man. Eur J Anaesthesiol 1989;6:335-342.

41. Pavy T, Medley C, Murphy DF. Effect of indomethacin on pain relief after thoracotomy. Br J Anaesth 1990;65:624-627.

42. Maunuksela EL, Olkkola KT, Korpela R. Intravenous indomethacin as postoperative analgesic in children; acute effects on blood pressure, heart rate, body temperature and bleeding. Ann Clin Res 1987;19:359-363.

43. Serpell MG, Thomson MF. Comparison of piroxicam with placebo in the management of pain after total hip replacement. Br J Anaesth 1989;63:354-356.

44. Hutchison GL, Crofts SL, Gray IG. Preoperative piroxicam for postoperative analgesia in dental surgery. Br J Anaesth 1990;65:500-503.

45. Todd PA, Sorkin EM. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 1988;35:244-285.

46. Lindgren U, Djupsjo H. Diclofenac for pain after hip surgery. Acta Orthop Scand 1985;56:28-31.

47. Buchanan JM, Baldasera J, Poole PH, Halshaw J, Dallard JK. Postoperative pain relief; a new approach: narcotics compared with non-steroidal anti-inflammatory drugs. Ann R Coll Surg Engl 1988;70:332-335.

48. Hodsman NBA, Burns JW, Blyth A, Kenny GNC, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 1987;42:1005-1008.

49. Colquhoun AD. Failure of rectal diclofenac to augment opioid analgesia after cholecystectomy. Anaesthesia 1989;44:57-60.

50. Tigerstedt I, Janhunen L, Tammisto T. Efficacy of diclofenac in a single prophylactic dose in postoperative pain. Ann Clin Res 1987;19:18-22.

51. McLoughlin C, McKinney MS, Fee JPH, Boules Z. Diclofenac for day-care arthroscopy surgery: comparison with a standard opioid therapy. Br J Anaesth 1990;65:620-623.

52. Campbell WI, Kendrick R, Patterson C. Intravenous diclofenac sodium. Does its administration suppress postoperative pain?. Anaesthesia 1990;45:763-766.

53. Watters CH, Patterson CC, Mathews HML, Campbell W. Diclofenac sodium for post-tonsillectomy pain in children. Anaesthesia 1988;43:641-643.

54. Bone ME, Fell D. A comparison of diclofenac with intramuscular papaveretum or placebo following tonsillectomy. Anaesthesia 1988;43: 277-280.

55. Moores MA, Wandless JG, Fell D. Paediatric postoperative analgesia. A comparison of rectal diclofenac with caudal bupivacaine after inguinal herniotomy. Anaesthesia 1990;45:156-158.

56. Syntex Research. Monograph for clinical investigation of RS-37619-00-31-3 (ketorolac tromethamine). Palo Alto, California:1986.

57. Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. Clin Pharm 1990;9:921-935.

58. Rooks II WH, Tomolonis AJ, Maloney PJ, Wallach MB, Schuler ME. The analgesic and anti-inflammatory profile of (+/-)-5-benzoyl-1,2-dihydro-3H-pyrrolo-1-carboxylic acid (RS-37619). Agents Actions 1982;12:684-690.

59. Rooks II WH, Maloney PJ, Shott LD et al. The analgesic and anti-inflammatory profile of ketorolac and its tromethamine salt. Drugs Exp Clin Res 1985;11:479-492.

60. Brandon Bravo LJC, Mattie H, Spierdijk J, Bovill JG, Burm AGL. The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 1988;35:491-494.

61. Murray AW, Brockway MS, Kenny GNC. Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. Br J Anaesth 1989;63:602-603.

62. Rubin P, Yee JP, Murthy VS, Seavey W. Ketorolac tromethamine (KT) analgesia: no post-operative respiratory depression and less constipation. Clin Pharmacol Ther 1987;41:182.

63. Lopez M, Waterbury LD, Michel A, Seavey W, Yee JP. Lack of addictive potential of ketorolac tromethamine. Pharmacologist 1987;29:136.

64. Macdonald FC, Gough KJ, Nicoll RAG, Dow RJ. Psychomotor effects of ketorolac in comparison with buprenorphine and diclofenac. Br J Clin Pharmacol 1989;27:453-459.

65. Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular, and oral administration. Eur J Clin Pharmacol 1988;35:423-425.

66. Jung D, Mroszczak EJ, Wu A, Ling TL, Sevelius H, Bynum L. Pharmacokinetics of ketorolac and p-hydroxy-ketorolac following oral and intramuscular administration of ketorolac tromethamine. Pharmac Res 1989;6:62-65.

67. Buckley MMT, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1990;39:86-109.

68. Walker JJ, Johnstone J, Lloyd J, Rocha CL. The transfer of ketorolac tromethamine from maternal to foetal blood. Eur J Clin Pharmacol 1988;34:509-511.

69. Jallad NS, Garg DC, Martinez JJ, Mroszczak EJ, Weidler DJ. Pharmacokinetics of single-dose oral and intramuscular ketorolac tromethamine in the young and elderly. J Clin Pharmacol 1990;30:76-81.

70. Martinez JJ, Garg DC, Pages LJ et al. Single dose pharmacokinetics of ketorolac in healthy young and renal impaired subjects. J Clin Pharmacol 1987;27:722.

71. Diebschlag W, Nocker W, Bullingham R. A double-blind study of the efficacy of topical ketorolac tromethamine gel in the treatment of ankle sprain, in comparison to placebo and etofenamate. J Clin Pharmacol 1990;30:82-89.

72. Flach AJ, Graham J, Kruger LP, Stegman RC, Tanenbaum L. Quantitative assessment of postsurgical breakdown of the blood-aqueous barrier following administration of 0.5% ketorolac tromethamine solution. Arch Opthalmol 1988;106:344-347.

73. Flach AJ, Kraff MC, Sanders DR, Tanenbaum L. The quantitative effect of 0.5% ketorolac tromethamine solution and 0.1% dexamethasone sodium phosphate solution on postsurgical blood-aqueous barrier. Arch Opthalmol 1988;106:480-483.

74. Bloomfield SS, Mitchell J, Cisell GB, Barden TP, Yee JP. Ketorolac versus aspirin for postpartum uterine pain. Pharmacotherapy 1986;6:247-252.

75. Vangen O, Doessland S, Lindbaek E. Comparative study of ketorolac and paracetamol/codeine in alleviating pain following gynaecological surgery. J Int Med Res 1988;16:443-451.

76. McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RES, Moore RA. Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 1986;39:89-93.

77. Honig WJ, Vanochte J. A multiple-dose comparison of ketorolac tromethamine with diflunisal and placebo in post-menisectomy pain. J Clin Pharmacol 1986;26:700-705.

78. Galasko CSB, Russel S, Lloyd J. Double-blind investigation of multiple oral doses of ketorolac tromethamine compared with dihydrocodeine and placebo. Curr Ther Res 1989;45:844-852.

79. Fricke J, Angelocci D. The analgesic efficacy of intramuscular ketorolac and meperidine for the control of postoperative dental pain. Clin Pharmacol Ther 1987;41:181.

80. Estenne B, Julien M, Charleux H, Arsac M, Arvis G, Loygue J. Comparison of ketorolac, pentazocine, and placebo in treating postoperative pain. Curr Ther Res 1988;43:1173-1183.

81. Alexander JI, Harris C, Johnson RW, Thomas TA. A double-blind, randomized comparison of the analgesic and side-effects of ketorolac and morphine when used as premedicants for surgery. Curr Ther Res 1991;49:1-9.

82. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556-561.

83. Yee JP, Koshiver JE, Allbon C, Brown CR. Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Pharmacotherapy 1986;6:253-261.

84. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine. Anaesthesia 1987;42:727-731.

85. Owen H, Glavin RJ, Shaw NA. Ibuprofen in the management of postoperative pain. Br J Anaesth 1986;58:1371-1375.

86. Elhakim M. A comparison of intravenous ketoprofen with pethidine for postoperative pain relief following nasal surgery. Acta Anaesthesiol Scand 1991;35:279-282.

87. Nuki G. Pain control and the use of non-steroidal analgesic anti-inflammatory drugs. Br Med Bull 1990;46:262-278.

88. Mann RD. The yellow card data: the nature and scale of the adverse drug reactions problem. In: Mann RD, ed. Adverse drug reactions. Carnforth: Parthenon Publishing,1987;5-66.

89. Peplow PV. Properties and actions of non-steroidal anti-inflammatory drugs, including their effects on prostaglandins and macromolecular biosynthesis. Prostaglandins Leukot Essent Fatty acids 1988;33:239-252.

90. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Eng J Med 1984;310:563-572.

91. Forbes CD, Greer IA. Physiology of haemostasis and the effect of pregnancy. In: Greer IA, Turpie AGG, Forbes CD, eds. Haemostasis and thrombosis in obstetrics and gynaecology. London: Chapman Hall, 1991 (in press).

92. Narumiya S, Ushikubi F, Nakajima M, Hirata M, Okuma M. Purification and characterisation of the human platelet TxA_2/PGH_2 receptor. In: Samuelsson B, Ramwell PW, Paoletti R, Folco G, Granstrom E, eds. Advances in prostaglandin, thromboxane, and leukotriene research. Vol 21A. New York: Raven Press, 1991;339-346.

93. Morinelli TA, Naka M, Masuda A et al. Characterization of thromboxane A_2/prostaglandin H_2 receptors of various tissues using a new radioiodinated thromboxane A_2/prostaglandin H_2 mimetic, I-BOP. In: Samuelsson B, Ramwell PW, Paoletti R, Folco G, Granstrom E, eds. Advances in prostaglandin, thromboxane, and leukotriene research. Vol 21A. New York: Raven Press, 1991;331-337.

94. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. J Clin Inves 1968;47:2169-2180.

95. Rorarius M, Miralles J, Baer GA, Palomaki E. Diclofenac versus indomethacin given as intravenous infusions: their effect on haemodynamics and bleeding time, and side effects in healthy subjects. Ann Clin Res 1985;17:306-309.

96. Mueller BA, Talbert RL, Tegeler CH, Prihoda TJ. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. J Clin Pharmacol 1991;31:185-190.

97. Watson CJE, Deane AM, Doyle PT, Bullock KN. Identifiable factors in post-prostatectomy haemorrhage: the role of aspirin. Br J Urol 1990;66:85-87.

98. Bashein G, Nessly ML, Rice AL, Counts RB, Misbach GA. Preoperative aspirin therapy and reoperation for bleeding after coronary artery bypass surgery. Arch Intern Med 1991;151:89-93.

99. Drvota V, Vesterqvist O, Green K. Effects of non-steroidal anti-inflammatory drugs on the in vivo synthesis of thromboxane and prostacyclin in humans. In: Samuelsson B, Ramwell PW, Paoletti R, Folco G, Granstrom E, eds. Advances in prostaglandin, thromboxane, and leukotriene research. Vol 21A. New York: Raven Press, 1991;153-156.

100. Cronberg S, Wallmark E, Soderberg I. Effect on platelet aggregation of oral administration of 10 non-steroidal analgesics to humans. Scand J Haematol 1984;33:155-159.

101. Banos G, Reyes PA. A comparative study of the effect of ten non-steroidal anti-inflammatory drugs (NSAIDs) upon some mitochondrial and platelet functions. Int J Biochem 1989;21:1387-1394.

102. Conrad KA, Fagan TC, Mackie MJ, Mayshar PV. Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 1988;43:542-546.

103. Spowart K, Greer IA, McLaren M, Lloyd J, Bullingham RES, Forbes CD. Haemostatic effects of ketorolac with and without concomitant heparin in normal volunteers. Thromb Haemost 1988;60:382-386.

104. Khazan U, Toth M, Mutgi A. Diclofenac sodium and bruising. Ann Int Med 1990;112:472-473.

105. Goucke CR. Prophylaxis against venous thromboembolism. Anaesth Intens Care 1989;17:458-465.

106. McKenzie PJ. Deep venous thrombosis and anaesthesia. Br J Anaesth 1991;66:4-7.

107. Toon S, Holt BL, Mullins GP, Bullingham R, Aarons L, Rowland M. Investigations into the potential effects of multiple dose ketorolac on the pharmacokinetics and pharmacodynamics of racemic warfarin. Br J Clin Pharmacol 1990;30:743-750.

108. Carmichael J, Shankel SW. Effects of nonsteroidal anti-inflammatory drugs on prostaglandins and renal function. Am J Med 1984;78:992-1000.

109. Murray MD, Brater DC. Adverse effects of nonsteroidal anti-inflammatory drugs on renal function. Ann Int Med 1990;112:559-560.

110. Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. Ann Int Med 1990;112:568-576.

111. Stillman M, Schlesinger PA. Nonsteroidal anti-inflammatory drug nephrotoxicity. Arch Int Med 1990;268-270.

112. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. Kidney Int 1987;32:1-12.

113. Morlans M, Laporte JR, Vidal X, Cabeza D, Stolley PD. End-stage renal disease and non-narcotic analgesics: a case-control study. Br J Clin Pharmacol 1990;30:717-723.

114. Sun FF, Taylor B, McGuire JC, Wong PYK. Metabolism of prostaglandins in the kidney. Kidney Int 1981;19:760-770.

115. Levenson DJ, Simmons CE, Brenner BM. Arachidonic acid metabolism, prostaglandins, and the kidney. Am J Med 1982;72:354-374.

116. Baer PG. Renal Physiology. In Curtis-Prior PB, ed. Prostaglandins: Biology and chemistry of prostaglandins and related eicosanoids. London: Churchill Livingstone, 1988:269-282.

117. Larsson C, Anggard E. Regional differences in the formation and metabolism of prostaglandins in the rabbit kidney. Eur J Pharmacol 1973;21:30-36.

118. Mangino MJ, Jendrisak MD, Murphy MK, Halstead M, Anderson CB. Prostanoids and hypothermic renal preservation injury. Prostaglandins Leuk Essent Fatty Acids 1990;41:173-179.

119. Lifschitz MD. Prostaglandins and renal blood flow: in vivo studies. Kidney Int 1981;19:781-785.

120. Bailey RR. Adverse renal reactions to non-steroidal anti-inflammatory drugs and potassium-sparing diuretics. Adverse Drug Reaction Bulletin 1988;131:492-495.

121. Weissman C. The metabolic response to stress: an overview and update. Anesthesiology 1990;73:308-327.

122. Kehlet H. Surgical stress: the role of pain and analgesia. Br J Anaesth 1989;63:189-195.

123. Mercatello A. Modifications de la fonction renale induites par l'anesthesie. Ann Fr Anesth Reanim 1990;9:507-524.

124. Mazze RI. Renal physiology. In: Miller RD, ed. Anesthesia. 3rd ed. New York: Churchill Livingstone, 1990:601-619.

125. Mirenda JV, Grissom TE. Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. Anesth Analg 1991;72:667-683.

126. Terragno NA, Terragno DA, McGiff J. Contribution of prostaglandins to the renal circulation in conscious, anesthetized, and laparotomized dogs. Circ Res 1977;40:590-595.

127. Lokhandwala MF, Jandhyala BS. Sympathetic nerve function and renal hemodynamics during hemorrhage: role of pre- and postsynaptic interactions between angiotensin II and prostaglandins. J Pharmacol Exp Ther 1979;211;539-545.

128. Barber JD, Moss NG. Reduced renal perfusion pressure causes prostaglandin-dependent excitation of R2 chemoreceptors in rats. Am J Physiol 1990;259:R1243-R1249.

129. Rubinger D, Wald H, Scherzer P, Popovtzer MM. Renal sodium handling and stimulation of medullary Na-K-ATPase during blockade of prostaglandin synthesis. Prostaglandins 1990;39:179-194.

130. Simmons NL. Chloride secretion stimulated by prostaglandin E_1 and by forskolin in a canine renal epithelial cell line. J Physiol 1991;432:459-472.

131. Angeli P, Gatta A, Caregaro L et al. Effects of iloprost, a prostacyclin analog derivative, on renal plasma flow, renal function, and renin-aldosterone system in humans. Clin Pharmacol Ther 1988;44:211-216.

132. Patrono C, Pugliese F, Ciabattoni G et al. Evidence for a direct stimulatory effect of prostacyclin on renin release in man. J Clin Inves 1982;69:231-239.

133. Clive DM, Stoff JS, Cardi M, MacIntyre DE, Brown RS, Salzman EW. Evidence that circulating 6keto prostaglandin E_1 causes the platelet defect of Bartter's Syndrome. Prostaglandins Leukot Essent Fatty Acids 1990;41:251-258.

134. Zusman RM. Prostaglandins, vasopressin, and renal water reabsorption. Med Clin North Am 1981;65:915-925.

135. Weinstock RS, Moses AM. Desmopressin and indomethacin therapy for nephrogenic diabetes insipidus in patients receiving lithium carbonate. South Med J 1990;83:1475-1477.

136. Strom BL, West SL, Sim E, Carson JL. The epidemiology of the acute flank pain syndrome from surprofen. Clin Pharmacol Ther 1989;46:693-696.

137. Douthwaite AH, Lintott GAM. Gastroscopic observation of the effect of aspirin and certain other substances on the stomach. Lancet 1938;2:1222-1225.

138. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. Br Med J 1990;300:278-284.

139. Axon AR. Duodenal ulcer: the villain unmasked? Br Med J 1991;302:919-920.

140. Ivey KJ. Gastrointestinal intolerance and bleeding with non-narcotic analgesics. Drugs 1986;32(suppl 4):71-89.

141. Levine RA, Nandi J, King RL. Aspirin potentiates prestimulated acid secretion and mobilizes intracellular calcium in rabbit parietal cells. J Clin Invest 1990;86:400-408.

142. Levine RA, Petokas S, Nandi J, Enthoven D. Effects of nonsteroidal antiinflammatory drugs on gastrointestinal injury and prostanoid generation in healthy volunteers. Dig Dis Sci 1988;33:660-666.

143. Laporte J-R, Carne X, Vidal X, Moreno V, Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. Lancet 1991;337:85-89.

144. Tarnawski A, Stachura J, Gergely H, Hollander D. Gastric microvascular endothelium: a major target for aspirin-induced injury and arachidonic acid protection. An ultrastructural analysis in the rat. Eur J Clin Invest 1990;20:432-440.

145. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet 1988;2:1277-1280.

146. Ehsanullah RSB, Page MC, Tildesley G, Wood JR. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. Br Med J 1988;297:1017-1021.

147. Levi S, Goodlad RA, Lee CY, Stamp G, Walport MJ, Wright NA, Hodgson HJF. Inhibitory effect of non-steroidal anti-inflammatory drugs on mucosal cell proliferation associated with gastric ulcer healing. Lancet 1990;336:840-843.

148. Parashevaides EC, Wilson MC. Near-fatal peptic ulceration and non-steroidal anti-inflammatory drugs (NSAIDs): two case reports. Br J Clin Prac 1990;44:421-422.

149. Lanza FL, Karlin DA, Yee JP. A double-blind placebo controlled endoscopic study comparing the mucosal injury seen with an orally and parenterally administered new nonsteroidal analgesic ketorolac tromethamine at therapeutic and supratherapeutic doses. Am J Gastroenterol 1987;82:939.

150. Banerjee AK. Enteropathy induced by non-steroidal anti-inflammatory drugs. Br Med J 1989;298:1539-1540.

151. Tanner AR, Ragnunath AS. Colonic inflammation and nonsteroidal anti-inflammatory drug administration. Digestion 1988;41:116-120.

152. Whittle BJR. Temporal relationship between cyclooxygenase inhibition, as measured by prostacyclin biosynthesis, and the gastrointestinal damage induced by indomethacin in the rat. Gastroenterology 1981;80:94-98.

153. Banerjee AK, Peters TJ. Experimental non-steroidal anti-inflammatory drug-induced enteropathy in the rat: similarities to inflammatory bowel disease and effect of thromboxane synthetase inhibitors. Gut 1990;31:1358-1364.

154. Satchithanandam S, Cassidy MM, Kharroubi AT, Calvert RJ, Leeds AR, Vahouny GV. Alterations in rat intestinal mucin patterns following luminal infusion of acetylsalicylic acid and prostaglandin derivatives. Dig Dis Sci 1990;35:1518-1527.

155. Bjarnason I, Williams P, So A et al. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. Lancet 1984;2:1171-1174.

156. Jenkins AP, Trew DR, Crump BJ et al. Do non-steroidal anti-inflammatory drugs increase colonic permeability? Gut 1991;32:66-69.

157. Bjarnason I, Zanelli G, Smith T et al. Nonsteroidal antiinflammatory drug-induced intestinal inflammation in humans. Gastroenterology 1987;93:480-489.

158. Morris AJ, Madhok R, Sturrock RD, Capell HA, MacKenzie JF. Enteroscopic diagnosis of small bowel ulceration in patients receiving non-steroidal anti-inflammatory drugs. Lancet 1991;337:520.

159. Slepian IK, Mathews KP, McLean JA. Aspirin-sensitive asthma. Chest 1985;87:386-391.

160. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. Br Med J 1975;1:67-69.

161. Springall DR, Holwarth PH, Counihan H, Djukanovic R, Holgate ST, Polak JM. Endothelin immunoreactivity of airway epithelium in asthmatic patients. Lancet 1991;337:697-701.

162. Nagase T, Fukuchi Y, Jo C et al. Endothelin-1 stimulates arachidonate 15-lipoxygenase activity and oxygen radical formation in the rat distal lung. Biochem Biophys Res Commun 1990;168:485-489.

163. Marquette CH, Joseph M, Tonnel AB et al. The abnormal in vitro response to aspirin of platelets from aspirin-sensitive asthmatics is inhibited after inhalation of nedocromil sodium but not of sodium cromoglycate. Br J Clin Pharmacol 1990;29:525-531.

164. Ayres JG, Fleming DM, Whittington RM. Asthma death due to ibuprofen. Lancet 1987;1:1082(c).

165. Lim TK, Turner NC, Watson A, Joyce H, Fuller RW, Pride NB. Effects of nonsteroidal anti-inflammatory drugs on the bronchial hyperresponsiveness of middle-aged smokers. Eur Resp J 1990;3:872-879.

166. Zimmerman HJ. Effects of aspirin and actaminophen on the liver. Arch Int Med 1981;141:333-342.

167. Freeland GR, Northington RS, Hedrich DA, Walker BR. Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. Clin Pharmacol Ther 1988;43:473-479.

168. Breen EG, McNicholl J, Cosgrove E, McCabe J, Stevens FM. Fatal hepatitis associated with diclofenac. Gut 1986;27:1390-1393.

169. Helfgott SM, Sandberg-Cook J, Zakim D, Nestler J. Diclofenac-associated hepatotoxicity. JAMA 1990;264:2660-2662.

170. Campbell WI, Watters CH. Venous sequelae following i.v. administration of diclofenac. Br J Anaesth 1989;62:545-547.

171. O'Brien W. Adverse reactions to nonsteroidal anti-inflammatory drugs. Diclofenac compared with other nonsteroidal anti-inflammatory drugs. Am J Med 1986;80(4B):70-80.

172. Edwards AD, Wyatt JS, Richardson C et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet 1990;335:1491-1495.

173. Vegh A, Szekeres L, Parratt JR. Protective effects of preconditioning of the ischaemic myocardium involve cyclo-oxygenase products. Cardiovasc Res 1990;24:1020-1023.

174. Gracely RH. Methods of testing pain mechanisms in normal man. In: Wall PD, Melzack R eds. Textbook of pain. 2nd ed. Edinburgh: Churchill Livingstone, 1989:257-268.

175. Reading AE. Testing pain mechanisms in persons in pain. In: Wall PD, Melzack R eds. Textbook of pain. 2nd ed. Edinburgh: Churchill Livingstone, 1989:269-280.

176. Murrin KR, Rosen M. Pain measurement. In: Smith G, Covino BG, eds. Acute pain. London: Butterworths, 1985:104-132.

177. Masson AHB. Clinical assessment of analgesic drugs (1). Anaesthesia 1962;17:373-378.

178. Masson AHB. Clinical assessment of analgesic drugs (2). Anaesthesia 1962;17:411-418.

179. Sechzer PH. Objective measurement of pain. Anesthesiology 1968;29:209-210.

180. Dodson ME. The management of postoperative pain. London: Edward Arnold, 1985;31-52.

181. Merskey H. Pain terms: a list with definitions and notes on usage. Recommended by the IASP subcommittee on taxonomy. Pain 1979;6:249-252.

182. Glynn C. Clinical methods in pain relief research. In: Newton DEF, Webster NR, eds. Bailliere's clinical anaesthesiology. International practice and research: clinical research in anaesthesia. London: Bailliere Tindall, 1988;89-105.

183. Power I, Spence AA. Drug trials and statistical validation. In: Scurr C, Feldman S, Soni N, eds. Scientific foundations of anaesthesia. 4th ed: The basis of intensive care. London: Heinemann, 1990;656-663.

184. Burns JW, Hodsman NBA, McLintock TTC, Gillies GWA, Kenny GNC, McArdle CS. The influence of patient characteristics on the requirements for postoperative analgesia. Anaesthesia 1989;44:2-6.

185. Stapleton JV, Austin KC, Mather LE. A pharmacokinetic approach to postoperative pain: continuous infusion of pethidine. Anaesth Intens Care 1979;7:25-32.

186. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191-1198.

187. Wallenstein SL, Heidrich G, Kaiko R, Houde RW. Clinical evaluation of mild analgesics: The measurement of clinical pain. Br J Clin Pharmacol 1980;10:319S-327S.

188. Seymour RA. The use of pain scales in assessing the efficacy of analgesics in postoperative dental pain. Eur J Clin Pharmacol 1982;23:441-444.

189. Thomas TA, Griffiths MJ. A pain slide rule. Anaesthesia 1982;37:960-961(c).

190. Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain 1975;1:275-299.

191. Bromage PR. Spirometry in assessment of analgesia after abdominal surgery - a method of comparing analgesic drugs. Br Med J 1955;2:589-593.

192. Chudler EH, Dong WK. The assessment of pain by cerebral evoked potentials. Pain 1983;16:221-244.

193. Beecher HK. The powerful placebo. JAMA 1955;159:1602-1606.

194. Lumley P, Humphrey PPA. A method for quantitating platelet aggregation and analysing drug-receptor interactions on platelets in whole blood. J Pharmacol Methods 1981;6:153-166.

195. Fox SC, Burgess-Wilson M, Heptinstall S, Mitchell JRA. Platelet aggregation in whole blood determined using the Ultra Flo 100 platelet counter. Thromb Haemost 1982;48:327-329.

196. Saniabadi AR, Lowe GDO, Barbenel JC, Forbes CD. A comparison of spontaneous platelet aggregation in whole blood with platelet rich plasma: additional evidence for the role of ADP. Thromb Haemost 1984;51:115-118.

197. Blackwell GJ, Flower RJ, Russell-Smith N, Salmon JA, Thorogood PB, Vane JR. Prostacyclin is produced in whole blood. Br J Pharmacol 1978;64:436P.

198. Bergqvist D. Postoperative thromboembolism. New York: Springer Verlag, 1983;106-107.

199. Greer IA. Thromboembolic problems in pregnancy. Fetal Medicine Review 1989;1:79-103.

200. Ivy AC, Nelson D, Bucher G. The standardisation of certain factors in the cutaneous venostasis bleeding time technique. J Lab Clin Med 1941;26:1812-1822.

201. Mielke CH, Kaneshiro MM, Maher IA, Weiner JM, Rapaport SI. The standarised normal Ivy bleeding time and it's prolongation by aspirin. Blood 1969;34:204-215.

202. Greer IA, Walker JJ, Calder AA, Forbes CD. Inhibition of platelet aggregation in whole blood by adrenoreceptor antagonists. Thromb Res 1985;40:631-643.

203. Kelly RW, Deam S, Cameron MJ, Seamark RF. Measurement by radioimmunoassay of prostaglandins as their methyloximes. Prostaglandins Leukot Med 1986;24:1-14.

204. Laurell CB. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Anal Biochem 1966;15:45-52.

205. Breckenridge RT, Ratnoff OD. Studies on the nature of the circulating anticoagulant directed against antihemophilic factor: with notes on an assay for antihemophilic factor. Blood 1962;20:137-149.

206. MacGregor IR, MacDonald S, Dawes J, Micklem L, James K. A monoclonal antibody enzyme linked immunosorbent assay (ELISA) directed towards a fibrin binding region of tissue-type plasminogen activator. Fibrinolysis 1987;1:247-252.

207. Brash AR, Jackson EK, Saggese CA, Lawson JA, Oates JA, Fitzgerald GA. Metabolic disposition of prostacyclin in humans. J Pharmacol Exp Ther 1983;226:78-87.

208. Klassen DK, Stout RL, Spilman PS, Whelton A. Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. J Clin Pharmacol 1989;29:1037-1042.

209. O'Brien WF, Williams MC, Benoit R, Sawai SK, Knuppel RA. The effect of magnesium sulfate infusion on systemic and renal prostacyclin production. Prostaglandins 1990;40:529-538.

210. Watson ML, Lambie AT, Thom A, Ungar A. Role of prostaglandins in mediating excretion by the kidney of an intravenous infusion of sodium chloride in normal human subjects. Clin Sci 1982;62:27-33.

211. Gore SM, Altman DG. Statistics in practice. London: British Medical Association, 1982:6-8.

212. Greene J, d'Oliveira M. Learning to use statistical tests in psychology: a student's guide. Milton Keynes: Open University Press, 1982.

213. Ryan BF, Joiner BL, Ryan TA. Minitab handbook. 2nd ed. Boston: PWS-Kent Publishing Company, 1985.

214. Powell H, Smallman JMB, Morgan M. Comparison of intramuscular ketorolac and morphine in pain control after laparotomy. Anaesthesia 1990;45:538-542.

215. Kenny GNC, Aitken H, Burns JW, McArdle CS. Morphine sparing effect of continuous and intermittent ketorolac. Anesthesiology 1989;71:A766.

216. Kenny GNC. Ketorolac trometamol - a new non-opioid analgesic. Br J Anaesth 1990;65:445-447.

217. Loew D, Brocke P, Simma W, Vinazzer H, Dienstl E, Boehme K. Acetylsalicylic acid, low dose heparin and a combination of both substances in the prevention of postoperative thromboembolism. Thromb Res 1977;11:81-86.

218. Yett HS, Skillman JJ, Salzman EW. The hazards of aspirin plus heparin. N Eng J Med 1978;298:1092.

219. Stuart MJ, Miller ML, Davey FR, Wolk JA. The post-aspirin bleeding time: a screening test for evaluating haemostatic disorders. Br J Haematol 1979;43:649-659.

220. Bricker SRW, Savage ME, Hanning CD. Peri-operative blood loss and non-steroidal anti-inflammatory drugs: an investigation using diclofenac in patients undergoing transurethral resection of the prostate. Eur J Anaesthesiol 1987;4:429-434.

221. Granstrom E. Minireview: radioimmunoassay of prostaglandins. Prostaglandins 1978;15:3-17.

222. Kaukinen S, Seppala E, Kaukinen L, Ojanen R, Vapaatalo H. Effects of halothane and enflurane on prostanoid concentrations in operation patients. Prostaglandins Leukot Med 1987;29:85-94.

223. Kaukinen S, Ojanen R, Kaulinen L, Seppala E, Vatpaatalo H. Plasma thromboxane B2 levels and thromboxane B2 production by platelets are increased in patients during spinal and epidural anesthesia. Prostaglandins Leukot Essent Fatty Acids 1989;37:83-88.

224. Goto F, Fujita N, Kato S, Fujita T. The effect of surgical stress on plasma 6-keto-$PGF_{1\alpha}$ concentrations in laparotomised patients under general anaesthesia. Prostaglandins Leukot Med 1984;15:137-142.

225. Hudson TC, Wurm HW, O'Donnell TF et al. Ibuprofen pretreatment inhibits prostacyclin release during abdominal exploration in aortic surgery. Anesthesiology 1990;72:443-449.

226. Bodnar RJ. Neuropharmacological and neuroendocrine substrates of stress-induced analgesia. Ann N Y Acad Sci 1986;467:345-360.

227. Yirmiya R, Ben-Eliyahu S, Shavit Y, Marek P, Liebeskind JC. Stimulation of the hypothalamic paraventricular nucleus produces analgesia not mediated by vasopressin or endogenous opioids. Brain Res 1990;537:169-174.

228. MacDonald R. Aspirin and extradural blocks. Br J Anaesth 1991;66:1-3.

229. Woolf CJ. Recent advances in the pathophysiology of acute pain. Br J Anaesth 1989;63:139-146.

230. Wall PD. The prevention of postoperative pain. Pain 1988;33:289-290.

231. Armitage EN. Postoperative pain - prevention or relief? Br J Anaesth 1989;63:136-138.

232. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. Br J Anaesth 1990;64:518-520.

233. Virgolini I, Peskar BA, Sinzinger H. Thiopental and ether anaesthesia decrease the prostaglandin receptor density of the rat liver. Prostaglandins Leukot Essent Fatty Acids 1991;43:25-28.