STUDIES ON FLUNIXIN MEGLUMINE IN DOGS UNDERGOING ANAESTHESIA AND SURGERY

by

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DEDICATION

This work is dedicated to my parents, Sherene and Rahoul.

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I wish to thank my supervisor Professor N.T. Gorman for accepting me in the Department of Surgery, and for the valuable advice and support he provided throughout my training period. I am grateful, for his continuous motivation and encouragement and for installing in me a confidence, which will be beneficial for years to come.

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DECLARATION

I, Anita Sauri Maitra, do hereby declare that the work in this dissertation is original, was carried out by myself or with due acknowledgement, and has not been presented for the award of a degree at any other university.

Signed:

Dated: 3|12|93

SUMMARY

In this study, flunixin meglumine, 1.1 mg/kg, was administered intravenously to two groups of dogs undergoing routine anaesthesia and surgery. The first group of dogs (Group A), were given the drug during anaesthesia, prior to the start of surgery, while the second group of dogs (Group B), were given the drug immediately on termination of anaesthesia and surgery. A pharmacokinetic study was undertaken to determine the presence of any alterations in the kinetics of flunixin, between the two groups of dogs. The results obtained in this study indicated that the time of administration of flunixin to the anaesthetised dog had no effect on the pharmacokinetic parameters measured. There was no significant difference between the elimination half-lives (7.86 $\pm$ 1.18 hours; 6.10 $\pm$ 0.74 hours), mean residence time (8.73 $\pm$ 2.53 hours; 4.52 $\pm$ 0.36 hours), or body clearance (34.88 $\pm$ 5.64 ml/kg.hr; 34.55 $\pm$ 4.58 ml/kg.hr) of the drug, between these two groups of dogs.

However, when the results of this study were compared with the results of other workers (Hardie *et al,* 1985; McKellar *et al,* 1991b), who had investigated the pharmacokinetics of flunixin in the conscious dog, differences in the pharmacokinetics of flunixin were found to exist. In this trial, the distribution and elimination half-lives obtained in anaesthetised dogs were double that obtained in conscious dogs by Hardie *et al* (1985) and McKellar *et al* (1991b). Also, the body clearance of the drug in the anaesthetised dog was found to be half that in the conscious dog (Hardie *et al,* 1985; McKellar *et al,* 1991b). Ideally during this trial a parallel study in conscious dogs should have been undertaken simultaneously, to clarify that the distribution and elimination half-lives obtained in the anaesthetised dogs were indeed double that in the conscious dog.

There was no correlation between mean arterial blood pressure and any pharmacokinetic parameter.

Each individual dog was screened for evidence of renal damage using biochemical markers and the results were compared with a third group of dogs (Group C), who had undergone routine anaesthesia and surgery, but had not received flunixin. Flunixin meglumine caused a significant rise in BUN levels in dogs in the trial, when administered during anaesthesia. Thus, some renal damage occurred, irrespective of whether the drug was administered to the anaesthetised animal prior to the start of surgery or immediately on termination of

anaesthesia, and this occured in some cases, despite mean arterial blood pressure readings being within the normal range. The rise in BUN took place during the first 12 hours of flunixin administration in the anaesthetised dog, and in 75% of the cases, was seen to be resolving within 30 hours of its administration. In all cases, renal damage was not considered severe and did not produce any clinical signs except in one dog, which remained polydipsic for 2 months after anaesthesia. The study demonstrated, however, that the rise in BUN produced when flunixin was administered during anaesthesia, prior to the start of surgery, was greater than that produced when the drug was given immediately on termination of anaesthesia. This was demonstrated by a significant difference still existing in BUN levels, from 0 to 30 hours, between dogs in group A and control group C, while no significant difference existed in BUN levels from 0 to 30 hours between dogs in group B and control group C.

1. INTRODUCTION

1.1 PAIN

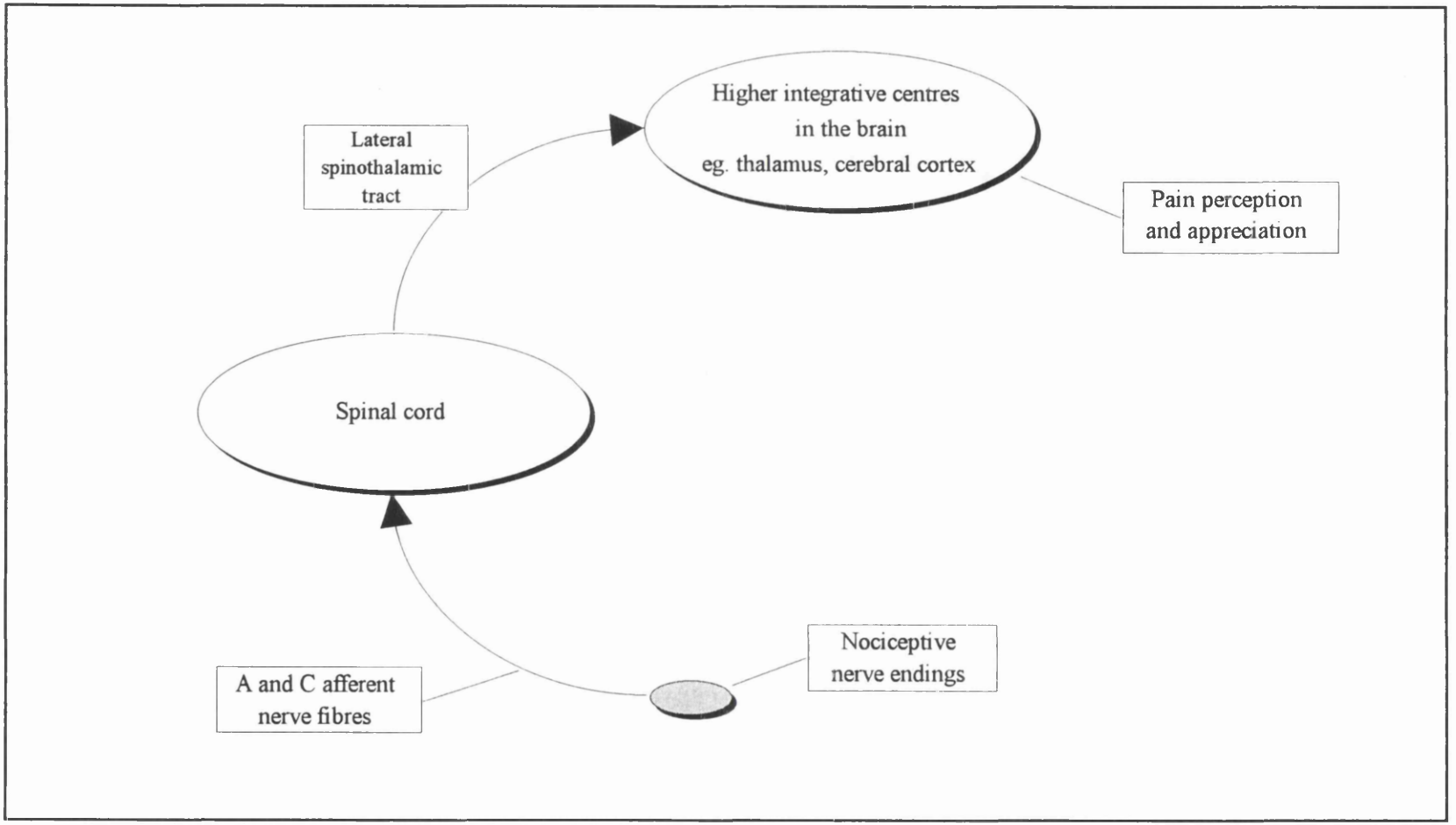
Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey, 1979); a definition which was adopted by the 'International Association for the study of pain' in 1986. Although most vertebrate species appear capable of perceiving pain because they possess appropriate central and peripheral neural pathways, neurotransmitters and receptors (Kitchell and Erickson, 1983), the exact mechanisms of pain are poorly understood.

Tissue damage can be caused by trauma and surgery, as well as by exposure to metabolic, bacterial or viral diseases and toxins. However, irrespective of the aetiology of the tissue damage or the tissues involved, the resulting inflammatory process is identical. Although the cardinal signs of inflammation were described as early as 1650 B.C., it was not until this century that the presence of histamine release at the site of tissue injury demonstrated that, just as nerve impulses are transmitted by released chemicals, so are the signs of inflammation caused by released chemical mediators (Lewis and Grant, 1924).

The physiology of pain has been reviewed in detail by Kitchell and Erickson (1983). Briefly, when damage to tissues occurs, perception of pain associated with this process depends upon the activation of a discrete set of pain receptors called nociceptors. Nociceptors are found in all body tissues, but are particularly numerous in the skin and internal tissues, such as the periosteum, joint capsule, arterial wall, muscles, tendons, and tentorium of the cranial vault (Lasagna, 1986). Once nociceptors are activated, they convert the noxious stimuli into nerve impulses, which are transmitted along afferent nerve fibres to synapse in the dorsal horn of the spinal cord. The mechanism of this activation (transduction) is not fully understood. However, studies of nociceptive transduction, have indicated that chemical mediators, synthesized and/or released in response to tissue damage, are responsible for the initiation of specific sensory impulses. These sensory impulses in turn activate neurons in the lateral spinothalmic tract, which then convey the impulse to the thalamus and from the thalamus to the cerebral cortex in the brain, to evoke the sensation of pain (figure 1).

The sensation of pain can be controlled by pharmacological intervention at numerous sites within the relay systems responsible for carrying the appropriate sensory impulse to the brain (Besson and Chauoch, 1987; Mohrland, 1982). Analgesics are, therefore, often classified according to their site of action into centrally-acting analgesics e.g. the opioids

Figure 1: Pain pathways



which act at selective receptors in the CNS as well as in other tissues (Martin, 1984; Lefebvre, 1986), and peripherally-acting analgesics which block the generation of painful impulses by inhibiting or modifying excitation of nociceptors (Jenkins, 1987). The non-steroidal anti-inflammatory drugs (NSAIDs) represent the largest group of peripherally acting analgesics. Until recently, the distinction between these two classes of drug

had been fairly clear. However Ferreira and Nakamura in 1979, demonstrated that opioids have peripheral analgesic effects, while NSAIDs have been shown to have a powerful central analgesic action (Malmberg and Yaksh, 1992).

Plants rich in salicylic acid, the progenitor of NSAIDs, were among the earliest components of herbal therapy, and were almost universally used as antipyretics and antirheumatics. Notable physicians such as Hippocrates, Pliny, Elder, and Celsus all recorded the beneficial effects of these plants in the treatment of ailments such as gout, fever, sciatica and earaches. However with the collapse of the Roman empire, rational herbal therapy was lost for more than 1000 years to the literate world (Roueche', 1958). In 1763, Reverend E. Stone discovered that a herb containg salicylates (Willow bark) was being used to treat malarial fevers and chills in the folk medicine of the English countryside. He reintroduced the willow's antipyretic powers to an emerging scientific community. A century later, Kolbe manufactured synthetic salicylic acid (Roueche', 1958). In 1899, the most famous descendent of salicylic acid, acetylsalicylic acid (Aspirin) was marketed. It rapidly became the most widely used drug in the world (Roueche', 1958; Sneader, 1985). However because of its widespread use, aspirin's toxic effects became apparent (Hart *et al,* 1979; Roth, 1985). Efforts to improve upon the side effects of aspirin led to the development of many more drugs of this type.

In human medicine, approximately 40 NSAIDs have been licensed for use in the UK. By comparison, fewer agents are available with veterinary product licences. These drugs have been the mainstay of treatment for the low grade chronic pain which occurs in conditions such as osteoarthritis, whereas the narcotic analgesics have been considered as the drugs of choice for acute pain. However, recent years have seen a revival of interest in the use of NSAIDs, both in human and veterinary medicine, for the treatment of acute pain associated with trauma or surgery. In 1991, Reid and Nolan showed that the NSAID flunixin meglumine is as effective an analgesic as the opioid agonist, papavertum, in the treatment of post-surgical pain in the dog. In humans, NSAIDs such as diclofenac, have

been shown to be as effective as the opioids in controlling pain after hip surgery (Buchanan *et al,* 1988).

Recently, the importance of the timing of analgesia has been suggested to be of potential major importance in the treatment of post-operative pain (Wall, 1988; Woolf, 1989; Woolf 1991). Many experimental studies have been performed by human anaesthetists to determine whether acute pain behaviour or hyperexcitability of dorsal horn neurons may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by pre-injury neural blocks with local anaesthetics (Woolf and Wall, 1986b; Coderre and Melzack, 1987; Coderre *et al,* 1990), or if the excitability of the CNS can be supressed before it receives a nociceptive input (Woolf and Wall, 1986a; Dickenson and Sullivan, 1987). Other classes of drugs which have been suggested as being potentially useful for this so called pre-emptive analgesia are the opioids and the NSAIDs. However, there is still no firm evidence that pre-emptive analgesia does lessen post-operative pain (Dahl and Kehlet, 1993) and better designed clinical studies, need to be performed before it is possible to definitively evaluate the clinical effectiveness of the pre-emptive use of analgesics (Dahl and Kehlet, 1993). At present, the prevention of the functional changes in the central nervous system by pre-emptive analgesia or other techniques, is still a fascinating working hypothesis.

1.2 INFLAMMATION

Inflammation may be considered to be a series of events which results from local tissue injury, and is mediated by vasoactive amines (histamine, serotonin), lymphokines, leukocyte products (enzymes, oxygen radicals), and the products of arachidonic metabolism (eicosanoids). Other substances which assist in modulating the inflammatory process are kinins, complement and coagulation protein (Jenkins, 1987).

As a result of local tissue injury, vasoactive substances are released from mast cells, white blood cells and local platelet aggregations. These substances give rise to pain, heat and swelling (Higgins and Lees, 1984). Sackman (1991) reviewed the inflammatory process in the following manner. There is relaxation of the precapillary sphincter and the arterioles, venules and lymphatics dilate, causing the capillary beds to leak, spilling plasma into the intestitial space. This exudation of fluid and the subsequent swelling give rise to pain by exerting pressure on the local nerve endings. Kinins maintain the plasma transudation from the capillaries while bradykinin causes hyperalgesia and further loss of vascular integrity.

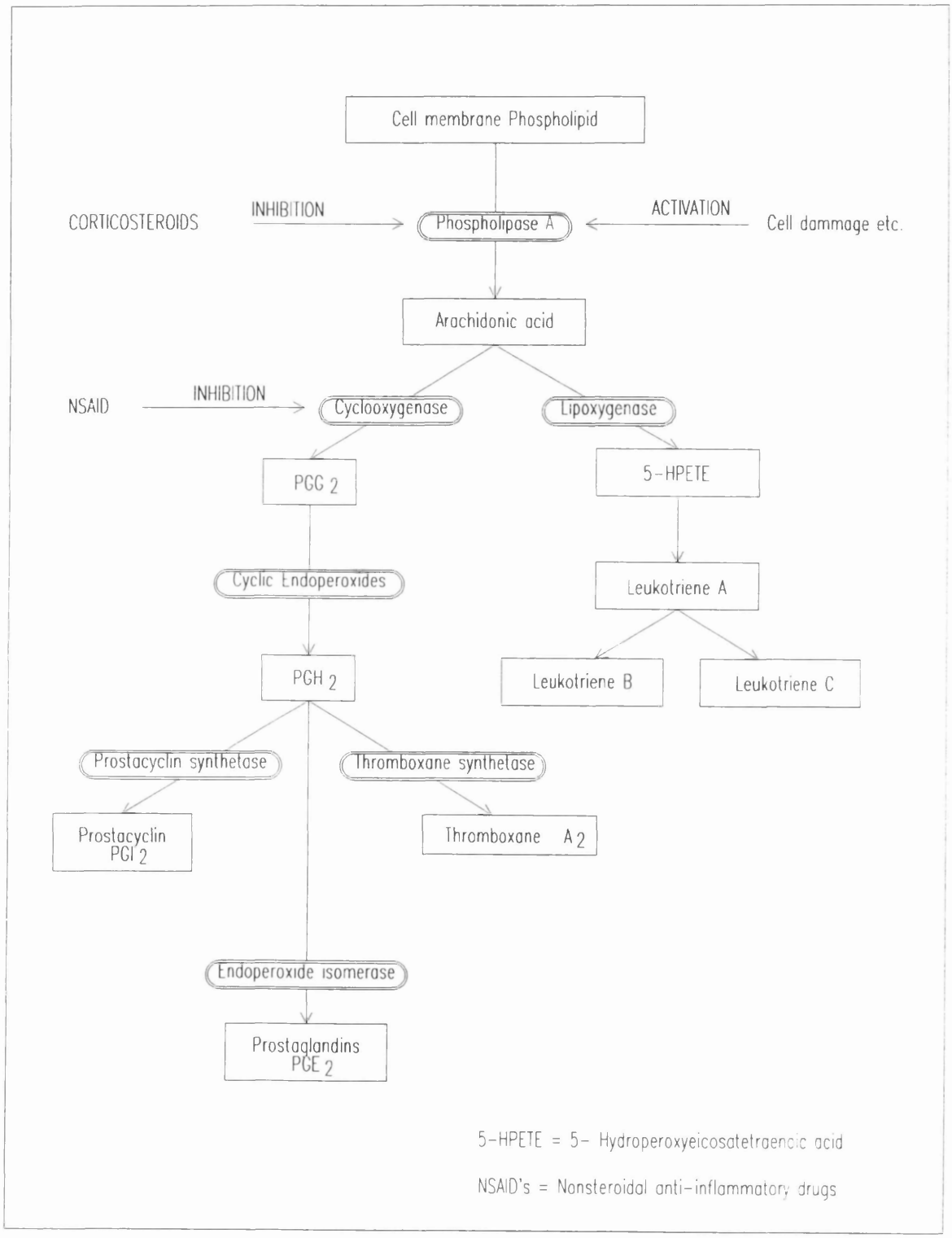
Concurrent with these vascular changes occurring at the damaged tissue site, neutrophils and monocytes start migrating towards the injured tissue in response to local chemotactic factors. The phagocytic cells then ingest and destroy any foreign material present at the site of injury, using enzymes and toxic oxygen radicals, thereby further generating pain (Conlon, 1988).

Products of arachidonic acid metabolism are mediators of inflammation. Phospholipase enzyme, activated in response to cell injury, causes the release of arachidonic acid from phospholipids embedded in cell membranes (Boothe, 1984). Metabolism of arachidonic acid proceeds in two directions: The enzyme cyclo-oxygenase, which is present in all cells except mature red blood cells, utilizes arachidonic acid as a substrate to form, first, the unstable cyclic endoperoxides PGG_2 and PGH_2, and then immediately, by the action of further specific enzymes, the classical prostaglandins, such as PGE_2, prostacyclin (PGI_2) and thromboxanes A_2 (TXA_2) (Moncada and Vane, 1977). The enzyme lipoxygenase, located mainly in the lungs, platelets and white blood cells, catalyses the hydroxylation of the straight chained fatty acids to leukotrienes and related compounds (Samuelsson, 1987) (figure 2).

Eicosanoids (Derivatives of eicosatetraenoic acid):-

Eicosanoids, particularly prostaglandins, appear to have a major role in peripheral nociception, and may also be involved in the modulation of the central neurotransmission of impulses, associated with pain perception (Moore, 1985). When prostaglandins are produced from cell membrane phospholipids after cellular injury, they bind to receptors on the sensory nerve endings facilitating the discharge of impulses, thus intensifying pain. Prostaglandins appear to sensitize pain receptors to the effects of various physical and chemical stimuli and to other inflammatory mediators such as bradykinin and histamine (Ferreira, 1986; Williams and Higgs, 1988). Ferreira (1986) has shown that prostaglandins increase the response frequency of the receptors to control stimuli, probably by lowering the normally high threshold of polymodal nociceptors associated with C-fibres. He observed that prostacyclin produced an immediate hyperalgesia of short duration. Eicosanoids are not stored in cells. They are synthesized *de novo* as needed and are rapidly eliminated. The half-life of most prostaglandins range from seconds to minutes (Goldyne, 1987).

Figure 2: **Diagrammatic representation of the inflammatory mediators formed from archidonic acid and the possible sites of action of NSAID's and steroids.**



1.3 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which share certain therapeutic actions and side effects (Verbeeck *et al,* 1983). They are classified into three principal classes of agents: Carboxylic acid, enolic acid and others. The carboxylic acid group of agents inhibit cyclo-oxygenase enzymes while the enolic acid group of agents block endoperoxide isomerase.

A) The carboxylic acids include:

1) Salicylic acids and esters:----------	Sodium salicylate Acetyl salicylic acid (Aspirin)
2) Acetic acid	
a) Phenylacetes:----------	Diclofenac Alclofenac
b) Indole-acetates:----------	Indomethacin Sulindac
3) Propionic acids:----------	Ibuprofen Naproxen Ketoprofen Carprofen
4) Fenamic Acid:----------	Mefenamic acid Meclofenamic acid Tolfenamic acid
5) Quinolones:----------	Cinchophen

B) The Enolic acids include

1) Pyrazolones: ----------	Phenylbutazone Oxyphenylbutazone Dipyrone Isopyrin
2) Oxicams:----------	Piroxicam Tenoxicam Meloxicam

C) The others include

1) Nicotinic acid derivative:----------	Flunixin meglumine

1.3.1. Mechanism of action of NSAIDs

NSAIDs probably share a common mechanism of action. They are considered to exert their analgesic effects peripherally and their activity appears to be due to inhibition of prostaglandin synthesis by reversible or irreversible inhibition of the cyclo-oxygenase enzyme system (Vane, 1971). Aspirin irreversibly inhibits the enzyme cyclo-oxygenase, and hence its effects are especially potent and long-lasting. Most acidic NSAIDs compete with arachidonic acid for the active site of the cyclo-oxygenase enzyme and, unlike aspirin, reversibly inhibit cyclo-oxygenase (Ferriera and Vane, 1973).

NSAIDs also inhibit the vascular, and in certain instances, the cellular phases of inflammation (Strørm and Thomsen, 1990). Whereas the vascular effects of most NSAIDs in inflammation are largely accounted for by inhibition of prostaglandin synthesis (Vane, 1971), the mechanism invoved in inhibition of phagocyte function is less firmly established (Abramson *et al,* 1984a,b).

1.3.2. Pharmacology of NSAIDs

NSAIDs share certain pharmacological actions, therapeutic uses and side effects.

Analgesia

They are usually accepted as being effective against pain associated with inflammation (Dubinsky *et al,* 1987). According to a review by Tobin *et al,* 1986, NSAIDs have no direct effect on pain perception, but they reduce hypersensitivity to pain, by virtue of the fact that they inhibit prostaglandin production. The analgesia produced by NSAIDs varies from moderate to quite marked, depending on the particular drug and the clinical condition. In the treatment of post-operative pain, NSAIDs can be as effective as, or more effective than opioid analgesics (Reid and Nolan, 1991; Nolan and Reid, 1993).

Anti-inflammatory action

Certain prostanoids (PGE_2 and PGI_2) are important mediators of the vascular changes in inflammation (Ferreira *et al,* 1974; Jones, 1977). Inhibition of their formation by NSAIDs markedly reduces, but does not abolish, prostanoid-dependent swelling, oedema, erythema, and hypersensitivity to pain in inflamed tissues (Tobin *et al,* 1986), and is therefore very useful for the treatment of soft tissue swelling. In recent years, it has been recognised increasingly that NSAIDs possess other properties, which are likely to

contribute to their anti-inflammatory action (Lee and Foster, 1992), such as free radical scavenging activity and inhibition of the release of lysosomal enzymes. Other nonprostaglandin-related effects of NSAIDs are inhibition of neutrophil activation and aggregation, and inhibition of superoxide anion generation by neutrophils (Brooks and Day, 1991).

Antipyretic action

Pyrogens induce the synthesis of prostaglandin E_2 in the hypothalamus, which alters the set point of temperature regulation and thereby acts as a powerful pyretic agent (Frey, 1992). NSAIDs inhibit both the generation of prostaglandins in the CNS and the fever caused by the pyrogens, and are therefore anti-pyretic in their action (Moncada and Vane, 1979).

Anti-thrombotic action

When platelets aggregate, they release thromboxane A_2, a potent platelet aggregator. NSAIDs block the formation of thromboxane A_2, thus reducing thrombosis and haemostasis (Meyers *et al,* 1979). Aspirin acetylates platelets and inhibits cyclo-oxygenase for their life span, whereas the action of the other NSAIDs is reversible and the effect is generally maximal at 3 hours and has worn off by 24 hours (Henry, 1988). An exception to this rule may be piroxicam which, because of its long plasma half-life, appears to inhibit platelet function for at least 72 hours after dosing to steady state (McQueen *et al,* 1986).

1.3.3 Effect of NSAIDs on organ systems

In addition to sharing many therapeutic activities with respect to their anti-inflammatory, anti-pyretic and analgesic effects, NSAIDs also share many adverse effects (Sedor *et al,* 1986), of which those affecting the gastrointestinal and renal systems are the most commonly described. However toxicity differs markedly between species and from one NSAID to another (Mazué *et al,* 1983).

a) Gastrointestinal

The most common side effects of NSAIDs involve the gastrointestinal tract. Specific side effects and their severity vary between drugs but include vomiting, gastrointestinal pain, diarrhoea or constipation, and mucosal damage ranging from petechial haemorrhages to severe ulceration and even perforation (Carson and Strom, 1988). Because of the blood

and plasma protein loss, gastric and intestinal ulcerations are often accompanied by secondary anaemia and hypoproteinaemia (Jenkins, 1987). The primary cause of the gastrointestinal side effects is the inhibition of prostaglandin synthesis in the gastric mucosa. Mucosal prostaglandins normally inhibit gastric acid secretions and appear to have a "cytoprotective effect" by promoting gastric and intestinal mucus production and strengthening the mucosa against the back-diffusion of acid from the lumen of the stomach into the submucosal tissue, where it can cause damage (Ivey, 1986). Also, gastric prostaglandins are important in the maintenance of gastric submucosal blood flow (Rainsford, 1975). NSAIDs are generally weak organic acids with pKa values of 3-6 and so the drug remains largely unionised in the acid medium of the stomach. Being lipid soluble in the stomach, NSAIDs are able to diffuse through the lipid bilayer of the gastric lining cells. Once in these cells where there is a relatively higher pH, the NSAID re-ionises and becomes trapped, resulting in prolonged and relatively high concentrations of drug within the gastric lining cells. This causes cells to die with the development of an ulcer (Ivey, 1986). The drug's anti-inflammatory effect itself then inhibits the inflammatory reaction and repair process around the dead cell and ulcer, thereby preventing the ulcer from healing. Gastrointestinal intolerance can occur whether the NSAID is given orally or systemically. However, the gastric effects are worse when the drug is administered orally rather than parenterally, as this results in higher local concentrations (Ivey, 1986).

b) Renal

Prostaglandins PGE_2, and PGI_2 are potent renal vasodilators in dogs (Fulgraff *et al*, 1974; Hill and Moncada, 1979). They are produced and metabolised locally by the kidney, where they contribute to the autoregulation of renal blood flow, renin release, tubular ion transport, and water metabolism (Lifschitz, 1981; Schnermann and Briggs, 1981; Kokko, 1981; Walker *et al*, 1981). In the normal animal renal prostaglandins do not appear to be important in the control of resting renal blood flow or glomerular filteration rate (Kore, 1990). However, in adverse conditions where systemic vasoconstriction has been induced by mediators such as noradrenaline, alpha adrenergic stimulation and angiotensin II, renal prostaglandins act as vasodilators to maintain renal blood flow and urine output, thereby preserving renal perfusion and preventing the development of acute renal failure (Rhymer, 1985; Pirson and van Ypersele de Strihou, 1986; Patrono and Dunn, 1987; Boothe, 1989). In general, stimuli that produce renal vasoconstriction, renal ischaemia or both, produce an increase in the renal synthesis of PGE_2, which is considered to be compensatory, in that these vasodilatory compounds attenuate the extent of renal vasoconstriction (McGiff *et al*,

1970). In these situations if the potentially vasodilating effects of PGE_2 and PGI_2 are eliminated by the use of NSAIDs, renal plasma flow and the glomerular filteration rate decrease, resulting in prerenal azotemia and renal failure from unopposed renal vasoconstriction (Jenkins, 1987; Boynton, 1988; Aronoff, 1992).

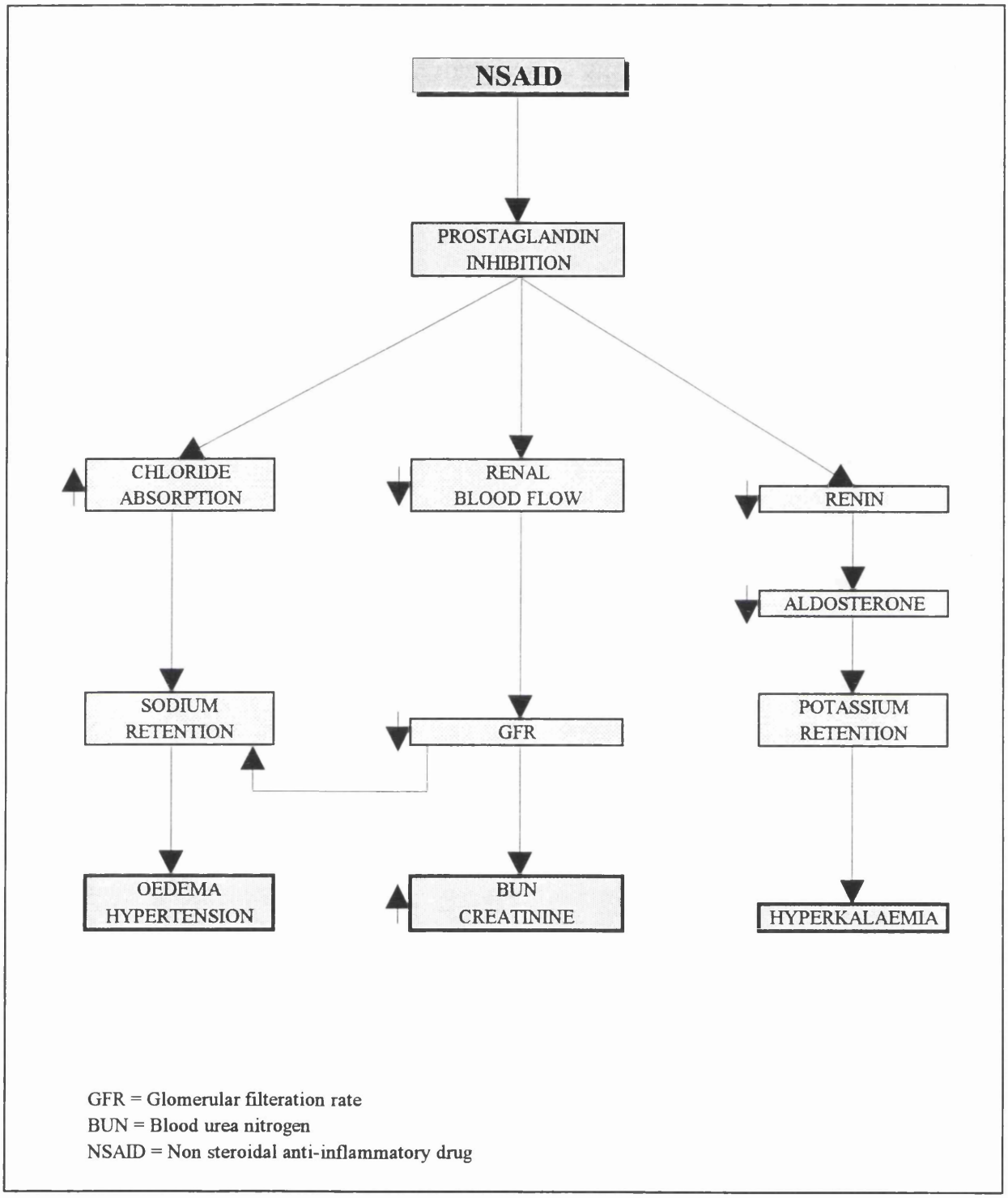
Prostaglandins in the kidney also play an important role in salt and water homeostasis. Prostaglandins are known to be natriuretic and NSAIDs, by interfering with this action, can cause sodium and water retention and oedema (Kimberley and Plotz, 1977; Kincaid-Smith, 1986).

With chronic use, and again in the presence of predisposing factors, NSAIDs have been incriminated in the development of papillary or renal crest necrosis and chronic intestitial nephritis (Abraham and Keane, 1984). However the precise pathogenesis of these lesions remains unclear. In humans, acute allergic interstitial nephritis has been reported as a direct effect of NSAIDs (Abraham and Keane, 1984). It is an idiosyncratic reaction, where the patient develops acute renal failure with proteinuria. It can occur any time after initiation of NSAID treatment, however it is usually seen 2 weeks to 18 months after initiation of chronic NSAID therapy. Recovery is usual when NSAID therapy is terminated (Aronoff, 1992) (Figure 3).

1.3.4. Pharmacokinetics of NSAIDs

Most NSAIDs, being relatively small weak acids, are readily absorbed from the proximal small intestine or stomach (Jenkins, 1987). However a number of factors may influence this process (Davis, 1983), the most important being species, gastrointestinal motility, intragastric pH, presence of food, pathological lesions, and concentration of the drug (Jenkins, 1987). Peak concentrations are delayed and reduced when NSAIDs are administered with food but feeding generally has no effect on the bioavailability of the drug (Lombardino, 1985). However, differences in drug disintegration and dissolution may lead to differences in bioavailability of some drugs (Brater, 1988). Although the oral route of administration is the most commonly used, a few NSAIDs are available as solutions for parental administration. However, with the exception of flunixin meglumine and carprofen, most of these preparations are highly alkaline and are, therefore, irritant to the tissue when administered by intramuscular or subcutaneous injection (Jenkins, 1987). Because NSAIDs are largely ionised at physiological pH, they are essentially confined to plasma and extracellular fluid (Flower *et al,* 1986; Brater, 1988; Conlon, 1988). The

Figure 3 : The effect of NSAID-induced prostaglandin synthetase inhibition on renal physiology.



volume of distribution of NSAIDs is small, often less than 10% of body weight (Verbeeck,1983). This is because a very large amount of drug is bound to albumin, leaving only a small portion unbound and pharmacologically active (Verbeeck,1983; Murray and Brater, 1990). Despite that, their lipid solubility enhances penentration of cell membranes (Boothe, 1989) and the extravasation of plasma proteins through damaged capillaries into inflamed tissue further concentrates the amount of NSAID at the target site. Consequently, because of the acidic pH of inflamed tissues the local therapeutic concentrations of NSAIDs may be retained in the inflamed tissue after plasma concentrations have declined to subtherapeutic levels (Higgins, 1985; Lees *et al,* 1987). As a result of this, NSAIDs have a duration of analgesic activity far in excess of that predicted by their relatively short half-lives and there is increasing evidence to suggest that such drugs can be given less frequently than would be predicted by their plasma concentrations, without compromising their effectiveness.

Metabolism of NSAIDs is usually hepatic, mediated by the mixed function oxidase system (Davis, 1983; Dubinsky *et al,* 1987; Verbeeck, 1988). Enterohepatic circulation is common in dogs (Duggan *et al,* 1975; Risdall *et al,* 1978; McKellar 1989). Conjugates in the bile may be cleaved in the gut to generate the free acid which can then be reabsorbed in the lower intestine. This regeneration of active drug may cause local mucosal irritation and damage, and it also prolongs the half-life of the drug.

Excretion is mainly renal, usually by glomerular filtration and tubular secretion but some biliary elimination of conjugates is possible (Jenkins, 1987). The rate of renal excretion is frequently pH dependent (Flower *et al,* 1986) and the reabsorption from the renal tubules of acidic NSAIDs, which have a pKa of between 3 and 7.5, is sensitive to alterations in urinary pH. Excretion is increased as the urine is alkalinised, a factor which is important in the treatment of drug overdose.

There is species variation in both metabolism and excretion of the different NSAIDs (Lees and Higgins, 1985). This variation in the elimination kinetics of NSAIDs makes interspecies extrapolation extremely hazardous because cumulative tissue concentrations of NSAIDs may result in frank toxicity and are potentially fatal (Jenkins, 1987). The classic example of this phenomenon is the plasma half-life of aspirin in the horse, dog and cat, which is 1, 8 and 38 hours respectively. In addition, within the canine species, different breeds are said to demonstrate different rates of drug clearance. Beagles are said

to clear certain drugs more quickly than do mongrels (Runkel *et al,* 1972; Freh *et al,* 1979; Freh and Rieh, 1981; Freh and Löscher, 1985).

NSAIDs are without exception characterised by a high degree of binding to plasma proteins, some as high or higher than 99% e.g. meclofenamic acids (99.8%); flunixin and naproxen > 99% (Murray and Brater, 1990). Because of the high protein binding of NSAIDs, the pharmacokinetics of these compounds and the availability of free pharmacologically active drug can be altered by hypoproteinemia and the presence of other highly protein bound drugs.

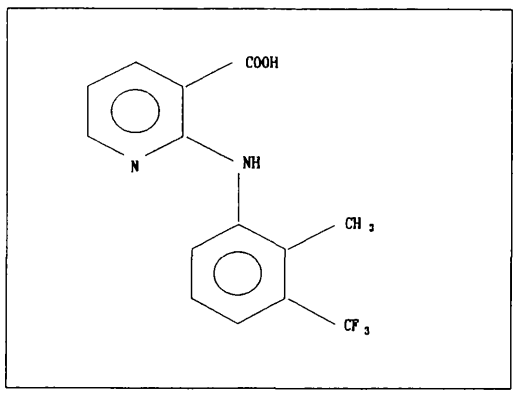
1.4 FLUNIXIN MEGLUMINE

Flunixin meglumine (2{2-methyl-3 trifluromethylanilino}-nicotinic acid) is a nicotinic acid derivative with both analgesic and antipyretic activity (Sackman, 1991). It was approved for equine use alone in 1977 (Ciofalo, 1977), and was licensed for use in the dog in the U.K. in 1989. It is available both as an oral (granules and tablets) and a parental formulation (sub-cutaneous, intramuscular and intravenous routes). Figure 4 shows the chemical structure of flunixin.

1.4.1 Mechanism of action of flunixin

Flunixin meglumine acts as a reversible inhibitor of the enzyme cyclo-oxygenase (Semrad *et al,* 1985; Higgins *et al,* 1986; McKellar *et al,* 1989).

Figure 4- Chemical structure of flunixin meglumine



1.4.2 Uses of flunixin

Flunixin is a potent analgesic especially in inflamed soft tissue, and is effective in controlling both somatic and visceral pain (Zederfeldt *et al,* 1977; Jenkins, 1987). It is indicated for the alleviation of inflammation and pain in acute episodes of musculoskeletal disorders (McKellar *et al,* 1991a). Dubinsky *et al* (1987), as well as Reid and Nolan (1991), found flunixin to be as effective as opioids in controlling post-operative pain. It can be used as the sole analgesic for moderate to severe pain or as an adjunct to opioids when pain is extremely severe and difficult to control. Flunixin can also be used as an adjunct in the therapy of endotoxic or septic shock (McKellar *et al,* 1991a). It is useful in the treatment of inflammatory occular conditions, as it inhibits the prostaglandins which are thought to cause conjunctival hyperaemia and congestion of the iris vasculature (McKellar *et al,* 1991a). It is generally thought to be more effective if it can be given prophylactically in ocular cases, prior to surgery (Vestre and Krohne, 1988).

1.4.3 Pharmacokinetics of flunixin

The pharmacokinetics of flunixin have been studied in conscious healthy dogs (Hardie *et al,* 1985; McKellar *et al,* 1989; McKellar, 1991b) and its average half-life after i.v. administration of 1.1 mg/kg, was found to be approximately 3.5 hours. As flunixin penentrates acute inflammatory exudate readily and is cleared from it slowly, the actual elimination of the drug from the site of inflammation is considerably slower than the plasma elimination half-life, thereby providing analgesic and anti-inflammatory effects at the site of injury well beyond the half-life of the drug (Rubin and Papich, 1988). In horses, concentrations of flunixin in exudate may be up to four times as high as concentrations in plasma after intravenous administration of 1.1 mg/kg, and significant eicosanoid inhibition remains at the site of inflammation for up to 24 hours (Lee and Higgins, 1984; Higgins *et al,* 1986). It is likely that similar peripheral disposition of flunixin will occur in the dog (McKellar *et al,* 1989; McKellar *et al,* 1991a). Hence, despite the relatively short plasma elimination half-life in the dog, the recommended interdosage interval of 24 hours can be justified. This localisation of the drug at the site of injury may allow for a high level of therapeutic effect while simultaneously avoiding undesirable side effects.

1.4.4. Toxicity of flunixin

Flunixin is a potent analgesic but has a narrow therapeutic index in the dog (McKellar *et al,* 1989). A once daily regimen of flunixin (1.1 mg/kg) has been recommended by McKellar *et al* (1989) as this allows the elimination of most of the drug from plasma, provides a wash out period for circulating drug and thus minimises any risk of systemic accumulation and toxicity (McKellar *et al,* 1989). It should however only be used for a maximum of 3 days, with the course repeated after 4 days (i.e. 3 days on/4 days off schedule), since prolonged continuous therapy often results in gastrointestinal problems (Cosenza, 1984; Dow *et al,* 1990). It is for this reason that its use is limited in osteoarthritis to the control of pain and inflammation only in acute exacerbations of the clinical signs and not for long term control of the condition.

1.5 ANAESTHESIA AND RENAL BLOOD FLOW

According to Schwenzer and Miller (1989), renal blood flow (RBF), in healthy animals far exceeds the kidney's metabolic demands, with each kidney receiving approximately 10 percent of the cardiac output, while they constitute only 0.4 percent of the body weight (Rosen, 1972). Almost all of the blood supplied to the kidney flows through the afferent arterioles of the glomeruli (Rosen, 1972). The cortex receives three-quarters of the total renal blood flow, while the juxtamedullary cortex and outer medulla receive one-fifth of the flow at a slower rate. The flow to the inner medulla is even slower, allowing the maintenance of the high concentration of solute observed in this region. Renal blood flow is regulated by both intrinsic and extrinsic factors. Local and humoral factors govern passive changes in the vascular resistance of the afferent and efferent arterioles to maintain renal blood flow over a wide range of mean arterial pressures (80-180 mm Hg). The ability of the kidney to autoregulate its blood flow and hence control its glomerular filtration rate over a wide range of perfusion pressures has been described by numerous theories (Bevan *et al,* 1979), but is probably centred in the afferent arteriole (Schwenzer and Miller, 1989) .

General anaesthesia produces haemodynamic changes that indirectly alter renal blood flow and function (Schwenzer and Miller, 1989). For many years it was thought that anaesthesia decreased renal blood flow due to lowered blood pressure and a compensatory renal vasoconstriction. However, Priano (1985) demonstrated that a moderate level of halothane does not significantly decrease renal blood flow in dogs but decreases renal

vascular resistance in the face of decreased blood pressure, thus maintaining renal blood flow, i.e., autoregulation is preserved (Schwenzer and Miller, 1989). Hunter *et al* (1981), recorded similar results. They stated that in dogs given Halothane at 1 MAC, renal autoregulation was preserved and renal blood flow and urine production well maintained, until a marked fall in cardiac output and mean arterial blood pressure occurs.

Antidiuretic hormone (ADH) is secreted by the hypothalamus to osmoregulate and conserve volume, by increasing the permeability of the collecting ducts and allowing reabsorption of water (Schwenzer and Miller, 1989). It was originally thought that anaesthesia caused a direct release of ADH and decreased urine output (Papper *et al*, 1957). However, Philbin and coworkers (Philbin and Coggins, 1978) demonstrated that light halothane anaesthesia did not measurably affect ADH levels in man. Surgical stimulation, however, produced marked increases in plasma ADH levels. Levels return to normal over 2-3 days after major surgery as long as there is haemodynamic stability (Moran *et al*, 1964).

The renin-angiotensin-aldosterone system is intimately involved in the regulation of blood pressure and electrolyte balance, as well as in the regulation of renal blood flow (Schwenzer and Miller, 1989). A reduction in blood volume or pressure, or vasoconstriction of renal arteries as a result of sympathetic stimulation accompanying surgery, decreases afferent arteriole pressure which leads to renin release from the kidney (Blaine and Davis, 1971). Renin converts angiotensinogen, to angiotensin I, which is then converted to angiotensin II by converting enzymes in the lungs and plasma. Angiotensin II is a potent renal vasoconstrictor decreasing renal blood flow (Bevan *et al*, 1973). It also stimulates the adrenal cortex to release aldosterone which increases tubular resorption of sodium and excretion of potassium, leading to expansion of the extracellular fluid compartment and correction of blood pressure. By causing a rise in blood pressure, aldosterone acts as a feedback mechanism to shut off further renin release (Schwenzer and Miller, 1989). There are conflicting reports on the effect of anaesthesia and surgery on the renin-angiotensin system, Pettinger and colleagues (1975) demonstrated increased plasma renin activity in rats, using halothane while Robertson and Michelakis (1972), Bailey *et al* (1975) and Miller *et al* (1978) all showed no change in plasma renin activity in man and in rats using halothane anaesthesia. Most agree, however, that plasma renin activity rises significantly with surgical incision.

Anaesthesia has been associated with increased aldosterone levels (Schwenzer and Miller, 1989) which may indirectly be due to changes in arterial blood pressure and sympathetic stimulation via the renin-angiotensin system rather than changes in electrolyte balance. The mechanism of this is not been clearly understood.

Vasodilating prostaglandins have been isolated from the renal medulla (Horton, 1972). The effect of renal prostaglandins in regulating renal blood flow remains controversial. Arachidonic acid stimulates renin release in several animal models via its conversion to prostaglandins, specifically PGE_2 and PGI_2 and prostacyclins (Freeman *et al,* 1984). Oates *et al* (1979), through the use of pharmacological inhibition of prostaglandin synthesis with NSAIDs have provided evidence of prostaglandins modulating role rather than a controlling role in renin-angiotensive system release. Angiotensin II also stimulates the secretion of prostaglandins. Prostaglandins, specifically PGE_2 appear to oppose the vasoconstrictive effects of angiotensin in acute renal failure (Schwenzer and Miller, 1989). By using NSAIDs which inhibit prostaglandin synthesis, angiotensin release is unopposed and can severely compromise renal blood flow (Stoff and Clive, 1983).

1.6 OBJECTIVE OF STUDY

NSAIDs are convenient and useful drugs to use as analgesics in dogs undergoing surgery. As flunixin was shown to be a potent analgesic, it was considered the NSAID of choice, to treat post-operative pain in dogs. Experimental studies, have shown that acute pain may be eliminated or reduced if the excitability of the CNS is suppressed with opioids before it receives a nociceptive input (Woolf and Wall, 1986b; Dickenson and Sullivan, 1987). Similarly, anti-nociceptive procedures were found to be less effective when applied post-injury (Woolf and Wall, 1986a and b; Dickenson and Sullivan, 1987; Coderre *et al*, 1990). Consequently, the of timing of analgesia has been considered important in the treatment of post-operative pain (Woolf and Wall, 1986a and b; Wall, 1988; Woolf, 1989). In order, to obtain the maximum benefit from its anti-inflammatory action, it appeared reasonable to administer flunixin before tissue trauma occured, i.e. before surgery. Recently however, flunixin given peri-operatively has been implicated in renal toxicity in dogs following surgery (McNeil,1992; Elwood, 1992). Both reported cases of fatal renal toxicity in dogs given flunixin in the intra-operative period along with other drugs, and they suggested that flunixin administration was best avoided intraoperatively. Consequently, the manufacturers of flunixin, have since recommended that flunixin administration should be delayed until the end of surgery.

Pharmacokinetic studies on flunixin have been performed in conscious dogs (Hardie, 1985; McKellar *et al,* 1989; McKellar *et al,* 1991b), but no kinetic studies have been carried out on dogs under, or just recovering from anaesthesia, which is the period when the drug is most frequently used in clinical practice. All general anaesthetics alter renal haemodynamics (Deutsch and colleagues, 1969) and clinically useful concentrations of halothane cause a reduction in the glomerular filtration rate which may theoretically enhance the toxicity of NSAIDs. General anaesthetics also cause a decrease in hepatic blood flow (Ahlgren *et al,* 1967) which may affect metabolism and pharmacokinetics of drugs given to the anaesthetised animal. This study was undertaken to determine the pharmacokinetics of flunixin in the anaesthetised dog, injected prior to the start of surgery, as well as in the immediate post-operative period, and to determine whether there was any significant difference in the pharmacokinetic parameters obtained between these 2 groups. Alterations in kinetic parameters contributing to higher plasma levels of the drug and prolongation of its action might be expected to contribute to drug toxicity such as that described by McNeil (1992) and Elwood (1992).

A further objective was to monitor renal function in a group of dogs which had anaesthesia and surgery but no NSAID and to compare this with the dogs given flunixin pre and post surgery. BUN, serum creatinine and phosphate were used as indices of renal function, as most patients suffering from NSAID-induced renal damage, experience a sudden decrease in their glomerular filtration rate (Aronoff, 1992), and demonstrate increases in BUN and serum creatinine levels within the first 24 hours of treatment with the NSAID (Aronoff, 1992). In the light of these findings it was hoped to elucidate whether giving flunixin post surgery is indeed safer than the pre-operative use of the drug.

2. MATERIALS & METHODS

2.1 ANIMAL DETAILS

Thirty mixed breed dogs undergoing anaesthesia and surgery were included in this study. The animals were between 7 months and 7 years of age and they weighed between 17 and 44 kg. Details of individual animals and surgical procedures are shown in Table 1 and Table 2. All dogs were free from signs of cardiovascular and respiratory disease and had not received any non-steroidal anti-inflammatory drugs (NSAID) or corticosteriod medication for at least ten days prior to anaesthesia.

2.2 DRUG AND DOSING

A commercially available formulation of flunixin meglumine injection, 50 mg/ml, was used in this study (Finadyne, Schering-Plough Animal Health, Suffolk, U.K.).

The manufacturer's recommended dose of flunixin meglumine, 1.1 mg/kg was administered intravenously (i.v.) to each dog involved in the study.

2.3 TRIAL DESIGN

The dogs were allocated randomly into 3 groups of 10 dogs each. Group A (n=10) received flunixin meglumine, 1.1 mg/kg, i.v. during anaesthesia, prior to the start of surgery, Group B (n=10) received flunixin meglumine, 1.1 mg/kg, i.v., immediately after surgery and anaesthesia had been terminated and Group C (n=10) received no flunixin.

2.3.1 Anaesthetic regime for dogs in the study

All dogs in the trial were examined clinically and weighed the day prior to anaesthesia and surgery. They were starved overnight and water was withheld on the morning of anaesthesia and surgery. On the day of anaesthesia, the dogs were re-examined. In dogs trial No: 4, 6, 7, 8, 9 and 10 (group A), and all dogs in group B (Trial No: 11-20) indirect blood pressure readings were taken using the DINAMAP (Critikon, Model number:1846sx; Tampa FL 33630).

All animals were premedicated with an intramuscular injection of acepromazine maleate (ACP Injection; C-Vet limited; 2 mg/ml) at a dose rate of 0.05 mg/kg for medium sized

TABLE 1

Details of individual animals used in the study together with the surgical procedure undertaken. Dogs numbered 1-10 received flunixin meglumine, 1.1 mg/kg, i.v. during anaesthesia before the start of surgery, while dogs numbered 11-20 received flunixin meglumine, 1.1 mg/kg, i.v. immediately after surgery and anaesthesia had terminated.

TRIAL NO	BREED	SEX	AGE	WT (Kg)	SURGICAL PROCEDURE
1	Greyhound	F	4 years	22.5	Implant removal
2	Rottweiler	M	10 months	38.5	OCD flap removal
3	German Shepherd Cross	F	2.5 years	37	Flexor tendon repair
4	Newfoundland	F	3.8 years	44	Biopsy mass
5	Labrador/ Retriever Cross	M	7 months	33	Removal of ununited coronoid process
6	German Shepherd	F	5 years	39	Anal furunculosis
7	Dalmatian	M	8 months	29.8	Arthrotomy-shoulder
8	Cross-Breed	M	4.5 years	28	Castration
9	German Shepherd Cross	M(N)	5.5 years	36	Explore wound in neck
10	Grey Hound	F	4.5 years	28.75	Elective dental
11	Irish Spinone	F	9 months	31	OCD flap removal
12	Labrador Cross	F(N)	4.5 years	44	Carpal arthrodesis
13	Rottweiler	F(N)	1.5 years	17.8	Cruciate repair
14	Bernese Mountain Dog	M	1 year	44.5	OCD flap removal
15	Grey Hound	F	7 years	26.25	Elective dental
16	Lurcher Cross	M	4 years	26	Internal fixator application
17	Border Collie	M	4 years	27	Anal furunculosis
18	Retriever	F(N)	2.1 years	35	Cruciate repair
19	Border Collie	M	3.5 years	22.75	Enucleation
20	German Shepherd	F	5.5 years	36	Ovario-hysterectomy

ABBREVIATIONS USED

No - Number
WT - Weight
Kg - Kilogramme
F - Female
F(N) - Neutered female
M(N) - Neutered male
M - Male
OCD - Osteochondrosis

dogs or 0.03 mg/kg for large breed dogs. The dogs were left undisturbed for approximately 45-60 minutes while sedation took effect.
A sterile indwelling over-the-top type teflon intravenous catheter (Intraflon 2; Vygon Laboratoires Pharmaceutiques, France) with a 3-way tap attached was placed in the cephalic vein. Anaesthesia was induced using 2.5% thiopentone sodium (Intraval sodium; Rhoñe Mérieux limited) given intravenously through the preplaced catheter at a dose of approximately 10 mg/kg. Endotracheal intubation was performed immediately after induction and anaesthesia was maintained with halothane (Fluothane; ICI Pharmaceuticals,U.K.) in a 2:1 nitrous oxide/oxygen mixture delivered via a non-rebreathing Magill circuit with a fresh gas flow of 200 ml/kg/minute. Immediately after anaesthesia was induced, Hartmann's solution (Aqupharm; Animal Care Limited) was administered via the catheter already present in the cephalic vein, at a rate of 5 ml/kg/hr.

Monitoring during anaesthesia

Pulse and respiratory rates were monitored throughout anaesthesia and recorded at 5 minute intervals. Blood pressure was measured using the DINAMAP which measures blood pressure indirectly using the principle of doppler shift sphygmomanometry. In order to ensure that indirect blood pressure readings were relatively accurate, care was taken to ensure firstly, that the cuff fitted snugly around the chosen appendage. This was achieved by using a cuff the width of which was 0.4 x the circumference of the limb in centimeters (Hassler et al, 1977; Geddes et al, 1980), at the site of application and secondly, that the cuff lay at the level of the heart whilst the blood pressure readings were being taken. Recordings were taken every 5 minutes from induction of anaesthesia until the dog regained sternal recumbency. End tidal carbon dioxide ($ETCO_2$) levels were measured during surgery in dogs trial number 1, 2, 3, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19 and 20, using an infrared carbon dioxide analyser (Normocap CO_2 & O_2 monitor; Datex Instrumentarium, Finland) and were recorded from the beginning of surgery every 5 minutes until the trachea was extubated.

Ten minutes before the end of anaesthesia, 100% oxygen was administered as the sole carrier gas for the remainder of the procedure. As the halothane was switched off, administration of Hartmann's intravenous fluid was terminated. The dogs were placed in recovery kennels after extubation until they regained full consciousness.

In all 20 dogs undergoing the trial, blood was collected prior to the induction of anaesthesia and flunixin administration, and biochemical analysis was performed on the samples. The biochemical parameters examined were urea, creatinine and phosphate, together with total protein, albumin, globulin, sodium, potassium and chloride, if the samples were large enough to permit these further tests. Blood samples at 12 and 30 hours after flunixin administration, were also sent for biochemical analysis, to determine whether there was a significant rise in the above mentioned parameters as a result of flunixin administration. In dog no 8, a further blood sample was taken for biochemical analysis, 60 days after flunixin administration, while in dogs no 10 and 15, 15 day and 60 day samples were taken and in dog no 10, a 150 day sample was taken for biochemical analysis.

To determine whether anaesthesia and surgery without flunixin administration altered biochemical parameters, a control group of 10 dogs, Group C (Trial Nos: C1 - C10) were used. These dogs underwent exactly the same anaesthetic regime as the trial dogs in Group A and Group B, the only difference being that they received papavertum (Omnopon 10 paediateric; Roche), 0.2-0.4 mg/kg i.m., as the analgesic in the intra- and post-operative period. Details of the individual animals in the control group, and the surgical procedure undertaken by them are given in Table 2.

2.3.2 Administration of Flunixin meglumine

Group A

After induction of anaesthesia and before the start of surgery, once the dog was considered to be in a stable plane of anaesthesia, flunixin meglumine, 1.1 mg/kg, was administered through the indwelling cephalic catheter as a slow intravenous injection over a period of 30 seconds. Blood samples were taken from a catheter placed in the lateral saphenous vein.

Group B

On completion of surgery and immediately on termination of anaesthesia, flunixin meglumine, 1.1 mg/kg, was administered through the indwelling cephalic catheter as a slow intravenous injection over a period of 30 seconds. Blood samples were taken from the saphenous catheter.

2.3.3 Blood sampling details

Blood samples (2-3 ml) were withdrawn from the lateral saphenous vein catheter into heparinised plain sterile plastic 10 ml tubes (Monovette® blood collection system, SARSTEDT, Germany) immediately before intravenous administration of flunixin meglumine (pre-sample); then 2, 5, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 12, 20, 24 and 30 hours after administration of flunixin. After collection, the blood samples were gently mixed and placed immediately in an ice box. The patency of the saphenous vein catheter was maintained during the 30 hour bleeding period by flushing it with diluted heparin saline solution (10 units of heparin/ ml of saline) after every blood sample was taken. Care was taken to discard the heparin solution before each blood sampling time.

2.4 STORAGE OF SAMPLES

The heparinised blood samples from each dog were centrifuged at 1400 g* force for 15 minutes in a refrigerated centrifuge at 4°C within 4 hours of collecting the blood. The plasma was then decanted into 5 ml plastic bottles and was frozen at -20°C until analysed, within 2 months of collection. Previous studies carried out in the Department of Veterinary Pharmacology, Glasgow University, indicated that there was no loss of drug when stored over this time period.

2.5 ANALYSIS OF SAMPLES FOR FLUNIXIN

The concentration of flunixin meglumine in plasma was analysed by High Performance Liquid Chromatography (HPLC).

2.5.1 Extraction and reconstitution of drug

Each plasma sample was defrosted at room temperature, and 0.25 ml of plasma was placed in a 10 ml stoppered glass test-tube. Seventy-five microlitres of citrate/phosphate buffer (PH 3) [20.5% M/5 Na_2HPO_4 : 79.5% M/10 Citric acid] was added to the sample in order to acidify it. Six ml of chloroform (HPLC Grade - Rathburn Chemicals limited) was then added to the buffered plasma and a clean glass stopper placed tightly on the test-tube. The mixture was shaken gently for 10 minutes on a rotary mixer and then

centrifuged at 2800 g* force for 15 minutes in a refrigerated centrifuge at 4°C. Following centrifugation, 4 ml of the lower chloroform layer was recovered and transferred into clean 10 ml thin walled glass centrifuge tube. The aliquot was then evaporated to dryness on a Dri-block (Model DB.3 Techne, Cambridge ltd) at 50°C under a gentle stream of air. Following evaporation to dryness, the residue was reconstituted in 150 µl of methanol. (HPLC Grade - Rathburn Chemicals limited). This sample was vortexed for 5 seconds, placed in a sonic bath for 2 minutes and revortexed for 5 seconds to ensure reconstitution of the drug in methanol. Subsequently, 125 µl of this mixture was transferred into a clean glass vial which was capped with cling film and placed in an autoinjector.

2.5.2 Injection of Drug

All samples were analysed on an HPLC system (Spectra Physics Isochrome LS Pump, Model 231) which was equipped with an autoinjector (Gilson Auto-sampling Injector, Model 231-401) and a variable wavelength detector (Spectra 100 UV-Vis Detector, Model No A009-307A 4/89). The output from the detector was connected to a chart recorder (RIKADENKI Kogyo Co ltd, Model No R-01).

The samples were chromatographed on a C-8, 5 µ BDS Hypersil column with guard, using 70:30 methanol: water mobile phase containing 400µl/100ml perchloric acid [1/55 dilution of 70% H_3P04]. Permaganate distilled water was used instead of undistilled water as impurities capable of degrading the HPLC column are present in undistilled water. The mobile phase was pumped through the column at a flow rate of 1 ml/minute. Complete chromatographic parameters are listed in Table 3

2.5.3 Drug recovery and calculations

In order to calculate the concentration of flunixin in the plasma sample, a known standard concentration of flunixin (External standards) was injected after every plasma sample. The peak height of flunixin in the plasma sample was then compared to the peak height of the external standard. Allowances were made for the physical recovery of the drug from plasma, as described below.

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* g = gravitational

TABLE 2: Details of individual animals used in the control study together with the surgical procedure undertaken. Dogs numbered C1-C10 received flunixin meglumine, 1.1 mg/kg, i.v. during anaesthesia before the start of surgery.

TRIAL NO	BREED	SEX	AGE	WT (Kg)	SURGICAL PROCEDURE
C1	Newfoundland	F(N)	4 years	40	Cruciate repair
C2	Border Terrier	F	7.5 years	6.5	Cataract removal
C3	Labrador	M	7 months	29.5	OCD flap
C4	Cross	M	6 years	15.5	Trephination of eye
C5	Cross	M	5 years	15.5	Examine eye
C6	Bouvier	F(N)	2.5 years	32	Repair metacarpal fracture
C7	Rottweiler	M	2 years	53	Cruciate repair
C8	Airedale	F(N)	7.5 years	31	Total ear canal ablation
C9	Rottweiler	F	4 years	37	Cruciate repair
C10	Staffordshire Terrier	M	2.5 years	17	Cruciate repair

ABBREVIATIONS USED

No - Number WT - Weight Kg - Kilogramme M - Male
F - Female F(N) - Neutered female OCD - Osteochondrosis

TABLE 3 - Chromatographic settings used for the determination of flunixin in dog plasma

SYSTEM CONTROLLER	
Flow Rate:	1 ml/minute (PSI = 1500 -1800)
Loop Size:	20 µl
AUTOINJECTOR	
Injection volume:	15 µl
Analysis Time:	6.5 minutes
DETECTOR	
Wave length:	287 nm
Absorbance	variable depending on the drug concentration (0.001 - 0.05)
CHART RECORDER	
Chart Speed:	30 cm/hr
Recorder setting:	10 mV

EXTERNAL STANDARDS

A stock solution of flunixin meglumine, 1 mg/ml in methanol was prepared using flunixin meglumine powder (QC Number: 091889, CAS Number: 42461-84-7, Expiry date: 1994). From this stock solution the following flunixin standards were prepared, 500, 200, 100, 40, 20, 10, 5, 2, 1 and 0.5 µg/ml. The standards were stored under refrigeration at 4°C when not in use. Fresh standards were made every 3 months.For each batch of extracts that were performed, spiked plasma samples with known concentrations of flunixin (0.25, 1, 2, 5, 10 and 25 µg/ml) were extracted simultaneously, so as to determine the mean recovery of flunixin in every batch of extractions that were carried out. Allowances were made for the physical recovery of the drug from plasma. The expected proportion of flunixin extracted from chloroform was 66 %, as only 4 ml of chloroform from the original 6 ml added was recovered.

SPIKED SAMPLES

Spiked plasma samples were prepared by adding 12.5 µl of known concentrations of flunixin meglumine (external standards), to 0.25 ml of blank canine plasma. The following spiked plasma samples were made:

0.25 μg/ml flunixin- Add 12.5 μl of 5 μg/ml flunixin (ext std)[46] to 0.25 ml canine plasma
1 μg/ml flunixin----- Add 12.5 μl of 20 μg/ml flunixin (ext std) to 0.25 ml canine plasma
2 μg/ml flunixin----- Add 12.5 μl of 40 μg/ml flunixin (ext std) to 0.25 ml canine plasma
5 μg/ml flunixin----- Add 12.5 μl of 100 μg/ml flunixin (ext std) to 0.25 ml canine plasma
10 μg/ml flunixin--- Add 12.5 μl of 200 μg/ml flunixin (ext std) to 0.25 ml canine plasma
25 μg/ml flunixin--- Add 12.5 μl of 500 μg/ml flunixin (ext std) to 0.25 ml canine plasma

The concentration of flunixin in spiked samples was determined by comparing the peak height of the spiked sample with the peak height of flunixin meglumine in external standards and adjusting the ratio for the expected 66.66% recovery. This allowed the mean recovery of flunixin for a specific extraction to be calculated.

The formula below was used to calculate the concentration of flunixin recovered in the spikes after extraction.

$$\% \text{ RECOVERY} = \frac{\text{Concentration of flunixin recovered}}{\text{Actual concentration of flunixin}}$$

$$\%\text{RECOVERY} = \frac{\text{Spike peak ht.*}}{\text{Std peak ht.*}} \times \text{Std conc.} \times \frac{\text{Analysis vol.}}{\text{Plasma sample vol.}} \times \frac{100}{66.66} \times \frac{1}{\text{Spike conc.}} \times 100$$

(* = Chromatogram peak height and Std = Standard)

Once the mean recovery of flunixin was determined for the particular extraction, the plasma concentration of flunixin in the test samples was calculated in a similar manner. A conversion factor (the reciprocal of the recovery determined from the analysis of the spikes) was used to adjust the calculated concentration in the extracted sample to derive the actual plasma drug concentration.

$$\text{FLUNIXIN RECOVERY} = \frac{\text{Sample peak ht.*}}{\text{Std peak ht.*}} \times \text{Std conc.} \times \frac{\text{Analysis vol.}}{\text{Plasma sample vol.}} \times \frac{100}{66.66} \times \frac{1}{\%\text{ Spike recovery}}$$

[46]ext std = external standard

2.5.4 Pharmacokinetic calculations

The plasma concentration data for flunixin in each dog was calculated by analysing the changes in the plasma drug concentration versus time, following a single intravenous bolus administration of the drug. All the pharmacokinetic analyses of concentration versus time data for each animal were performed using a non linear regression Fortran IV curve stripping pharmacokinetic computer programme, CSTRIP, (Sedman and Wagner, 1976). This programme generates up to 3 y-axis intercepts (B, A and P) and exponents (β, α and π) (last to first) for the equation best describing the data, and a linear correlation coefficient. The number of exponents best describing each data set was confirmed using Akaike's information criterion (Yamaoka *et al,* 1978).

The computed pharmacokinetic determinants obtained in CSTRIP were calculated using standard models and equations describing bi and tri-exponential decays. (Sedman and Wagner, 1976; Baggot, 1977)

The mathematical expression which best describes the plasma drug concentration-time profile for a bi-exponential decline following i.v. administration of a single dose of drug is :

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

Where Cp is the concentration of drug in plasm at at time t
A and B are "intercept" terms with dimensions of concentration (μg/ml)
α and β are the distribution and elimination rate constants respectively and are expressed in units of reciprocal time (hr^{-1})
e represents the base of the natural logarithm.

The mathematical expression which best describes the plasma drug concentration-time profile for a tri-exponential decline following i.v. administration of a single dose of drug is :

$$C_p = Pe^{-\Pi t} + Ae^{-\alpha t} + Be^{-\beta t}$$

Where P, A and B are "intercept" terms with dimensions of concentration (μg/ml)

π, α are the distribution rate constants and β is the elimination rate constant. The rate constants are expressed in units of reciprocal time (hr^{-1})

The elimination half life of a drug, $t_{1/2}$ β, is defined as the time required for the body to eliminate one-half of the particular drug.

$$t_{1/2}(\beta) = \frac{0.693}{\beta}$$

Vc (ml/kg) is the apparent volume of the central compartment calculated from Dose/Cp0.

Vdss (ml/kg) is the apparent volume of the distribution at steady state concentration calculated from Dose (i.v.).AUMC/AUC^2.

CL_b (ml/kg.hr) is the body clearance of a drug. It represents the sum of all clearance processes in the body and is calculated from Dose/AUC.

kel (hr^{-1}) is the first-order elimination rate constant for the disappearance of a drug from the apparent central compartment. It is calculated from the ratio of body clearance to the apparent volume of the central compartment.

Non compartmental analysis of the plasma flunixin concentration data was also carried out and mean residence time (MRT) calculated. MRT (hr) is a quantitative estimate of the persistence of a drug in the body, or the time for 63.2% of a drug to be eliminated. It is calculated from $AUMC_{obs}/AUC_{obs}$, where $AUMC_{obs}$ ($\mu g.hr^2/ml$) is the total area under the drug concentration time versus time or first moment curve, from time 0 to time infinity, after administration of a single dose. It is calculated using the trapezoid rule and from $A/\alpha^2 + B/\beta^2 + P/\pi^2$ (cal), and AUCobs ($\mu g.hr/ml$) is the total area under the drug concentration versus time or zero moment curve, from time 0 to time infinity, after administration of a single dose. It is calculated using the trapezoid rule (obs) and from $A/\alpha + B/\beta + P/\pi$ (cal). The observed area under the first moment curve value (AUMCob) and the the observed area under the curve value ($AUMC_{obs}$) were obtained from the C-STRIP FORTRAN IV compartmental computer programme.

2.5.5 Statistical analysis

Results are expressed as means ± standard error of the mean (SEM).

Comparison between weights, ages, anaesthetic and surgical times, in dogs in group A and group B,were made using an unpaired 't' test, as all these sets of results were found to be normally distributed, when normality plots were performed using MINITAB statistical computer package.

The difference in biochemical blood values, namely urea, creatinine, phoshate, total protein, albumin, globulin, sodium, potassium, chloride, and potassium from 0 hours to 12 hours, between the dogs in the control group C (Trial No C1-C10), were compared using a 'two sample t test', with the difference in biochemical values from 0 hours to 12 hours, in dogs in group A and group B. This was followed by determining whether there was any significant differences in the kidney biochemical blood values, in the same time period (0 hours to 12 hours) between dogs in group A (flunixin given prior to surgery) versus dogs in group B (flunixin given at the end of surgery), again using a 'two sample t test'. Similarly, comparisons between the differences in the biochemical blood parameters from 12 hours to 30 hours, between dogs in the control group C (Trial No C1-C10) versus dogs in group A and group B (Trial No 1-10) were made using the same test. This was followed by comparing the differences in biochemical parameters from 12 hours to 30 hours between dogs in group A versus group B.

The precision of the HPLC extraction procedure, in a given assay was assessed by determining the coefficient of variation, in replicated plasma samples, to which a known concentration of the drug flunixin was added (spiked samples) and the samples analysed in a single assay. This was known as intra-assay coefficient of variation or 'within day' variation, of the flunixin HPLC analysis procedure. Refer to appendix C, table C1. The degree of variation between the 20 assays (dogs trial numbers 1-20), performed on different days, the inter-assay coefficient of variation or 'between days' variation, is shown in appendix C, table C2.

Comparisons between pharmacokinetic parameters of dogs in group A versus dogs in group B were made using the Mann-Whitney U test, as these results were found not to be normally distributed when normality plots were performed using Minitab statistical software (version 7.2).

3. RESULTS

3.1 ANAESTHETIC DETAILS

Demographic details of the animals used in the study are given in table 4. All dogs were clinically normal prior to the start of the trial.

The mean age of dogs in group A was 3.19 $\pm$ 0.63 years (range, 7 months - 5.5 years), while in group B it was 3.38 $\pm$ 1.37 years (range, 9 months - 7 years). Dogs in group A weighed 33.66 $\pm$ 2.14 kg (range, 22.5 - 44 kg) and those in group B were 31.03 $\pm$ 2.94 kg (range, 17.8 - 44.5 kg). There were no significant differences in the ages or weights of the dogs in the 2 groups.

Details of the duration of anaesthesia and surgery together with the surgical procedure undertaken in each dog are documented in table 5. Details of the time at which the analgesic flunixin was administered relative to the start or end of anaesthesia are shown in table 6 (Group A) and table 7 (Group B). The mean anaesthetic time for dogs in group A was 109 $\pm$ 18 minutes, and in group B, 134 $\pm$ 19 minutes. The samples were normally distributed and there was no significant difference in the anaesthetic times between the 2 groups. The mean surgical time for dogs in group A was 50 $\pm$ 9 minutes, which was significantly less than for dogs in group B, 84 $\pm$ 13 minutes ($P < 0.05$). In group A, flunixin was administered approximately 12 $\pm$ 2 minutes after induction of anaesthesia and 45 $\pm$ 10 minutes prior to the start of surgery (table 6). In Group B, flunixin was administered approximately 6 $\pm$ 1 minutes after the termination of surgery and 4 $\pm$ 1 minutes after the termination of anaesthesia (table 7).

3.1.1 Physiological parameters

All animals in the trial remained stable throughout anaesthesia and recovery from anaesthesia was uneventful in all cases. Arterial blood pressure, pulse, respiration and $ETCO_2$ readings for individual dogs are presented in Appendix A (Table A1-A8). Graphical representation of individual dogs arterial blood pressure, pulse, respiration and $ETCO_2$ readings can also be found in Appendix A (Fig A1-A14).

A graph of the means $\pm$ SEM[47] of the mean arterial blood pressure, pulse, and respiratory readings was also plotted for dogs in group A and group B, versus time (Fig 5-7).

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[47]SEM = Standard error of means

TABLE 4 : DETAILS OF ANIMALS USED IN THE TRIAL

Dogs 1-10 (group A) received flunixin meglumine, 1.1 mg/kg, i.v, during anaesthesia before the start of surgery, while dogs 11-20 (group B) received flunixin meglumine, 1.1 mg/kg, iv, at the termination of anaesthesia. Anaesthesia was maintained in all cases with halothane in a 2:1 nitrous/oxygen mixture delivered via a non-rebreathing magill circuit, with a fresh gas flow of 200 ml/kg/minute.

TRIAL NO	BREED	SEX	AGE	WT (Kg)
1	Greyhound	F	4 years	22.5
2	Rottweiler	M	10 months	38.5
3	German Shepherd Cross	F	2.5 years	37
4	Newfoundland	F	3.8 years	44
5	Labrador/ Retriever Cross	M	7 months	33
6	German Shepherd	F	5 years	39
7	Dalmatian	M	8 months	29.8
8	Cross-Breed	M	4.5 years	28
9	German Shepherd Cross	M(N)	5.5 years	36
10	Greyhound	F	4.5 years	28.75
11	Irish Spinone	F	9 months	31
12	Labrador Cross	F(N)	4.5 years	44
13	Rottweiler	F(N)	1.5 years	17.8
14	Bernese Mountain Dog	M	1 year	44.5
15	Greyhound	F	7 years	26.25
16	Lurcher Cross	M	4 years	26
17	Border Collie	M	4 years	27
18	Retriever	F(N)	2.1 years	35
19	Border Collie	M	3.5 years	22.75
20	German Shepherd	F	5.5 years	36

ABBREVIATIONS

M = Male F = Female M (N) = Neutered male F (N) = Neutered female

WT = weight Kg = Kilogramme

Table 5 : Details of anaesthetic time, surgical time and surgical procedure undertaken in dogs 1-20, where dogs 1-10 (group A), received flunixin, 1.1 mg/kg, i.v., preoperatively, and dogs 11-20 (group B) received flunixin, 1.1 mg/kg, i.v., post-operatively.

TRIAL NO	ANAESTHETIC TIME	SURGICAL TIME	SURGICAL PROCEDURE
1	50 minutes	20 minutes	Implant removal
2	2 hours 28 minutes	50 minutes	Osteochondrosis flap removal
3	2 hours 41 minutes	1 hour 26 minutes	Flexor tendon repair
4	1 hour 14 minutes	11 minutes	Biopsy mass
5	2 hours 45 minutes	1 hour 12 minutes	Removal of ununited coronoid process
6	1 hour	40 minutes	Anal furunculosis
7	3 hours 5 minutes	1 hour 40 minutes	Arthrotomy-shoulder
8	1 hour 25 minutes	45 minutes	Castration
9	1 hour 57 minutes	33 minutes	Explore wound in neck
10	45 minutes	38 minutes	Elective dental
11	2 hours 45 minutes	1 hour 25 minutes	Osteochondrosis flap removal
12	3 hours 33 minutes	2 hours 13 minutes	Carpal arthrodesis
13	2 hours 33 minutes	1 hour 30 minutes	Cranial cruciate repair
14	3 hours 10 minutes	2 hours 10 minutes	Osteochondrosis flap removal
15	22 minutes	18 minutes	Elective dental
16	2 hours 11 minutes	1 hour 10 minutes	Internal fixator application
17	1 hour 15 minutes	50 minutes	Anal furunculosis
18	1 hour 58 minutes	58 minutes	Cranial cruciate repair
19	1 hour 40 minutes	1 hour 10 minutes	Enucleation
20	2 hours 51 minutes	2 hours 18 minutes	Ovario-hysterectomy

Table 6: Details of flunixin meglumine administration in dogs in group A (Trial No:1-10) from the start of anaesthesia and prior to the start of surgery.

Trial No	Time of administration of flunixin after inducing anaesthesia	Time of administration of flunixin prior to the start of surgery
1	10 minutes	15 minutes
2	12 minutes	1 hour 26 minutes
3	18 minutes	53 minutes
4	5 minutes	54 minutes
5	21 minutes	1 hour 12 minutes
6	10 minutes	10 minutes
7	18 minutes	1 hour 7 minutes
8	12 minutes	18 minutes
9	10 minutes	1 hour 12 minutes
10	8 minutes	4 minutes

Table 7: Details of flunixin meglumine administration in dogs in group B (Trial No: 11-20) from the termination of surgery and anaesthesia.

Trial No	Time of administration of flunixin after termination of anaesthesia	Time of administration of flunixin after termination of surgery
11	4 minutes	4 minutes
12	5 minutes	5 minutes
13	8 minutes	11 minutes
14	5 minutes	10 minutes
15	5 minutes	7 minutes
16	3 minutes	10 minutes
17	0 minutes	0 minutes
18	1 minutes	1 minutes
19	3 minutes	3 minutes
20	2 minutes	2 minutes

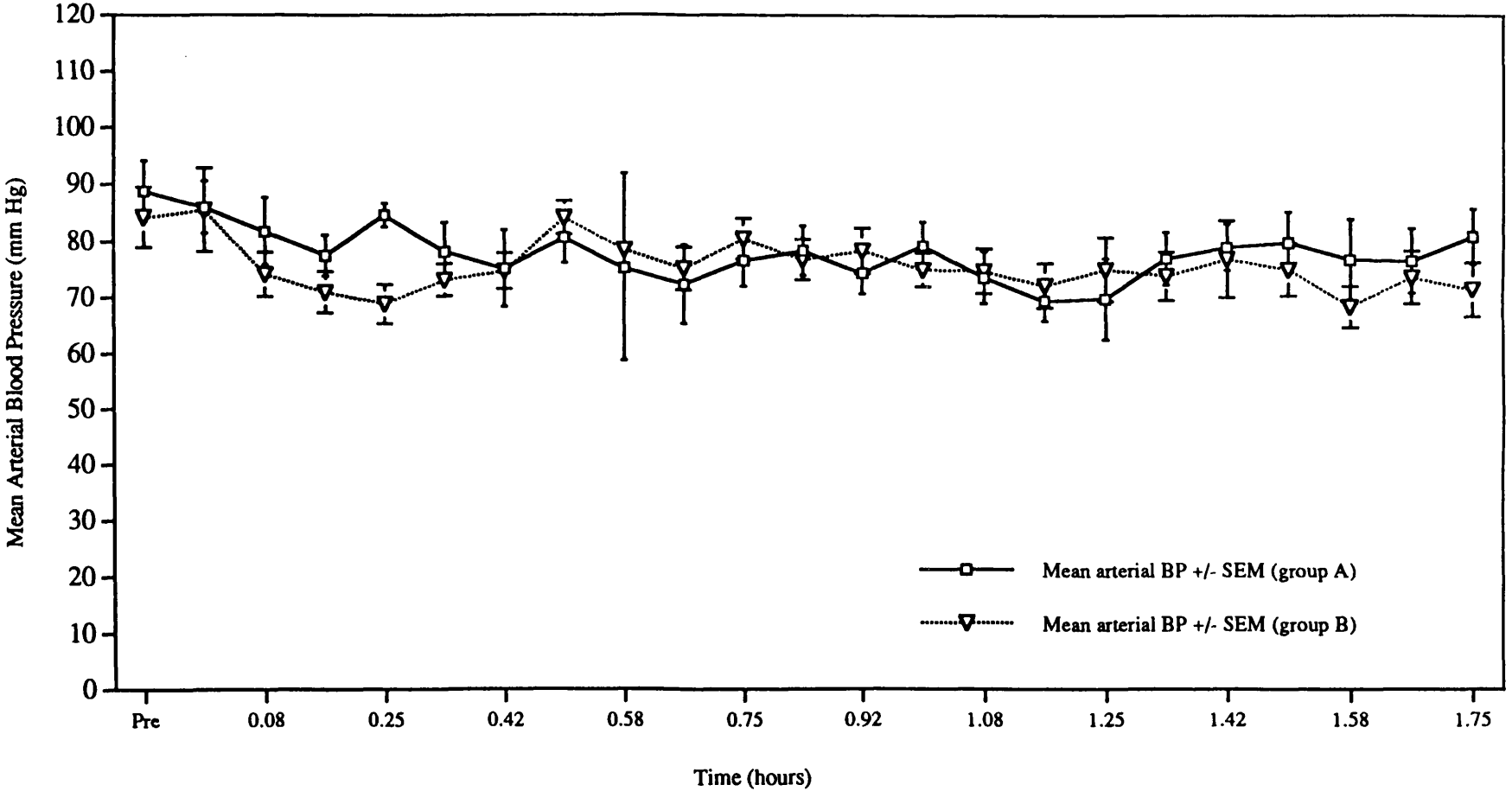
Because of the large variation in the anaesthetic times of the individual dogs in the trial, only mean values up to 1 hour 45 minutes into anaesthesia were plotted. As is evident from the graphs, mean blood pressure, pulse, and respiration of dogs in group A and B were very similar. Mean $ETCO_2$ readings were not plotted as there were too few readings to be meaningful. Because of the variations in the duration of the anaesthetic times between the individual dogs in both group A and group B, and because of some missing readings due to lack of availability of Dinamap and $ETCO_2$ monitors, it was not possible to carry out a statistical analysis of these results. However, it was possible to plot the individual blood pressure, pulse, respiration and $ETCO_2$ readings of each dog in the trial, and by observing the graph shape determine whether there was any distinct trend in the above readings between groups A and B. As is clearly evident from these graphs (appendix A, figures A1-A14), no trend was obvious in any of the clinical parameters analysed. Five dogs in group A (No's: 1, 5, 6, 7 and 10) and four dogs in group B (No's: 12, 14, 16 and 20) became hypotensive during anaesthesia i.e. their mean arterial blood pressure readings fell below 60 mm Hg. With the exception of dog 12 which remained hypotensive for 1 hour 10 minutes, these periods of hypotension were short lived and did not persist beyond 15 minutes at a time. In dog 12, blood pressure remained stable between 55-59 mm Hg, but clinical indicators of adequate perfusion such as pulse volume and mucus membrane colour remained good

Individual pulse readings were unremarkable in most dogs on trial, ranging between 75 to 120 beats/minute, except for Dogs 1, 16 and 20. Dog 1 suddenly became tachycardic on recovery from anaesthesia. Dog 16 was tachycardic throughout, but had a fast heart rate prior to the start of anaesthesia, while Dog 20 gradually became tachycardic during surgery.

Individual respiratory readings for dogs in group A and group B were unremarkable, with respirations ranging from 6-40 breaths/minute, except in dog 19, where it increased to 80 breaths/minute and dog 20, where it increased to 50 breaths/minutes immediately before anaesthesia was terminated.

$ETCO_2$ readings were normal throughout anaesthesia in all dogs examined in group A, ranging from 30-40 mm Hg. However 60% of the dogs examined in group B (dogs 12, 14, 16, 19 and 20), showed slightly elevated $ETCO_2$ readings ranging from 30-48 mm Hg.

FIG 5: Plot of mean arterial blood pressure readings (mm Hg) versus time (hours) for dogs in group A and group B.
Results are expressed as means +/- SEM.
Group A (No 1-10) received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.
Group B (No 11-20) received flunixin, 1.1mg/kg, i.v., after anaesthesia had terminated.



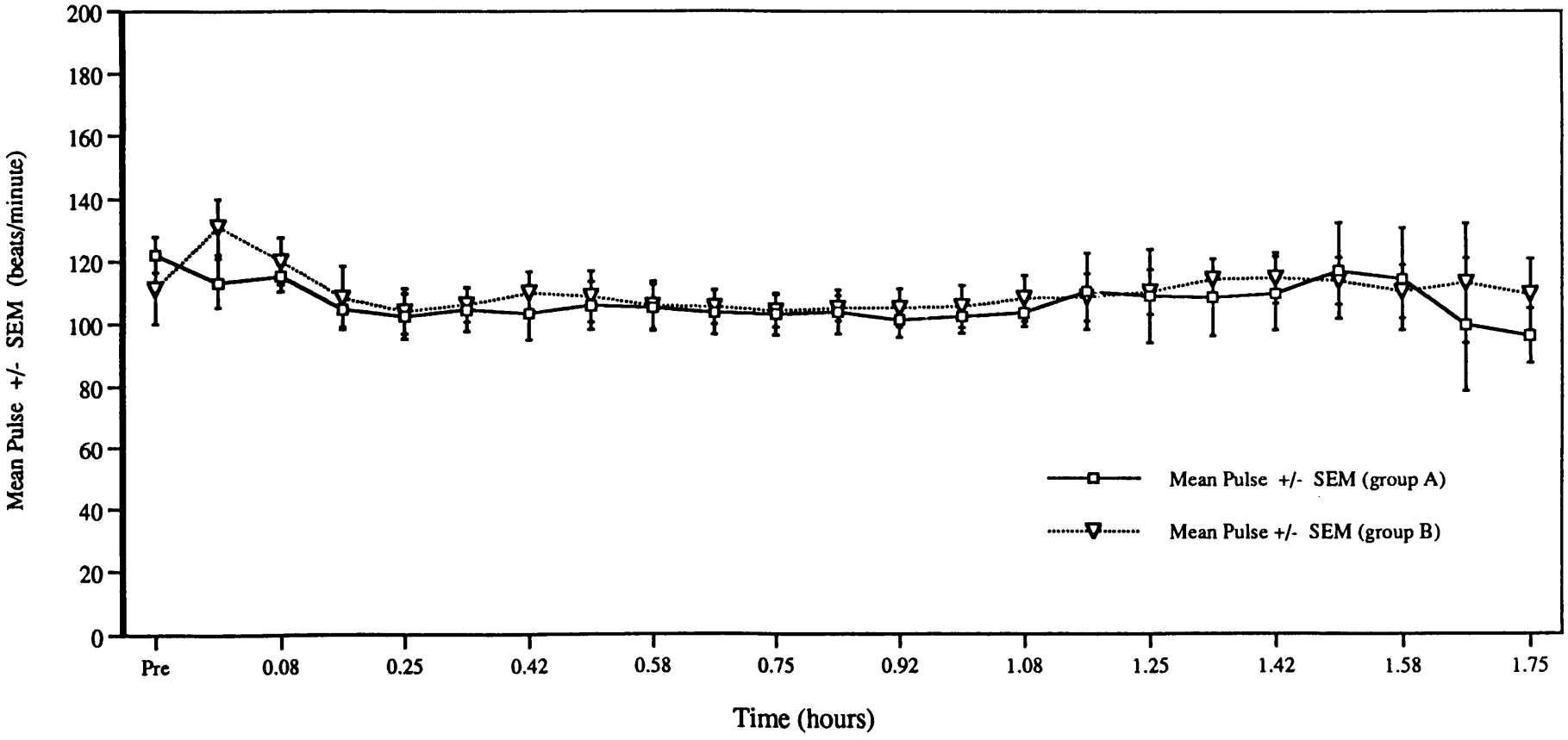
BP = Blood pressure

mm Hg = millimeters of mercury

SEM = Standard error of mean

Pre = Prior to induction of anaesthesia

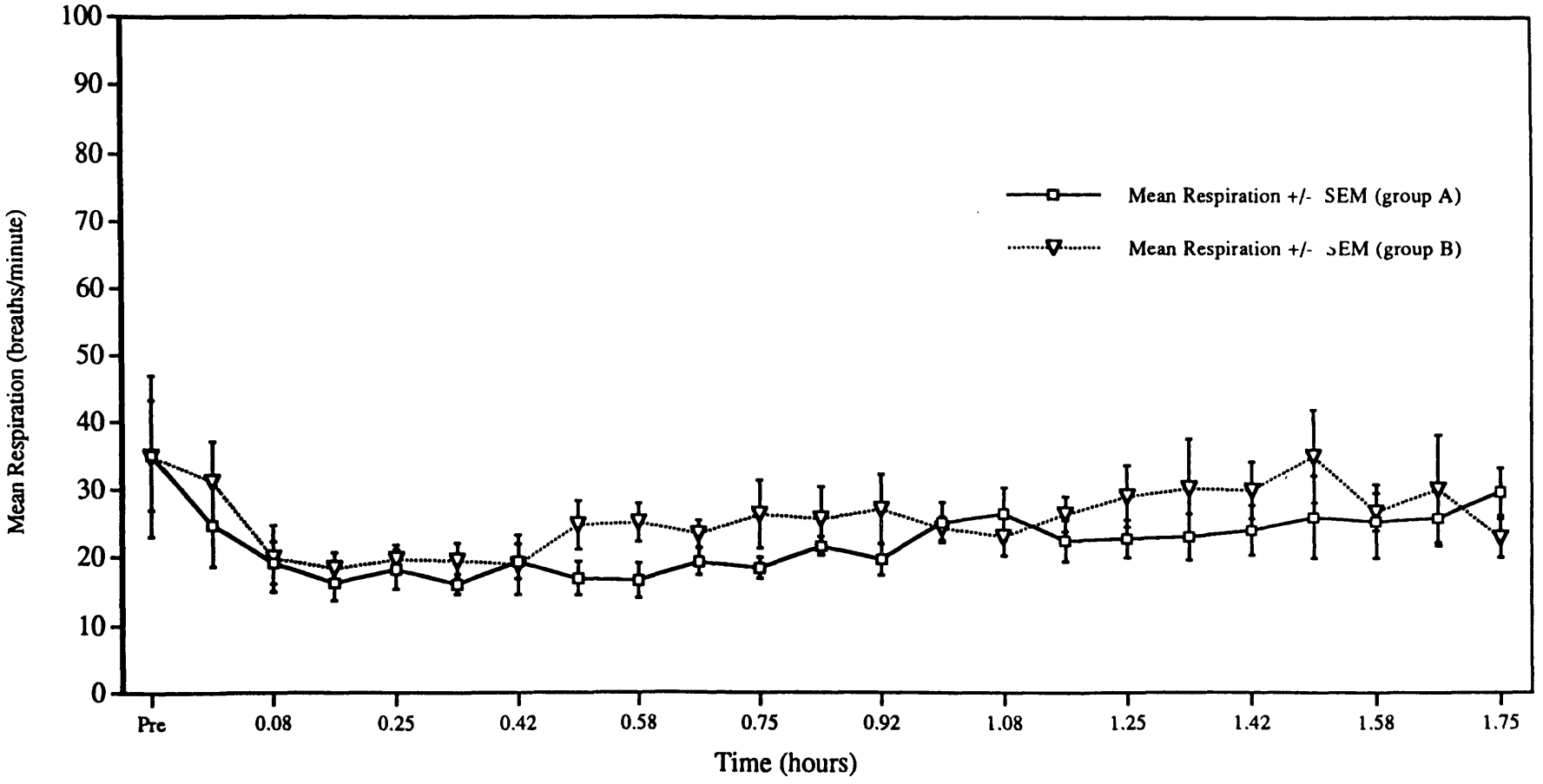
FIG 6: Plot of mean pulse rate +/- SEM (beats/minute) versus time (hours) for dogs in group A and group B.
Group A (No 1-10) received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.
Group B (No 11-20) received flunixin, 1.1mg/kg, i.v., after anaesthesia had terminated.



SEM = Standard error of mean

Pre = Prior to induction of anaesthesia

FIG 7: Plot of the mean respiratory rates +/- SEM (breaths/minute) versus time (hours) for dogs in group A and group B.
Group A (No 1-10) received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.
Group B (No 11-20) received flunixin, 1.1mg/kg, i.v., after anaesthesia had terminated.



SEM = Standard error of mean

Pre = Prior to induction of anaesthesia

3.1.2 Biochemical parameters

Refer to appendix B, table B1 for normal canine biochemistry values. Tables B3 and B4 shows the individual biochemistry parameters for dogs in group A and group B respectively, taken prior to the start of anaesthesia, and again 12 and 30 hours after flunixin administration. Table B2 gives the biochemical profile of each individual dog in the control group C (trial no's: C1-C10), taken at the same time points, as dogs in group A and B. There was no significant difference between the mean age, weight, anaesthetic or surgical times, between dogs in control group C, and dogs in group A and B. Table 8, 9 and 10, shows the mean biochemical values $\pm$ SEM, for dogs in group A, group B and group C respectively, at 0, 12 and 30 hours after flunixin administration. No biochemistry was performed on Dogs 1 and 3, as the volume of blood collected was only adequate to allow pharmacokinetic analysis of flunixin.

When the biochemical values obtained from the 3 groups of dogs (group A, group B and group C) were analysed statistically, it was found that there was no significant difference in any of the parameters except for blood urea nitrogen (BUN). A significant increase ($P < 0.05$) in the difference in the BUN values from 0 hours to 12 hours (2.7 mmol/l; 1.09 mmol/l), and from 12 hours to 30 hours (-1.04 mmol/l; -0.55 mmol/l), in dogs in group A and group B respectively i.e. dogs that had received flunixin as an analgesic, was seen, when compared with dogs in group C (0.71 mmol/l; -0.72 mmol/l) i.e. dogs that had not received flunixin. However, there was no significant difference in the changes in BUN levels from 0 to 12 hours (2.7 mmol/l) and 12 to 30 hours (-1.04 mmol/l), between dogs in group A, when compared to dogs in group B (1.09 mmol/l, -0.55 mmol/l). There was however a significant difference ($P = 0.011$) in the change in BUN levels from 0 to 30 hours (1.67 mmol/l) in dogs in group A, while dogs in group B (0.47 mmol/l) and group C (0.01 mmol/l) showed no significant difference.

In case of group A dogs, numbered 1, 4, 5, 7 and 8, the initial rise in BUN levels 12 hours after flunixin administration had decreased by 30 hours. Dog 2, showed a large increase in BUN, serum creatinine and phosphate levels 12 hours after flunixin administration, suggesting possible renal damage. This maybe due to the fact that this dogs blood pressure was on the low side (63-75 mm Hg) throughout anaesthesia. Its blood pressure only rose to above 80 mm Hg after anaesthesia had been terminated. As no 30 hour blood sample was taken, one cannot say if these parameters continued to rise or whether they returned to normal levels. The dog however made an unremarkable recovery and was exceedingly

Table 8: Mean biochemical values of dogs in group A ± SEM, taken prior to flunixin administration, and then 12 and 30 hours after its administration. Dogs in group A (trial no 1-10), received flunixin 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

	0 hours		12 hours		30 hours	
Biochemical parameters	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Urea (mmol/l)	4.53	0.45	7.24	0.535	6.20	0.34
Creatinine (umol/l)	93.00	7.37	114.30	11.30	98.75	4.83
Phosphate (mmol/l)	1.49	0.17	1.58	0.15	1.57	0.13
Total protein (g/l)	57.29	1.87	57.67	2.1	54.57	2.81
Albumin (g/l)	28.71	1.38	27.22	1.53	27.14	1.44
Globulin (g/l)	28.57	2.77	30.44	1.85	27.43	3.23
Sodium (mmol/l)	147.13	0.48	146.89	1.06	147.75	1.11
Potassium (mmol/l)	4.42	0.14	4.46	0.15	4.28	0.17
Chloride (mmol/l)	114.50	1.12	113.22	1.10	115.71	1.9

Table 9: Mean biochemical values of dogs in group B ± SEM, taken prior to flunixin administration, and then 12 and 30 hours after its administration. Dogs in group B (trial no 11-20), received flunixin 1.1 mg/kg, i.v., after anaesthesia had terminated.

	0 hours		12 hours		30 hours	
Biochemical parameters	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Urea (mmol/l)	4.29	0.21	5.34	0.29	4.76	0.72
Creatinine (umol/l)	84.90	5.74	87.80	6.58	89.30	7.4
Phosphate (mmol/l)	1.63	0.11	1.48	0.09	1.54	0.08
Total protein (g/l)	53.40	1.76	52.56	1.83	56.00	1.80
Albumin (g/l)	26.30	0.50	26.44	0.71	28.60	0.73
Globulin (g/l)	27.10	1.50	26.11	1.48	27.80	1.66
Sodium (mmol/l)	147.30	0.50	147	1.09	147.10	0.48
Potassium (mmol/l)	4.46	0.08	4.79	0.12	4.69	0.11
Chloride (mmol/l)	112.90	0.62	113.30	0.83	111.33	1.55

Table 10: Mean biochemical values of dogs in group C ± SEM, taken prior to anaesthesia, and then 12 and 30 hours after its termination. Dogs in group C (trial no C1-C10), received no flunixin, intra or post-operatively.

	0 hours		12 hours		30 hours	
Biochemical parameters	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Urea (mmol/l)	5.26	0.52	4.55	0.44	5.27	0.50
Creatinine (umol/l)	93.80	5.82	89.60	4.56	94.40	4.59
Phosphate (mmol/l)	1.46	0.11	1.46	0.13	1.53	0.16
Total protein (g/l)	62.70	1.43	60.10	1.26	62.10	1.99
Albumin (g/l)	32.60	1.22	31.20	1.27	31.60	1.41
Globulin (g/l)	30.00	1.26	28.90	1.35	30.50	1.85
Sodium (mmol/l)	148.90	0.48	146.70	1.35	145.80	0.55
Potassium (mmol/l)	3.90	0.11	4.45	0.20	4.56	0.19
Chloride (mmol/l)	111.70	1.37	110.00	1.19	108.80	1.65

bright with an excellent appetite throughout. No clinical evidence of kidney damage such as polyuria or polydipsia was reported by the owner. In dog number 8, the owner expressed concern regarding her dog being excessively thirsty after surgery for almost 2 months. This dog's blood urea and creatinine levels had risen 12 hours after flunixin administration. Its initial BUN level, prior to flunixin was 6.3 mmol/l, which increased to 8.7 mmol/l, 12 hours after flunixin administration. However, 30 hours later all values though still high were falling (8.1 mmol/l). It was decided to retake a blood sample 2 months after flunixin administration. Blood urea, creatinine and phosphate levels were found to be back to their original values prior to flunixin administration (4.1 mmol/l; 88 umol/l; 1.06 mmol/l respectively).

In case of dog trial numbers 6, 9 and 10, the BUN levels were still high at 30 hours. In dog number 10, another 3 blood samples were taken 15 days, 2 and 5 months after flunixin administration. Prior to flunixin administration, the dog's BUN was 3.6 mmol/l, which rose to 6.2 mmol/l 12 hours after flunixin administration, and had further increased to 6.8 mmol/l, at 30 hours. Plasma phosphate levels had also risen from 1.29 mmol/l (pre), to 1.63 mmol/l (12 hours), and 1.7 mmol/l (30 hours). The plasma creatinine levels however had fallen from 127umol/l (pre), 125 umol/l (12 hours) and 100 umol/l (30 hours). On day 15, the dog's BUN remained high at 6.6 mmol/l, but the plasma phosphate levels had returned to base level (1.21 mmol/l). 2 months later the BUN level showed a further rise and was 7.9 mmol/l. Inspite of this rise in blood urea level, the dog did not show any clinical signs of kidney damage. Five months later, a follow-up blood sample was taken and the BUN level had started to fall (7.4 mmol/l), but was still on the high side of normal. Both plasma phosphate (1.2 mmol/l) and plasma creatinine levels (113 umol/l) were back to their original basal levels before flunixin administration.

In all dogs in group B the rise in blood urea levels seen 12 hours after the flunixin injection had started to decrease to the pre-flunixin levels by 30 hours after flunixin administration. The only exception was in dog numbers 12 and 20. In dog number 12, the rise in BUN level at 30 hours post flunixin, was only slightly greater than at 12 hours. However, in dog 20, there was quite a large rise in the BUN, compared with 12 hours post flunixin, and a marginal increase in plasma creatinine and phosphate levels. The dog showed no clinical signs of renal damage. In the post-operative period regular contact with the owner was maintained, and the dog did not exhibit signs of polyuria or polydipsia. This animal was due back 10 days after the administration of anaesthetic, for suture removal. However, as the dog was doing so well, its owner had her own veterinarian remove the stiches, and

hence no follow-up blood sample was taken. Dog 15, had follow-up blood samples taken at 15 days, 1 month and 2 months after flunixin administration. The BUN level was found to stay low, and at 2 months post flunixin, was exactly the same value as it was prior to flunixin administration.

All other biochemical parameters analysed statistically, namely creatinine, phosphate, total protein, albumin, globulin, sodium, potassium and chloride, showed no significant difference between the 3 groups of dogs, from 0 hours to 12 hours and 12 hours to 30 hours post flunixin.

3.2 PLASMA DISPOSITION AND PHARMACOKINETICS

3.2.1 HPLC method - Evaluation of sensitivity and precision of the technique

Refer to appendix C, table C1, for the intra-assay coefficient of variation and table C2 for the inter-assay coefficient of variation. The mean plasma concentrations $\pm$ standard error of the mean (SEM) are given in table C3, for dogs in group A (trial numbers 1-10) and table C4 for dogs in group B (trial numbers 11-20).

The limit of detection of flunixin meglumine in plasma by the HPLC technique used was 0.03 μg/ml. The mean percentage recovery of the drug flunixin was 81.5 %, extending over a range of approximately 10%. The coefficient of variation was less than 11% (Refer to table 11). The degree of variation between the 20 assays (dogs 1-20), performed on different days, was determined by the inter-assay coefficient of variation or 'between days' variation. The mean percentage recovery of flunixin was 82.2%, extending over a range of approximately 11%. The coefficient of variation was less than 20% (table 11).

3.2.2 Chromatograms

Flunixin meglumine was well chromatographed, with no odd peaks or interfering peaks. The retention time was 6.5 minutes. The typical chromatogram is presented in figure 8.

Table 11:

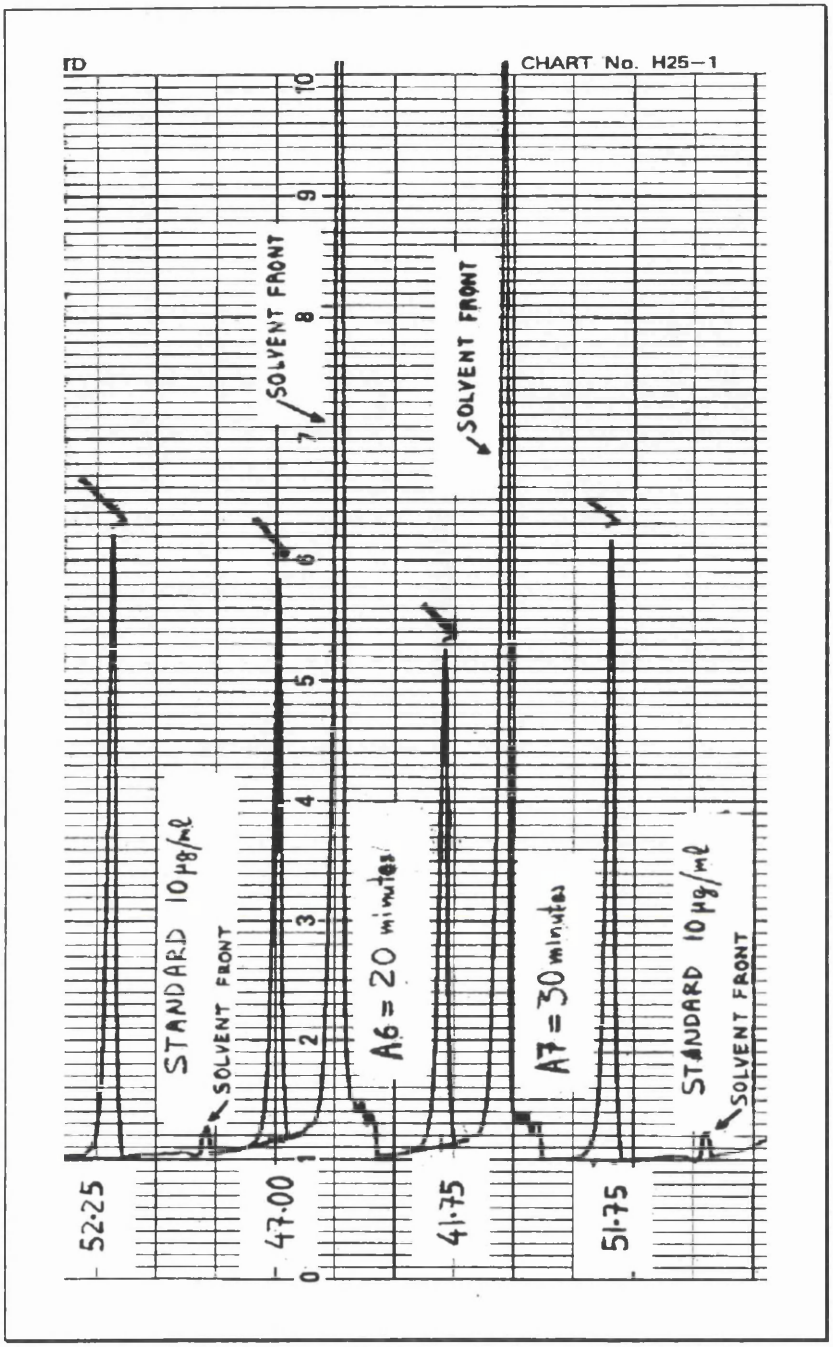
The intra-assay and inter-assay variations of the mean % recovery of flunixin, and the coefficient of variation for flunixin, for each spike concentration used in the HPLC extraction procedure.

Spike	Mean % recovery of flunixin		Coefficient of variation (%)	
Conc	Intra-assay variation	Inter-assay variation	Intra-assay variation	Inter-assay variation
0.25 ug/ml	76.5	79.9	8.6	19.9
1 ug/ml	83.8	76.8	7.1	13.6
2 ug/ml	80.2	79.4	6.5	10.3
5 ug/ml	83.5	84.9	10.7	10.4
10 ug/ml	84.4	87.1	3.0	10.0
Mean	**81.5**	**82.2**	**7.4**	**12.6**

ABBREVIATIONS

Conc = concentration
% = percentage

Figure 8: Flunixin chromatography



EXPERIMENT CODE: Flunixin dog No 19,
Date of collection of blood: 12/5/93,
Date of extraction and injection of drug: 21/5/93,
Solvent: MeOH:H2O 70:30, Perchloric Acid=400µl/100ml,
Flow rate: 1ml/min, **Column:** C8 with guard, **Detector:** spectra 100,
Pump: LS isochrome, **Wave length:** 287nm, **Injection volume:** 15µl,
Loop volume: 20µl,
Standard concentration: 10µg/ml,
Absorbance: 0.01, **Analysis time:** 5 min,
Graph speed: 30cm/hour, **Amplification:** 10mV.

3.2.3 Recovery

The mean percentage recovery of flunixin from canine plasma was 82.2% (range=11%) (table 11). The mean plasma concentration profile of flunixin, together with the standard error of the means versus time, after flunixin injection, in dogs in group A and group B, are shown in table 12, and is represented graphically in figure 9. In dog number 7, two blood samples taken at 48 and 60 hours, showed no flunixin. Flunixin was detected up to 30 hours in all dogs, except for numbers 3 and 8 in group A, and numbers 11 and 17 in group B. In dogs numbers 3, 8 and 11, flunixin was detected for up to 24 hours only. In dog number 17 flunixin was last detected in the plasma 12 hours after its administration.

Peak plasma concentrations seen within the first 2 minutes after the drug's administration, ranged from 38.57 μg/ml to 18.14 μg/ml, with a mean concentration of 24.48±1.84 μg/ml, for dogs in group A. Similarly in dogs in group B, peak plasma concentrations ranging from 41.16 μg/ml to 16.77 μg/ml, with a mean concentration of 28.71 ± 2.11 μg/ml were seen within the first 2 minutes. In both groups of dogs, there was a steady drop in plasma concentration of the drug for 10 minutes after its administration, following which there was little or no change in the plasma concentration until 30 minutes after administration, when once again plasma levels started to fall steadily. In dogs numbers 1, 3, 7, 13, 15, and 16 in group B, there was a slight rise in the plasma concentration of the drug, during this period. There was no significant difference in the plasma concentrations at 2 minutes, or 12, 24 and 30 hours post drug administration, between dogs in group A and group B. The plasma concentration of flunixin at 30 hours, in dogs in both groups, was 0.07 ± 0.02 μ g/ml. The semi-logarithmic plot of the mean plasma concentrations of flunixin of dogs in groups A and B versus time (figure 9) were very similar.

3.2.4 Pharmacokinetics

The pharmacokinetic parameters used to describe the plasma flunixin concentration versus time data, when compartmental analysis of data was performed in the individual dogs, are given in appendix D, table D1, for dogs in group A (trial numbers 1-10), and table D2 for dogs in group B (trial numbers 11-20).

Table12: Mean plasma concentration of flunixin, together with the standard errors of the means versus time, after an intravenous injection of flunixin, in dogs in group A and group B.

Group A dogs (trial no's 1-10) received flunixin, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.
Group B dogs (trial no's 11-20) received flunixin, 1.1 mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.

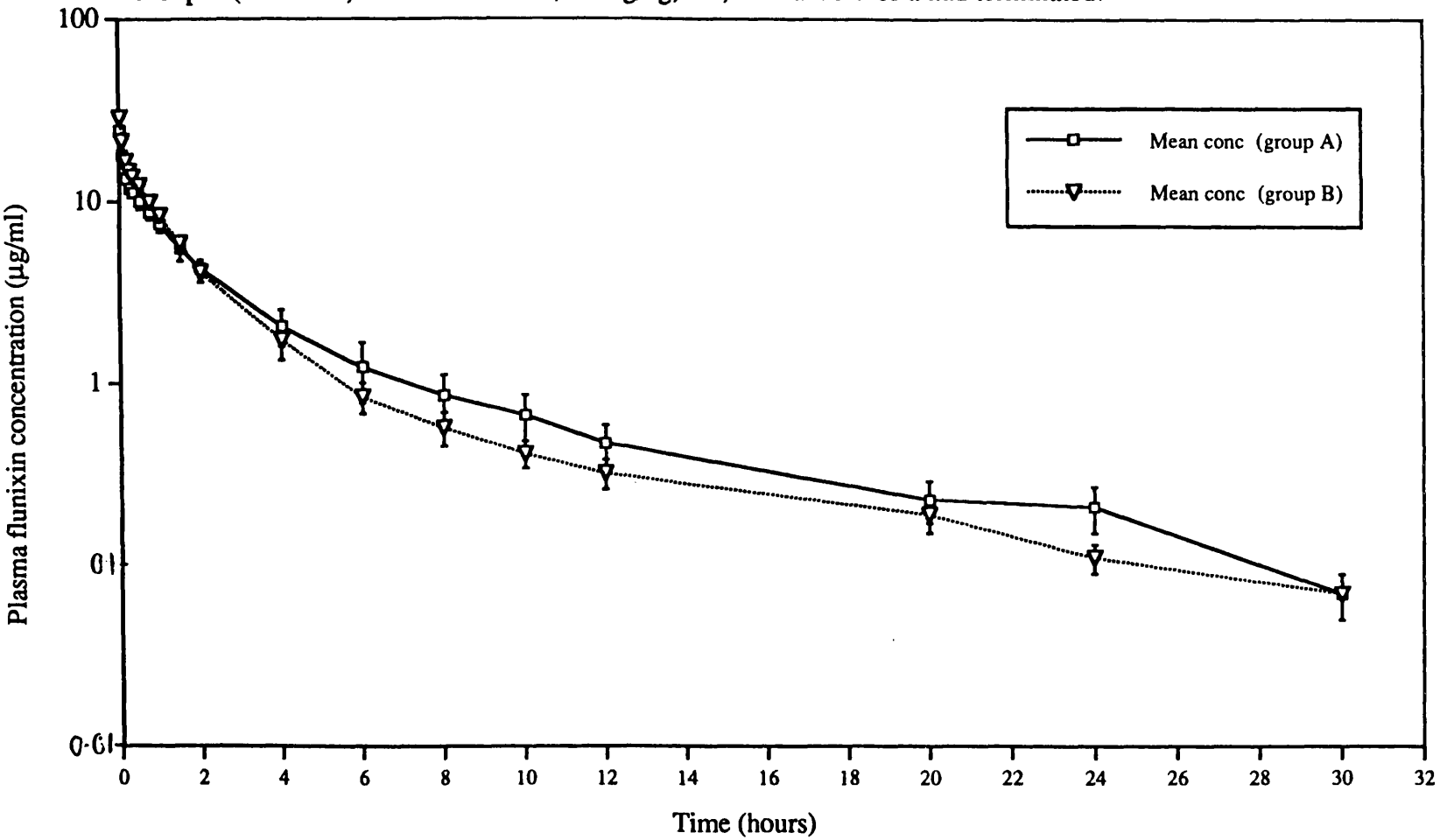
Time (hour)		Mean plasma concentration Group A (ug/ml)	SEM Group A (ug/ml)	Mean plasma concentration Group B (ug/ml)	SEM Group B (ug/ml)
	Pre	0	0	0	0
(2 min)	0.03	24.48	1.84	28.71	2.11
(5 min)	0.08	18.00	1.43	21.34	1.47
(10 min)	0.17	13.36	0.78	16.65	1.14
(15 min)	0.25	11.81	0.84	14.57	0.99
(20 min)	0.33	11.16	0.86	13.62	0.89
(30 min)	0.50	10.06	1.04	12.20	0.91
(45 min)	0.75	8.73	0.81	9.89	0.86
	1	7.55	0.78	8.40	0.69
	1.5	5.56	0.84	5.93	0.70
	2	4.32	0.46	4.11	0.48
	4	2.07	0.48	1.73	0.39
	6	1.23	0.45	0.84	0.16
	8	0.86	0.25	0.57	0.12
	10	0.67	0.19	0.41	0.07
	12	0.47	0.12	0.32	0.06
	20	0.23	0.06	0.19	0.04
	24	0.21	0.06	0.11	0.02
	30	0.07	0.02	0.07	0.02

ABBREVIATIONS

Pre = Prior to flunixin administration
min = minutes
SEM = Standard error of mean
ug/ml = micrograms per millilitre

FIG 9: Mean plasma flunixin concentration +/- SEM, after a single intravenous administration of 1.1 mg/kg flunixin, to dogs in group A and group B

Group A (No 1-10) received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.
Group B (No 11-20) received flunixin, 1.1mg/kg, i.v., after anaesthesia had terminated.



Plasma concentrations up to 30 hours were used to calculate the pharmacokinetic determinants. Compartmental as well as non-compartmental analyses of the plasma flunixin concentration, for dogs in groups A and B were performed. When the plasma concentration of flunixin was analysed by compartmental model analysis, the plasma flunixin disposition was best described by a tri-exponential decline curve in all dogs except numbers 6 and 16, where a bi-exponential equation was found to provide a better fit, as determined by using Akaike Inverse square of the concentrations to obtain the best fit model. The mean pharmacokinetic parameters $\pm$ SEM, of plasma flunixin obtained after compartmental analysis of data, for dogs in groups A and B, are shown in table 13. The mean elimination half-life of flunixin in dogs in group A, was 7.86 $\pm$ 1.18 hours (table 13), while in group B, it was 6.10 $\pm$ 0.74 hours (table 13). These were not significantly different. The mean area under the plasma concentration versus time curve for observed values (AUCob), for dogs in group A (35.7 $\pm$ 5.3 ug.hr/ml) and B (33.4 $\pm$ 3.3 ug.hr/ml), were similar. In group A, the mean total body clearance (CLb) was 34.88 $\pm$ 5.64 ml/kg.hr, volume of central compartment (Vc) was 34.58 $\pm$ 2.58 ml/kg, and apparent volume of distribution at steady state (Vdss) was 195.89 $\pm$ 38.5 ml/kg. Group B, had a mean CLb of 34.55 $\pm$ 4.58 ml/kg.hr, Vc of 32.49 $\pm$ 4.43 ml/kg, and a mean Vd(ss) of 132.63 $\pm$ 8.73 ml/kg. The mean elimination rate constant (Kel), in group A was 0.96 $\pm$ 0.09 per hour, and in group B it was 1.16 $\pm$ 0.17 per hour. There were no significant differences between the mean values obtained for CLb, Vc, Vdss, and Kel, for dogs in groups A and group B.

Non-compartmental analysis of the flunixin plasma concentration data for dogs in groups A and B, enabled the calculation of the area under zero moment curve (AUC), area under first moment curve for observed values (AUMCob), and mean residence time (MRT). Refer to appendix D, table D3 and D4, for individual results. Table 14 shows the mean $\pm$ SEM, of the same. The mean AUMCob for dogs in group A was 334.79 $\pm$ 94.5 $\mu g.h^2/ml$, giving a mean MRT of 8.73 $\pm$ 2.53 hours, while for dogs in group B, the mean AUMCob was 161.15 $\pm$ 23.9 $\mu g.h^2/ml$, giving a mean MRT of 4.52 $\pm$ 0.36 hours. Statistically, neither the mean AUMCob nor the mean MRT, of dogs in group A, was significantly different to that in group B. In addition, there was no significant difference between mean CLb (35.93 $\pm$ 5.96 ml/kg.hr) or Vdss(ob) (303.4 $\pm$ 94.8 ml/kg) for dogs in group A, when compared with dogs in group B (CLb=34.84 $\pm$ 3.93 ml/kg.hr, Vdss(ob)=152.8 $\pm$ 16.4 ml/kg).

When the lowest mean arterial blood pressure reading of each dog in the trial was plotted graphically against the elimination half life (Figure 10) and mean residence time

Table 13: Mean pharmacokinetic parameter +/- SEM, obtained after compartmental analysis of plasma flunixin concentration versus time data, for dogs in groups A and B

Group A dogs (trial no's 1-10) received flunixin, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery. Group B dogs (trial no's 11-20) received flunixin, 1.1 mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.

Pharmacokinetic variables	UNITS	Group A	SEM Group A	Group B	SEM Group B
1/2 LIFE P (distribution)	hrs	0.05	0.01	0.16	0.12
1/2 LIFE A (distribution)	hrs	0.90	0.12	0.76	0.08
1/2 LIFE B (elimination)	hrs	7.86	1.18	6.10	0.74
CPO	ug.hr/ml	33.45	2.52	37.38	3.08
AUC	ug.hr/ml	38.20	5.08	35.72	3.45
AUC (observed)	ug.hr/ml	35.65	5.24	33.40	3.27
Vc	ug/kg	34.58	2.58	32.49	4.43
Vd (ss)	ml/kg	195.89	38.50	132.63	8.73
CL(b)	ml/kg.hr	34.88	5.64	34.55	4.58
K el	/hr	0.96	0.09	1.16	0.17

Table 14: Mean pharmacokinetic parameter +/- SEM, obtained after non-compartmental analysis of plasma flunixin concentration versus time data, for dogs in groups A and B

Pharmacokinetic variables	UNITS	Group A	SEM Group A	Group B	SEM Group B
AUC (observed)	ug.hr/ml	38.71	6.10	34.61	3.15
AUMC (observed)	ug.hr/ml	334.79	94.50	161.15	23.90
MRT	hrs	8.73	2.53	4.52	0.36
Vd (ss)	ml/kg	303.40	94.80	152.80	16.40
CL(b)	ml/kg.hr	35.93	5.96	34.84	3.93

ABBREVIATIONS

SEM	= Standard error of means
1/2 LIFE P (distribution)	= Distribution half life
1/2 LIFE A (distribution)	= Distribution half life
1/2 LIFE B (elimination)	= Elimination half life
CPO	= Initial concentration of drug in plasma, following an intravenous injection
AUC	= Area under zero moment curve
AUC (observed)	= Area under the curve (observed values)
AUMC (observed)	= Area under the first moment curve (observed)
Vc	= Apparent volume of central compartment
Vd (ss)	= Apparent volume of distribution at steady state
CL(b)	= Body clearance of drug
K el	= Elimination rate constant
MRT	= Mean residence time

(Figure:11) of flunixin in the plasma of that dog, no correlation between the two could be seen. Table 15, shows the lowest arterial blood pressure readings recorded in each dog during anaesthesia, together with the elimination half-lives and MRT's of the individual dogs. Tables 16 and 17 illustrate the elimination half-lives and MRT's in ascending order to demonstrate more clearly the relationship between mean arterial blood pressure and elimination of flunixin from the body.

Table 15: Lowest mean arterial blood pressure reading of each dog in the trial (No:1-20), versus elimination half life and mean residence time (MRT) of plasma flunixin, in that dog.

Dogs no 1-10 (group A) received flunixin, 1.1 mg/kg iv, during anaesthesia, prior to the start of surgery. Dogs no 11-20 (group B) received flunixin, 1.1 mg/kg iv, immediately after anaesthesia terminated.

Trial No	Lowest BP (mmHg)	Elimination half life (Hours)	MRT (Hours)
1	52	9.70	4.49
2	60	7.73	6.94
3	78	11.86	30.40
4	68	4.75	6.37
5	59	15.40	7.71
6	40	3.83	4.83
7	48	9.48	12.36
8	55	5.76	4.72
9	78	5.64	6.32
10	57	4.47	3.19
11	58	3.76	3.32
12	47	8.29	3.85
13	74	9.53	6.09
14	57	5.64	6.35
15	74	5.48	5.29
16	52	5.37	3.69
17	71	3.59	4.98
18	62	5.12	3.52
19	60	4.66	3.26
20	53	9.58	4.87

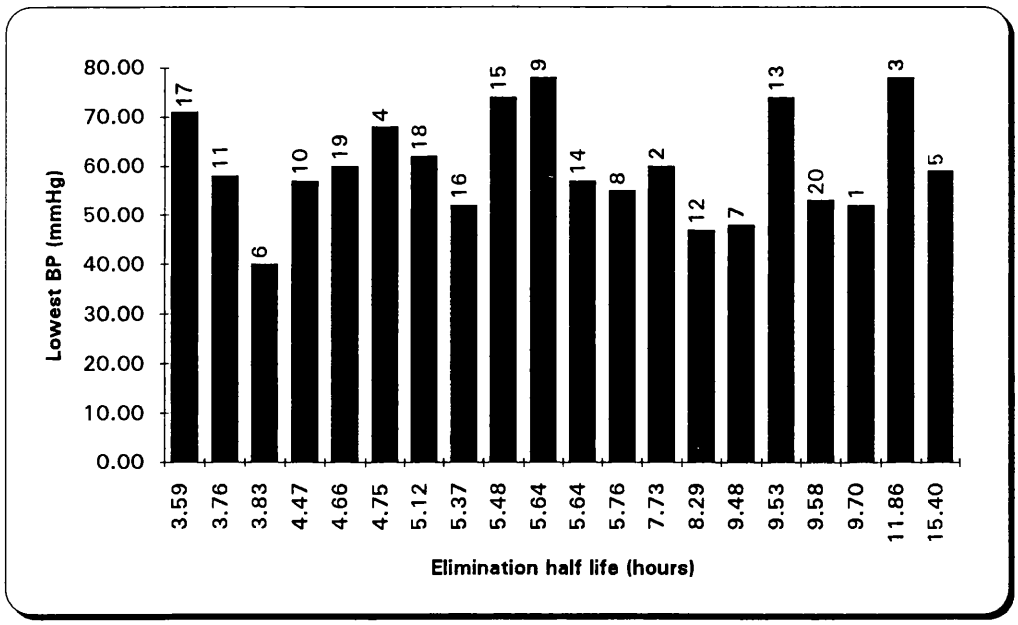
ABBREVIATION

BP = Blood pressure
MRT = Mean residence time
mm Hg = Millimeters of mercury

Table 16: Elimination half life (hours) of flunixin, in all dogs in the trial (No 1-20), together with the lowest arterial blood pressure readings recorded in these dogs during anaesthesia. The table has been arranged in ascending order of the elimination half lives.

Dog Trial Number	Elimination half life (Hours)	Lowest BP (mmHg)
17	3.59	71
11	3.76	58
6	3.83	40
10	4.47	57
19	4.66	60
4	4.75	68
18	5.12	62
16	5.37	52
15	5.48	74
9	5.64	78
14	5.64	57
8	5.76	55
2	7.73	60
12	8.29	47
7	9.48	48
13	9.53	74
20	9.58	53
1	9.70	52
3	11.86	78
5	15.40	59

FIG 10: Graphical representation of the above table.



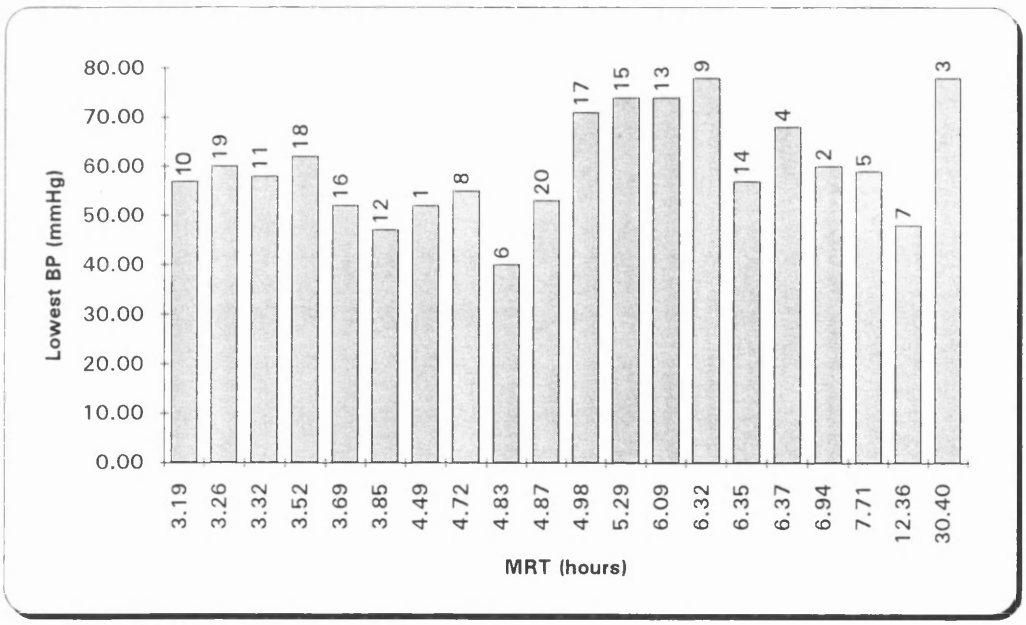
ABBREVIATIONS

BP = Blood pressure
mm Hg = Millimeters of mercury

Table 17: Mean residence time (hours) of flunixin, in all dogs in the trial (No 1-20), together with the lowest arterial blood pressure readings recorded in these dogs during anaesthesia. The table has been arranged in ascending order of the mean residence time (MRT).

Dog Trial No	MRT (Hours)	Lowest Blood Pressure (mmHg)
10	3.19	57
19	3.26	60
11	3.32	58
18	3.52	62
16	3.69	52
12	3.85	47
1	4.49	52
8	4.72	55
6	4.83	40
20	4.87	53
17	4.98	71
15	5.29	74
13	6.09	74
9	6.32	78
14	6.35	57
4	6.37	68
2	6.94	60
5	7.71	59
7	12.36	48
3	30.40	78

FIG 11: Graphical representation of the above table.



ABBREVIATION

BP = Blood pressure
mm Hg = Millimeters of mercury
MRT = Mean residence time

4. DISCUSSION

The NSAID flunixin meglumine has been used increasingly in veterinary clinical practice as a post-operative analgesic. Reid and Nolan (1991), found it to be as effective as the opioid papavertum in controlling the acute pain associated with surgery, and although analgesia was not evaluated in this study, all the dogs appeared comfortable in the post-operative period.

Flunixin was administered intravenously at a dose rate of 1.1 mg/kg, the dose licensed for use in the dog and recommended by Bottoms and colleagues (1983) and McKellar *et al* (1989). This was also the dose used by Hardie *et al* (1985), in their pharmacokinetic studies on flunixin meglumine in conscious dogs.

4.1. Physiological parameters

Although no comparative study has yet been undertaken in the anaesthetised dog to establish whether or not the intra-operative use of flunixin meglumine affects mean arterial blood pressure, pulse or respiration, Zellar and co-workers (1988), reported that a single intravenous dose of flunixinin did not alter these parameters in the anaesthetised horse during surgery.

Mean pulse and respiratory readings of dogs in group A were marginally lower than dogs in group B during anaesthesia, although this did not achieve statistical significance. When the dogs were considered individually, moderate tachycardia was seen in 3 animals (Dogs 1, 16 and 20). Dog 1 had a low blood pressure when the tachycardia started, and hence it may have been a compensatory mechanism. On the other hand, it was just recovering from anaesthesia, and the tachycardia may have been the result of pain. However, the dog seemed comfortable and recovery from anaesthesia was smooth. Dog 16, had a high heart rate to start with, and hence the fast heart rate seen during surgery was considered to be normal for that dog. The sudden increase in heart rate in dog 20 is difficult to explain. It may have been the result of inadequate depth of anaesthesia.

In this study mean arterial blood pressures recorded in individual dogs were quite variable throughout the anaesthetic period and 45% of the dogs (5 from group A and 4 from group B), had mean arterial blood pressures falling below 60 mm Hg. Adequate cerebral and coronary perfusion is considered to require a mean systemic blood pressure greater than 50 mm Hg (Haskins, 1987), and if impairment is severe or if the compensatory processes

are exhausted, hypoperfusion develops (Haskins, 1987). However despite these low measured values all 9 dogs appeared to have good cardiovascular function, with good mucous membrane colour, capillary refill time and strong pulse volume in the peripheral arteries. On the basis of clinical assessment, their condition gave no cause for concern.

Arterial blood pressure can be measured directly or indirectly, the more accurate method involving direct catheterization of a systemic artery (Hamlin *et al,* 1982; Pettersen *et al,* 1987). However as this was a study undertaken on healthy clinical cases, such an invasive technique could not be justified. Indirect methods of arterial blood pressure measurements depend on occlusion of a suitable artery by a pressure cuff and subsequent detection of Korotkoff sounds or of pressure oscillations as the cuff pressure falls from above systolic to below diastolic (Vincent *et al,* 1993). An alternative indirect method detects restoration of flow or movement of the arterial wall using the Doppler shift principle with an ultrasound source (Vincent *et al,* 1993).

In this study, blood pressure was measured indirectly using the Dinamap (Critikon). The Dinamap is designed for use in humans and uses the oscillometric principle (Kittleson and Olivier, 1983). It combines an automated inflation-deflation cycle with direct detection of pressure oscillation (Sykes *et al,* 1991), and has systems to eliminate artefacts. It displays systolic, diastolic and mean arterial blood pressures, together with heart rate. The Dinamap is the most widely used indirect blood pressure monitor (Vincent *et al,* 1993). Vincent *et al,* (1993) mentioned that Ward (1990) (unpublished data), carried out a series of preliminary tests using the Dinamap, and demonstrated impressive precision and reproducibility within dogs on different occasions, with the cuff applied to the tail. Ward (1990) obtained highly variable results when the cuff was applied to a limb, but this may have been due to the fact that he used conscious dogs, and was therefore unable to keep the dogs sufficiently still while readings were being taken. Other workers have also investigated the accuracy of indirect blood pressure measurements in the dog. Geddes and colleagues (1980) compared direct and indirect methods of measuring mean arterial blood pressure in anaesthetized dogs, and found that indirect mean pressures correlated well with direct mean arterial pressure when the cuff width used was 43% of the forelimb circumference. They measured mean pressures as low as 23 mm Hg, and observed that, when the correct sized cuff was applied to anaesthetised animals, the oscillometric method of measuring blood pressure was excellent, even at low blood pressure values. Weiser *et al* (1977) and Hamil *et al* (1982), reported good correlation between indirectly measured blood pressure and that obtained directly. Hamil *et al* (1982), found the Dinamap easy to

apply, harmless to the dog, and accurate in dogs weighing between 7 kg and 52 kg. Therefore it appears that blood pressure can be measured accurately by non-invasive means in anaesthetised dogs if the correct sized cuff is used, and if the dogs weigh more than 7 kgs. There is a conventional formula for the relationship between circumference of the limb and cuff width, cuff width = 0.4 x limb circumference (Coulter and Keith, 1984). In dogs, narrow cuffs cause an overestimated measure of arterial blood pressure while wide cuffs tend to underestimate the reading (Valtonen and Eriksson, 1970).

Before this study was undertaken, due consideration was given as to the siting of the pressure cuff. Application to the tail necessitates removal of hair from the tail base, a procedure which may not have met with owner approval. The limbs have a thinner hair coat which allows for easier pulse detection and as the lower forelimb was consistently easier to access during surgery, this was the chosen limb. Care was taken to measure the circumference of the limb to which the cuff was applied, and to use a cuff of the appropriate size. The limb was supported in the horizontal position and as all dogs weighed between 17 and 45 kg, which is within the range of accurate measurement for the Dinamap, the arterial blood pressure readings obtained, were assumed to be accurate.

However mean arterial blood pressure readings did on occasions seem low in the absense of clinical signs of hypotension, and variability within individuals was a feature. Pettersen *et al* (1987), found that a linear relationship existed between blood pressure and heart rate when measured indirectly and directly, but noted that the indirect values were an underestimate of the direct values. Their findings were similar to Coulter *et al* (1981) who obtained much lower diastolic pressure readings with indirect readings compared with direct measurements. There seems to be no such report in the literature of artefacts in the measurement of systolic pressures, and so it may be more appropriate to measure this rather than mean blood pressure when using indirect methods of measurement. Von Bergen *et al* (1954) suggested that systolic blood pressure can easily, quickly, and most accurately be accomplished by oscillometry rather than by auscultation and palpation, and it is interesting to note that, in human clinical studies where the Dinamap is used, systolic blood pressure seems to be used for comparative purposes rather than mean arterial blood pressures. Irrespective of the method and accuracy of its measurement, the importance of monitoring arterial blood pressure and heart rate during anaesthesia lies in the ability to be able to detect changes in blood pressure rather than to determine the absolute values (Glen, 1970; Pettersen *et al,* 1987).

The reasons for the low mean arterial blood pressure values measured in some dogs in this study are unclear. Blood loss during surgery, was not considered a possibility, as none of these dogs bled excessively (> 5% body weight loss). In all these animals except one (dog 12), the low blood pressure did not persist beyond 10-15 minutes. Dog 12, had a persistent low blood pressure for 1 hour 15 minutes. The reason for this is unknown, as the dog was not losing blood or excessive fluids during surgery, nor did the anaesthetic depth appear too deep. The low blood pressure may be a reflection of the dog's natural resting blood pressure.

According to Vincent and colleagues (1993), the true resting arterial blood pressures in young healthy dogs may indeed be lower than previously believed and, like humans, there probably is an age-related rise in blood pressure. Initial data from 800 dogs indicated a significant age-related rise in blood pressure, as well as increases associated with obesity (Mitchell *et al*, 1993). In this study, all dogs were young and healthy, and hence the low blood pressure readings obtained may well be physiological. Much work has been published on canine blood pressure, but 'normal' indirect blood pressure values of dogs as reported in one laboratory, seldom agree with those measured in another (Valtonen and Eriksson, 1970), thus making interpretation of arterial blood pressure readings difficult. In addition to biological variation, arterial blood pressure in dogs is known to be affected by psychological factors (Müller, 1963) and by respiratory variation (Valtonen and Eriksson, 1970). Anaesthesia, introduces several other variables, that make interpretation of blood pressure even harder (Cullen, 1974). Many of the drugs used for premedication, induction and maintenance of anaesthesia decrease arterial blood pressure. It can also be affected by changes in $PaC0_2$ and body temperature, body position, blood volume, surgical stimulation and depth and duration of anaesthesia (Cullen *et al*, 1972). NSAIDs have been shown to interfere with blood pressure control in hypertensive human patients (Durao *et al*, 1977; Watkins *et al*, 1980; Moore *et al*, 1981), but there is no evidence in veterinary literature to suggest that these drugs have a direct effect on arterial blood pressure in animals.

When arterial blood pressure falls during anaesthesia there is a decrease in both hepatic and renal blood flow which can affect the metabolism and excretion of drugs. Consequently it could be expected that there might have been evidence of higher flunixin plasma levels, prolonged whole body clearance, increased elimination half-lives and MRT in those dogs with the lowest recorded mean arterial blood pressures. However no such

correlation was found to exist between low arterial blood pressure readings and plasma levels of flunixin or the pharmacokinetics of flunixin.

4.2 Pharmacokinetics

Pharmacokinetic analysis provides a mathematical description of drug disposition, usually in plasma. It provides useful information both on the rate of drug passage into and its removal from the vascular compartment. Its importance to the clinician, lies in the fact that it gives a rational basis for selecting dosage schedules (Lees *et al*, 1990).

The fall in plasma flunixin concentrations was found to be tri-exponential except in dogs 6 and 16, where it was bi-exponential. This was contrary to results reported by Hardie *et al* (1985), and McKellar *et al* (1991b). These workers recorded that the plasma concentration versus time curve best fitted a 2-compartmental model. The discrepancy with the study by Hardie *et al* (1985) is probably related to the fact that, Hardie *et al* (1985) only sampled for 12 hours and less intensively than in the present study where animals were bled for 30 hours. Similarly McKellar *et al* (1991b) sampled less intensively, especially within the first hour of drug administration.

In this study, non-compartmental models were also used to analyse the concentration versus time data. Use of non-compartmental models is based on the statistical moments theory (Cutler, 1978; Yamoka *et al*, 1978). The main advantages of non-compartmental models over compartmental models, are firstly, that none of the 'non-central' pools are identified with any anatomical structures (DiStefano, 1982), and secondly, mathematical analyses of time-varying kinetic data can be accomplished with integral equations, rather than differential equations, in contrast to multicompartmental analysis (DiStefano, 1982; DiStefano and Landaw, 1984). Semrad *et al* (1985) also used non-compartmental models to evaluate the pharmacokinetics of flunixin in the horse, as they were unable to fit compartmental models to the experimental data. The use of non-compartmental models were considered appropriate in this study particularly because of the plateau effect seen from 10 - 30 minutes after intravenous flunixin administration.

After the intravenous administration of flunixin, high plasma concentrations were achieved immediately. In group A, the mean plasma drug concentration obtained at 2 minutes, was 24.5 ± 1.8 µg/ml, while in group B, it was 28.7 ± 2.1 µg/ml. In dogs 1, 3, 7, 15, and 16, a

slight rise in plasma flunixin was seen, while in dogs 2, 4, 10, 13 and 18 a very marginal fall in plasma flunixin concentration was seen 10-30 minutes after the intravenous flunixin injection. This unusual decline curve with concentrations falling from maximum plasma values but then increasing again to minor peak values and subsequently declining was also described by McKellar *et al* (1991b), during their pharmacokinetic trials on flunixin given intravenously to beagles at 1.1 mg/kg. This rise, or lack of fall, in plasma flunixin concentration from 10 minutes to approximately 30 minutes after flunixin administration may have been caused by enterohepatic circulation of the drug. Duggan *et al* (1975), and Risdall *et al* (1978), concluded that enterohepatic circulation of NSAIDs is common in dogs while McKellar *et al* (1991b), also felt that the pattern of elimination of flunixin in beagle dogs was consistent with enterohepatic cycling, although they did not indicate when the enterohepatic recirculation occurred. Lees and workers (1991), consistently noticed a small secondary peak in the plasma-concentration-time curve, when pharmacokinetic analyses of 2.2 and 8.8 mg/kg flunixin i.v. was performed on calves and suggested that this was a consequence of enterohepatic recirculation. Ivey (1986), suggested that enterohepatic recirculation and regeneration of active drug, could cause prolonged local concentrations of the drug in the intestinal mucosa, thereby producing local mucosal irritation. However, gastro-intestinal intolerance was not a feature of any of the dogs in this trial, probably because only a single dose of flunixin at therapeutic levels was administered. Ivey (1986) suggested that enterohepatic circulation may prolong the half-life of the drug. This was consistent with dogs 1, 2, 3, 7, and 13 whose elimination half-lives were prolonged, but not with dogs 4, 10, 15, 16 and 18 whose elimination half-lives were, in fact, less than the means for their particular group.

After the plateau effect, the rate of decline of the plasma drug concentration was reduced. The observed mean elimination half-life for dogs in group A (7.86 $\pm$ 1.18 hours), was slightly longer, but not significantly so, than for dogs in group B (6.10 $\pm$ 0.07 hours). These results were higher than the 3.67 $\pm$ 1.20 hours, reported by Hardie *et al* (1985) in intact awake mixed breed dogs given 1.1 mg/kg flunixin intravenously, and with those of McKellar *et al* (1991b) who administered i.v flunixin at the same dose to beagles (3.10 $\pm$ 0.85 hours). It is difficult to say whether the longer elimination half-life of flunixin found in this study was due to anaesthesia, or whether in fact Hardie *et al* (1985), had underestimated the elimination half-life, because of less sensitive assay and shorter blood sampling period. However, in support of the work of Hardie *et al* (1985), the pharmacokinetics of flunixin in other conscious species were found to be similar. In lactating cattle the mean elimination half-life was 3.14 hours (Anderson *et al*, 1990), while

in the horse it was of much shorter duration (1.55 hours) (Chay *et al*, 1982). In the cat too, the mean elimination half-life was short (0.7 to 1.5 hours) (Taylor *et al*, 1991), however, in this study there were insufficient data points, which precluded the accurate calculation of this parameter. The slower mean elimination half-life obtained in this study may suggest that anaesthesia does infact slow down the elimination of flunixin as compared to conscious animals. However, until a parallel study in conscious dogs is carried out, no firm conclusions can be drawn. Such a study was not possible, in this trial. McKellar *et al* (1991b) found a short elimination half-life in beagles, but other workers (Runkel *et al*, 1972; Frey and Rieh, 1981; Frey and Löscher, 1985; Lee *et al*, 1990) have suggested that beagles demonstrate differences in drug pharmacokinetics when compared with mixed breed dogs. However, McKellar *et al* (1989), suggested that the difference in flunixin pharmacokinetics between beagles and mixed-breed dogs is likely to be small, since their results in conscious beagles were similar to those of Hardie *et al* (1985) using a mixed breed group. Flower (1986) and Conlon (1988) found that renal elimination of NSAIDs is often pH dependent, with drug elimination occuring at a faster rate in alkaline urine. However, in this study no urine samples were collected, so this point could not be clarified.

The mean clearance of the drug from the body, CL(b), in both groups A and B, was almost identical i.e. 34.9 $\pm$ 5.6 and 34.6 $\pm$ 4.6 ml/kg.hr respectively. These values were half that reported by Hardie (63.6 $\pm$ 13.9 ml/kg.hr) and McKellar *et al* (1991b) (58.8 $\pm$ 4.8 ml/kg.hr). Considering the dogs individually, there were large variations. Clearance of flunixin was very quick in dog 5 (71.6 ml/kg.hr) and dog 17 (68.2 ml/kg.hr). The CL(b) values for dog 5 and 17, were consistent with that found to occur in awake dogs by Hardie *et al* (1985). Dog 9 had a slow CL(b) of 15.7 ml/kg.hr. The variation in the clearance of flunixin found in this study, correlates well with the observation made by Boothe (1989), who suggested that the clearance of NSAIDs varies greatly among individuals within a species, thereby accounting for considerable variability in plasma half-lives of these drugs. In this study, no correlation was found to exist between blood pressure and rate of clearance of the drug from the body.

The apparent volume of the central compartment, Vc, found in groups A and B (34.58 $\pm$ 2.58 and 32.49 $\pm$ 4.43 ml/kg) was half that found in Hardies study (78.8 $\pm$ 17.9 ml/kg). The reason for this is unclear, but may reflect changes in cardiovascular function during anaesthesia. The volume of distribution at steady state, Vdss, in group A was slightly, but not significantly higher than group B (195.89 $\pm$ 38.5 and 132.63 $\pm$ 8.73 ml/kg

respectively). These results were comparable to Hardie's values of 181 ± 79 ml/kg, and those of McKellar *et al* (1991b) (140 ± 24 ml/kg).

4.3. Biochemistry

Stegelmeier and colleagues (1988), observed that in normal conscious dogs, administering flunixin meglumine at 1.1 mg/kg i.v., caused no severe side effects or gross lesions. They based this observation on a study of 4 healthy dogs who were given flunixin 1.1 mg/kg i.v., for 3 days, and were then monitored clinically, together with urine and serum samples collected over a 72 hour period. All 4 dogs showed few physical or haematological changes. The dogs were euthanased after 72 hours and examined for gross and histological lesions. None were found.

Knodel and workers (1992), observed that acute renal failure could occur in any patient treated with NSAIDs, but felt that patients at greatest risk of developing acute renal failure from NSAIDs were those who required the vasodilating effects of prostaglandin to preserve renal blood flow and glomerular filtration. Crooks and Stevenson (1981) suggested that those healthy young patients who had suffered excessive blood loss during surgery, resulting in compromised renal perfusion, were most likely to develop this complication. It has been reported by Corcoran and Page (1943) and Glauser and Selkurt (1952), that anaesthesia in dogs depresses renal haemodynamics, reducing GFR and renal plasma flow. Rubin (1986), found that clinical and experimental conditions in which renal function was found to be prostaglandin dependent included low renal perfusion pressure induced by hemorrhagic shock, surgical stress and anaesthetic stress. Stillman *et al* (1984) and del Favero (1987) both mentioned anaesthesia as being one of the factors which predisposes the animal to functional renal impairment during treatment with NSAIDs. Since the dogs in this trial were having both anaesthesia and surgery, and these are known to produce an increase in renal vascular resistance and a decrease in renal blood flow (Eng and Stahl, 1970; Rubin, 1986), they were, theoretically, at risk of developing NSAID induced renal impairement.

As this was a clinical study, serum biochemistry, namely BUN, serum creatinine and serum phosphate, together with electrolytes, sodium, potassium and chloride, were used to identify changes in renal function in the individual animals, during the trial. These biochemical parameters were chosen, because BUN and plasma creatinine measurements

are the time-honoured means of estimating glomerular filtration rate (GFR) (Bovée and Joyce, 1979). Creatinine and urea are cleared from the blood primarily by glomerular filtration, and so their blood values are largely dependent on GFR (Bovée and Joyce, 1979). Plasma creatinine is influenced little by factors other than glomerular filtration and is, therefore, a valuable means of measuring GFR and renal function (Bovée and Joyce, 1979). Creatinine is an end product of muscle metabolism, and its end product is fairly constant and only slightly affected by protein intake, protein metabolism or physical activity (Bloch and Schoenheimer, 1939; Bleiler and Schedl, 1962). After its release from muscle, creatinine enters the plasma and is excreted almost entirely by glomerular filtration (Dominguez and Pomerene, 1945), and consequently, creatinine clearance can be used as a reasonable measure of filtration rate (Bovée and Joyce, 1979). According to Narayanan (1991), however, serum creatinine levels are not a good index for the early diagnosis of acute renal failure. Urea is formed only in the liver and may be regarded as the end product of protein catabolism, whether the protein is derived from dietary or tissue sources (Wills and Savory, 1981). BUN is, therefore, influenced by many factors other than glomerular filtration, principally nitrogen balance (Bovée and Joyce, 1979). For this reason, BUN does not reflect glomerular filtration as accurately as does serum creatinine (Bovée and Joyce, 1979). In patients with acute renal failure, however, there is a relatively good correlation between the severity of illness and BUN concentrations (Wills and Savory, 1981).

More sensitive measures of renal function are available. In addition to glomerular filtration rate (GFR) (Bovée and Joyce, 1979), effective renal plasma flow (ERPF) (Ram *et al*, 1968) is an important and valuable index of renal plasma flow. This is measured by the clearance of para-aminohippurate (PAH) (Smith *et al*, 1945), and is a more sensitive method of assessing renal function than BUN, but less sensitive than endogenous creatinine clearance (Smith *et al*, 1945). However, it is a time-consuming procedure, requiring urethral catheterization with its attendant risk of infection, accurate sampling of urine and blood and an i.v. infusion maintained at a constant rate over long periods (Ram *et al*, 1968). Because of its complicated nature, it has remained a research procedure and is not used in clinical practice (Ram *et al*, 1968). A simplified clinical method for measurement of ERPF is by using a single injection of I^{125} Hippuran (Ram *et al*, 1968). This, however, requires the use of radio-isotope labelled substance, which is impractical for routine renal assessment in veterinary medicine. The renal clearance of creatinine, has been advocated for clinical measurement of renal function (Finco, 1971; Bovée and Joyce, 1979). Creatinine is excreted almost exclusively by glomerular filtration in the dog (Finco

et al, 1981), so its clearance is used to estimate the GFR, but this method requires urethral catheterization to allow accurate measurements of urine volume over a given period of time. Since the dogs were young and known to be clinically normal prior to the start of the trial, such an invasive procedure could not be deemed to be in the individual animal's best interest. Consequently this was not acceptable to the Home-Office. Other attempts to collect urine accurately over the required 3 hour period for creatinine clearance were found to be impractical. Hence, BUN, serum creatinine and serum phosphate levels, though not as sensitive or accurate as the above mentioned methods, were considered the most practical for this study.

There was a significant difference in the change in BUN levels from 0 to 12 hours in dogs that had received flunixin as an analgesic (Groups A and B), compared to those dogs which had not received flunixin (Control group C). This suggested that flunixin, and not anaesthesia and surgery, nor the time of administration of the drug, was responsible for the rise in BUN levels, thereby suggesting that flunixin may have caused some degree of renal impairment, whether administered during or at the end of anaesthesia. In general, anaesthesia appears to cause modest, readily reversible decreases in ERPF and GFR (Bastron, 1980), but prolonged deep anaesthesia can have profound depressant effects on renal circulation (Bovée and Joyce, 1979). In this study, it was not possible to study ERPF and GFR, but it was evident by the minimal changes of BUN and serum creatinine levels in the control group, that anaesthesia and surgery alone caused few adverse effects. The marginal rise in serum creatinine levels in groups A, B and C, were probably caused by muscle damage incurred during surgery (Power *et al*, 1992). The changes in BUN levels in dogs in group A and B seen within the first 12 hours of drug administration, are consistent with Stillman and Schlesingers (1990) observations, that the onset of NSAID-induced renal changes occur abruptly following initiation of NSAID therapy.

In all dogs in group A, and in 8 dogs in group B (exceptions are dogs 12 and 20), BUN levels had begun to return to normal within 30 hours of flunixin administration. Kore (1990) and Aronoff, (1992) suggested that haemodynamic deterioration in renal function was often reversible after discontinuation of NSAID therapy, and that rapid recovery (24-72 hours) of baseline renal function generally occurred following discontinuation of the drug. These findings were confirmed by Corwin and Bonventre (1984); Carmichael and Shankel (1985) and Brater (1990). The results of this study were consistent with results reported by Blackshear and colleagues (1983), that the inhibitory effects of NSAIDs on renal cyclo-oxygenase weakened during 8 to 24 hours. There was still, however, a

significant difference in the changes in BUN levels from 0 to 30 hours in dogs in group A when compared with changes in group C, while there was no significant difference in BUN levels from 0 to 30 hours in dogs in group B, when compared with group C. This suggests that the renal damage produced by flunixin in group A was greater than that produced in group B, providing support for the suggestion of Smitherman (1992) that the risk of renal damage caused by flunixin may be reduced if the drug is given when the dog is recovering from rather than during anaesthesia.

None of the animals in this study appeared to develop serious renal impairment as a result of flunixin administration. Serious renal impairement was defined by Murray and Brater (1990) as at least a doubling of BUN or serum creatinine concentrations. This however, cannot be held true in all cases as shown below. In one dog (dog 4), BUN levels rose higher than 10 mmol/l during the 30 hour period after flunixin administration. In Dog 4, the BUN level had more than doubled in 12 hours after flunixin administration, but by 30 hours had begun to drop. This initial doubling of BUN did not cause too much concern, however, as the level was still within the normal range for the dog. The highest rises in BUN, creatinine and phoshate were seen in dog 2 (group A) 12 hours after the drugs administration and dog 20 (group B) 30 hours after flunixin administration. The high BUN, creatinine and phosphate levels seen in dog 2 may have been due to the fact that this dogs blood pressure was on the low-side (63-75 mm Hg) throughout anaesthesia, and only rose to above 80 mm Hg after anaesthesia had been terminated. Over a range of blood pressures from approximately 70 to 180 mm Hg there is normally very little change in either renal plasma flow or glomerular filtration rate (Bastron, 1980). Theoretically the administration of flunixin during anaesthesia, when the blood pressure was lower than 70 mm Hg, may have prevented PGE_2 and PGI_2 related vasodilation, causing a decrease in the rate of renal plasma flow and glomerular filtration, with the development of prerenal azotemia and renal damage from unopposed renal vasoconstriction. However, it is interesting to note that there was no direct correlation between the lowest recorded arterial blood pressure reading and a rise in BUN levels. The cause for the rise in BUN in this dog is, therefore, not clearly defined. Unfortunately no 30 hour sample was taken to know whether these levels had started to return to basal level. However, the dog made an unremarkable recovery and did not demonstrate any signs of depression, anorexia, polyuria or polydipsia, suggestive of clinical renal disease, at any stage. Dog 20, showed a sudden rise BUN, creatinine and phosphate levels at 30 hours. Throughout anaesthesia the animal's arterial blood pressure remained within the normal range and continued to remain within normal limits when flunixin was administered, at the end of anaesthesia. No other

drugs were given during the recovery period, which could have accounted for the sudden, unexpected rise in biochemical parameters. This dog underwent an ovario-hysterectomy, and in the correspondence relating to flunixin toxicity (Elswood, 1992), all the affected dogs underwent surgery for routine ovario-hysterectomy. Whether there is any connection, is difficult to say. This dog, however, showed no signs of clinical renal disease and made an unremarkable recovery.

One owner (group A, dog 8), stated that her dog drank excessively for 2 months after surgery, but was otherwise bright, alert and had a good appetite. BUN and creatinine levels of this dog measured 2 months after anaesthesia, were within the normal range, but the possible implications of flunixin in the development of the polydipsia and polyuria cannot be discounted.

In the 3 groups no other biochemical parameters examined, namely sodium, potassium or chloride, changed during the 30 hour trial period. This was not unexpected as all the dogs were normal healthy adults at the start of the trial, and was consistent with the observations of Brater (1988) and Whelton and Hamilton (1991). Brater (1988), concluded that, in most healthy patients, the risk of sodium retention is low. Hyperkalemia can result from NSAID treatment but is an unusual complication of NSAID treatment in healthy patients, presumably because of the multiplicity of factors that are capable of maintaining potassium balance, even in the absence of prostaglandins (Whelton and Hamilton, 1991). NSAID induced hyperkalaemia often occurs in the setting of NSAID induced acute renal deterioration or worsening of underlying renal impairement (Whelton and Hamilton, 1991).

4.4 Conclusion

From this study, it may be concluded that flunixin meglumine is best avoided in the anaesthetised dog, but if required, should be administered on termination of anaesthesia and surgery, rather than during anaesthesia and surgery. If administered to the anaesthetised dog, it is important to remember that the pharmacokinetics of the drug may be altered in comparison to that reported in conscious dogs and consequently, the drug need not be repeated as often as required in the awake dog. Moreover, as flunixin is found to elevate BUN and creatinine levels in dogs under anaesthesia, it is strongly advised that no other nephrotoxic drug is administered simultaneously or for the next 30 hours after

flunixin administration. Finally, flunixin should not be used in those animals known or suspected to have renal disease. While it has been stated that hypotension is best avoided during anaesthesia in those animals treated with NSAIDs as it increases the risk of acute renal damage occuring (Bush *et al*, 1991), in this study, no correlation was found to exist between low mean arterial blood pressure readings and rise in BUN levels. Also, low mean arterial blood pressure readings during anaesthesia and surgery did not appear to alter the pharmacokinetics of flunixin, and there was no correlation found between low mean arterial blood pressure readings, extended elimination half-life of the drug and rise in BUN.

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APPENDIX

APPENDIX A

TABLES

TABLE A1 - Mean arterial blood pressure readings ± SEM of individual dogs in group A, taken every 5 minutes after induction of anaesthesia, until the dog regained sternal recumbency.

TABLE A2 - Mean arterial blood pressure readings ± SEM of individual dogs in group B, taken every 5 minutes after induction of anaesthesia, until the dog regained sternal recumbency.

TABLE A3 - Pulse readings ± SEM of the individual dogs in group A, taken every 5 minutes throughout anaesthesia.

TABLE A4 - Pulse readings ± SEM of the individual dogs in group B, taken every 5 minutes throughout anaesthesia.

TABLE A5 - Respiratory rates (breaths/minute) ± SEM of the individual dogs in group A, taken every 5 minutes throughout anaesthesia.

TABLE A6 - Respiratory rates (breaths/minute) ± SEM of the individual dogs in group B, taken every 5 minutes throughout anaesthesia.

TABLE A7 - ETCO2 values (%) ± SEM of dogs No 1, 2, 3, 8, and 9 (group A), taken every 5 minutes on commencement of surgery, until termination of anaesthesia.

TABLE A8 - ETCO2 values (%) ± SEM of dogs No 11, 12, 14, 16, 17, 18, 19, and 20 (group B), taken every 5 minutes on commencement of surgery, until termination of anaesthesia.

FIGURES

FIGURE A1 - Graphical representation of mean blood pressure readings of dogs No 1-5 in group A versus time.

FIGURE A2 - Graphical representation of mean blood pressure readings of dogs No 6-10 in group A versus time.

FIGURE A3 - Graphical representation of mean blood pressure readings of dogs No 11-15 in group B versus time.

FIGURE A4 - Graphical representation of mean blood pressure readings of dogs No 16-20 in group B versus time.

FIGURE A5 - Graphical representation of individual pulse readings of dogs No 1-5 in group A versus time.

FIGURE A6 - Graphical representation of individual pulse readings of dogs No 6-10 in group A versus time.

FIGURE A7 - Graphical representation of individual pulse readings of dogs No 11-15 in group B versus time.

FIGURE A8 - Graphical representation of individual pulse readings of dogs No 16-20 in group B versus time.

FIGURE A9 - Graphical representation of individual respiration readings of dogs No 1-5 in group A versus time.

FIGURE A10 - Graphical representation of individual respiration readings of dogs No 6-10 in group A versus time.

FIGURE A11 - Graphical representation of individual respiration readings of dogs No 11-15 in group B versus time.

FIGURE A12 - Graphical representation of individual respiration readings of dogs No 16-20 in group B versus time.

FIGURE A13 - Graphical representation of individual $ETCO_2$ readings of dogs No 1, 2, 3, 8 and 9 in group A versus time.

FIGURE A14 - Graphical representation of individual $ETCO_2$ readings of dogs No 11, 12, 14, 16, 17, 18, 19 and 20 in group B versus time.

Table A1: Mean arterial blood pressure +/- readings in mm Hg, of individual dogs in group A, taken every 5 minutes after induction of anaesthesia until the dog regained sternal recumbency. Dogs trial numbers 1-10 (group A), received flunixin meglumine, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

Mean arterial blood pressure readings in mm Hg

Trial No-	1	2	3	4	5	6	7	8	9	10	Mean BP	SEM
Time												
Pre				87		94	105	80	72	95	88.83	5.26
0 min			82	70			82	92	98	92	86.00	4.49
5 min				95		67	64	91	90	84	81.83	5.89
10 min	75			86		64	68	86	85	79	77.57	3.66
15 min	80			86		93	82	89	84	79	84.71	2.05
20 min	75			95		69	82	84	86	57	78.29	5.10
25 min	85			102	65	40	74	84	81	71	75.25	6.83
30 min	72			100	65	70	78	83	85	93	80.75	4.50
35 min	60			98	75	73	72	87	88	79	75.25	16.56
40 min	60			100	59	74	65	89	86	76	72.38	7.04
45 min	83			68	75	70	55	90	92	80	76.63	4.64
50 min	75		82	68	75	93	55	83	96		78.44	4.39
55 min	62	69	85	92	64	72	65	78	83		74.44	3.74
1 hr	89	63	92	88	72	78	63	76	93		79.33	4.18
1 hr 5 min	70	63	82	90	72	80	55	59	92		73.67	4.69
1 hr 10 min	72	65	78	82	65		55	69			69.43	3.67
1 hr 15 min	52	69	86	95	60		48	55	94		69.88	7.27
1 hr 20 min	72	69	88	79	60	100	66	69	91		77.11	4.70
1 hr 25 min	69	70	92	80	74	89	84	60	94		79.11	4.12
1 hr 30 min	55	75	92	89	74		75	77	102		79.88	5.40
1 hr 35 min	55	65	90	108	62		68	70	97		76.88	7.16
1 hr 40 min	52	64	95	90	68		74	77	93		76.63	5.77
1 hr 45 min	64	68	94	98	77		74	79	94		81.00	4.85
1 hr 50 min	68	63	94		78		74		100		79.50	6.53
1 hr 55 min	68	60	94		72		72		86		75.33	5.56
2 hrs	70	78	95		84		76		78		80.17	3.82
2 hr 5 min		69	98		77		66		78		77.60	6.25
2 hr 10 min		71	85		82		68				76.50	4.77
2 hrs 15 min		79	80		79		70				77.00	2.71
2 hr 20 min		85	95		88		68				84.00	6.62
2 hrs 25 min		82	95		78		63				79.50	7.61
2 hr 30 min		79			84		75				79.33	3.19
2 hrs 35 min					72		66				69.00	4.24
2 hr 40 min					84		65				74.50	13.44
2 hrs 45 min					84		75				79.50	6.36
2 hr 50 min							66					
2 hrs 55 min							74					
3 hrs							78					
3 hrs 5 min							70					
3 hr 10 min							70					
3 hrs 15 min							66					
3 hr 20 min							68					
3 hrs 25 min							79					
3 hr 30 min							95					

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the mean arterial blood pressure readings
SEM = Standard error of means
min = minute
mm Hg = millimeters of mercury
hr = hour

Table A1: Mean arterial blood pressure +/- readings in mm Hg, of individual dogs in group A, taken every 5 minutes after induction of anaesthesia until the dog regained sternal recumbency. Dogs trial numbers 1-10 (group A), received flunixin meglumine, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

Mean arterial blood pressure readings in mm Hg

Trial No-	1	2	3	4	5	6	7	8	9	10	Mean BP	SEM
Time												
Pre				87		94	105	80	72	95	88.83	5.26
0 min			82	70			82	92	98	92	86.00	4.49
5 min				95		67	64	91	90	84	81.83	5.89
10 min	75			86		64	68	86	85	79	77.57	3.66
15 min	80			86		93	82	89	84	79	84.71	2.05
20 min	75			95		69	82	84	86	57	78.29	5.10
25 min	85			102	65	40	74	84	81	71	75.25	6.83
30 min	72			100	65	70	78	83	85	93	80.75	4.50
35 min	60			98	75	73	72	87	88	79	75.25	16.56
40 min	60			100	59	74	65	89	86	76	72.38	7.04
45 min	83			68	75	70	55	90	92	80	76.63	4.64
50 min	75		82	68	75	93	55	83	96		78.44	4.39
55 min	62	69	85	92	64	72	65	78	83		74.44	3.74
1 hr	89	63	92	88	72	78	63	76	93		79.33	4.18
1 hr 5 min	70	63	82	90	72	80	55	59	92		73.67	4.69
1 hr 10 min	72	65	78	82	65		55	69			69.43	3.67
1 hr 15 min	52	69	86	95	60		48	55	94		69.88	7.27
1 hr 20 min	72	69	88	79	60	100	66	69	91		77.11	4.70
1 hr 25 min	69	70	92	80	74	89	84	60	94		79.11	4.12
1 hr 30 min	55	75	92	89	74		75	77	102		79.88	5.40
1 hr 35 min	55	65	90	108	62		68	70	97		76.88	7.16
1 hr 40 min	52	64	95	90	68		74	77	93		76.63	5.77
1 hr 45 min	64	68	94	98	77		74	79	94		81.00	4.85
1 hr 50 min	68	63	94		78		74		100		79.50	6.53
1 hr 55 min	68	60	94		72		72		86		75.33	5.56
2 hrs	70	78	95		84		76		78		80.17	3.82
2 hr 5 min		69	98		77		66		78		77.60	6.25
2 hr 10 min		71	85		82		68				76.50	4.77
2 hrs 15 min		79	80		79		70				77.00	2.71
2 hr 20 min		85	95		88		68				84.00	6.62
2 hrs 25 min		82	95		78		63				79.50	7.61
2 hr 30 min		79			84		75				79.33	3.19
2 hrs 35 min					72		66				69.00	4.24
2 hr 40 min					84		65				74.50	13.44
2 hrs 45 min					84		75				79.50	6.36
2 hr 50 min							66					
2 hrs 55 min							74					
3 hrs							78					
3 hrs 5 min							70					
3 hr 10 min							70					
3 hrs 15 min							66					
3 hr 20 min							68					
3 hrs 25 min							79					
3 hr 30 min							95					

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the mean arterial blood pressure readings
SEM = Standard error of means
min = minute
mm Hg = millimeters of mercury
hr = hour

Table A2: Mean arterial blood pressure +/- SEM readings in mm Hg, of individual dogs in group B, taken every 5 minutes after induction of anaesthesia until the dog regained sternal recumbency. Dogs trial numbers 11-20 (group B), received flunixin meglumine, 1.1 mg/kg, i.v., immediately after anaesthesia had terminated

Mean arterial blood pressure readings in mm Hg

Trial No-	11	12	13	14	15	16	17	18	19	20	Mean BP	SEM
Time												
Pre	76	64	98	91	102	80	86	77	60	108	84.26	5.26
0 min	71	75	74	100	93	83	79	62	78	140	85.50	7.33
5 min	66	58	76	83	81	52	87	84	73	82	74.20	3.96
10 min	66	64	80	79	74	57	90	76	71	53	71.00	3.74
15 min	58	63	86	66	84	61	78	70	67	56	68.90	3.51
20 min	71	54	75	69	85	74	77	80	80	67	73.20	2.90
25 min	61	71	78	61	95	75	75	74	79	79	74.80	3.24
30 min	70	79	78	74	95	87	91	96	86	86	84.20	2.91
35 min	86	68	79	78	85	86	86	71	73	73	78.50	2.33
40 min	73	58	82	64	93	88	86	66	74	68	75.20	3.86
45 min	83	58	78	75	85	91	88	73	78	96	80.50	3.58
50 min	78	57	78	63	95	78	86	78	72	83	76.80	3.63
55 min	78	59	89	57	96	84	85	79	77	80	78.40	4.06
1 hr	70	59	84	69	92	77	79	72	72	76	75.00	2.99
1 hr 5 min	75	51	79	65	96	78	74	69	76	85	74.80	3.97
1 hr 10 min	72	51	82	66	93	58	71	78	71	80	72.20	4.03
1 hr 15 min	70	47	78	73	106	55	94	82	73	73	75.10	5.67
1 hr 20 min	78	53	86	72		59	93	78	72	75	74.00	4.35
1 hr 25 min	70	59	79	65		67	124	87	69	73	77.00	6.86
1 hr 30 min	73	58	85	80		56	100	72	79	73	75.11	4.73
1 hr 35 min	66	55	74	79		57		68	74	82	68.38	3.69
1 hr 40 min	68	57		89		66		74	75	87	73.71	4.66
1 hr 45 min	70	58		88		61		62	79	83	71.57	4.85
1 hr 50 min	65	55		83		70		66	60	73	67.43	3.72
1 hr 55 min	76	63		79		78		68	105	80	78.43	5.43
2 hrs	62	86		85		68		78	81	74	76.29	3.63
2 hr 5 min	66	72		75		70		79	81	85	75.43	2.72
2 hr 10 min	67	89		79		70		86	100	86	82.43	4.66
2 hrs 15 min	69	66		87		76		72		75	74.17	3.27
2 hr 20 min	70	72		81		102		83		90	83.00	5.31
2 hrs 25 min	81	57		70		94		85		79	77.67	5.72
2 hr 30 min	103	58		78		96				82	83.40	8.73
2 hrs 35 min	110	62		73		79				77	80.20	8.95
2 hr 40 min	100	55		80		81				80	79.20	8.00
2 hrs 45 min		62		76						77	71.67	5.93
2 hr 50 min		87		75						72	78.00	5.61
2 hrs 55 min		71		80						74	75.00	3.24
3 hrs		78		95						90	87.67	6.18
3 hrs 5 min		76		95						93	88.00	7.38
3 hr 10 min				78						88	83.00	7.07
3 hrs 15 min				92								
3 hr 20 min				84								
3 hrs 25 min				82								
3 hr 30 min												

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the mean arterial blood pressure readings
SEM = Standard error of means
min = minute
mm Hg = millimeters of mercury
hr = hour

Table A3 : Pulse readings +/-SEM, in beats/minute, of the individual dogs in group A, taken every 5 minutes throughout anaesthesia.
Dogs trial numbers 1-10 (group A), received flunixin meglumine, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

Pulse readings in beats/minute

Trial No-	1	2	3	4	5	6	7	8	9	10	Mean	SEM
Time												
Pre	160	120	132	100	120	112	128	100	130	120	122.20	5.80
0 min	110		100	120	120		122	120	142	71	113.13	7.84
5 min	90	110	110	130		110	118	130	132	107	115.22	4.86
10 min	100	80	110	120	120	108	88	134	89	98	104.70	5.63
15 min	90	60	90	118	112	125	95	134	110	91	102.50	7.19
20 min	110	60	100	130	112	120	95	128	100	90	104.50	6.89
25 min	120	60	100	140	130	90	90	128	90	85	103.30	8.39
30 min	140	80	100	140	120	82	100	120	93	83	105.80	7.64
35 min	138	79	100	130	130	80	100	118	90	86	105.10	7.41
40 min	130	75	108	130	120	80	92	118	100	82	103.50	6.92
45 min	130	85	108	130	120	90	90	115	80	82	103.00	6.62
50 min	130	80	108	128	120	82	90	118	108	73	103.70	6.99
55 min	120	79	108	120	120	90	83	110	100	82	101.20	5.56
1 hr	110	80	102	120	115	90	83	120	100		102.22	5.41
1 hr 5 min	105	95	110	120	120	90	83	100	108		103.44	4.50
1 hr 10 min	190	95	100	138	115	90	80	90	95		110.33	12.16
1 hr 15 min	200	78	100	120	108	90	80		95		108.88	14.88
1 hr 20 min	180	78	100	120	119	90	85		95		108.38	12.32
1 hr 25 min	180	80	100	120	115	92	92		98		109.63	11.79
1 hr 30 min	195	80	100	130	115		100		98		116.86	15.42
1 hr 35 min	200	79	100	118	115		90		98		114.29	16.39
1 hr 40 min		78	102	120	115		90		93		99.67	21.16
1 hr 45 min		78	107		118		80		98		96.20	8.62
1 hr 50 min		80	107		115		100		98		100.00	6.51
1 hr 55 min		78	110		120		100		90		99.60	8.23
2 hrs		76	110		120		100				101.50	10.89
2 hr 5 min		78	112		120		88				99.50	11.41
2 hr 10 min		78	112		120		95				101.25	10.78
2 hrs 15 min		78	110		120		98				101.50	10.43
2 hr 20 min		80	110		120		90				100.00	10.54
2 hrs 25 min		80	110		120		100				102.50	9.86
2 hr 30 min		79	110		125		100				103.50	11.14
2 hrs 35 min		70	100		130		100				100.00	14.14
2 hr 40 min		90	89		130		95				101.00	11.26
2 hrs 45 min		120	97		132		100				112.25	9.62
2 hr 50 min		120	97		140		105				115.50	10.92
2 hrs 55 min		93					100				96.50	4.95
3 hrs							100				100.00	
3 hrs 5 min							80				80.00	
3 hr 10 min							90				90.00	
3 hrs 15 min							80				80.00	
3 hr 20 min							90				90.00	
3 hrs 25 min							95				95.00	
3 hr 30 min							110				110.00	

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the pulse readings
SEM = Standard error of means
min = minute
pulse = beats/minute
hr = hour

Table A4 : Pulse readings +/-SEM, in beats/minute, of the individual dogs in group B, taken every 5 minutes throughout anaesthesia.
Dogs trial numbers 11-20 (group B), received flunixin meglumine, 1.1 mg/kg, i.v., immediately after anaesthesia had terminated.

Pulse readings in beats/minute

Trial No-	11	12	13	14	15	16	17	18	19	20	Mean	SEM
Time												
Pre	100	100	102	112	88	200	120	110	80	100	111.20	11.08
0 min		120			131	170	140	136	120	100	131.00	8.87
5 min	120	130	120	105	82	166	135	100	113	131	120.00	7.60
10 min	112	110	100	90	78	187	120	96	97	93	108.30	10.05
15 min	100	120	100	85	70	147	120	90	101	107	104.00	7.14
20 min	112	120	100	89	78	131	117	117	89	108	106.10	5.56
25 min	108	120	100	89	74	150	119	110	120	108	109.80	6.78
30 min	95	125	110	89	71	163	117	108	101	107	108.60	8.12
35 min	95	120	80	95	74	156	117	111	108	102	105.80	7.70
40 min	100	120	90	95	78	129	119	119	110	92	105.20	5.52
45 min	100	120	90	100	78	133	117	98	104	100	104.00	5.24
50 min	98	110	100	100	89	133	116	101	101	101	104.90	4.06
55 min	98	120	100	102	70	141	116	100	102	100	104.90	6.09
1 hr	105	110	90	98	77	153	119	97	104	100	105.30	6.73
1 hr 5 min	105	120	100	90	74	159	109	107	105	111	108.00	7.30
1 hr 10 min	100	120	100	82	84	163	111	107	104	113	108.40	7.53
1 hr 15 min	120	120	98	87	83	159	120	104	104	107	110.20	7.19
1 hr 20 min	95	120	98	92	129	156	130	104	102	115	114.10	6.69
1 hr 25 min	100	120	89	102		163	135	100	100	122	114.56	8.19
1 hr 30 min	120	125	84	96		156	120	97	104	120	113.56	7.50
1 hr 35 min	100	115	90	90		156		98	104	129	110.25	8.55
1 hr 40 min	110	120	90	89		156		97	89	153	113.00	19.14
1 hr 45 min	120	110	84	89		159		96	72	144	109.25	11.44
1 hr 50 min	98	120	80	108		159		94	115	150	115.50	10.29
1 hr 55 min	100	130	92	106		153		94	84	159	114.75	10.92
2 hrs	100	120	92	98		153		97	71	153	110.50	11.12
2 hr 5 min	100	130	100	99		150		98	73	163	114.13	11.52
2 hr 10 min	100	120	90	99		153		110	84	166	115.25	11.21
2 hrs 15 min	95	120	90	98		125		127		170	117.86	22.58
2 hr 20 min	95	120	80	102		136		111		170	116.29	12.12
2 hrs 25 min	100	130	72	98		138		110		170	116.86	13.06
2 hr 30 min	100	140	60	98		156				178	122.00	19.51
2 hrs 35 min	100	130		98		170				182	136.00	19.44
2 hr 40 min	98	125		98						182	125.75	22.86
2 hrs 45 min	100	130		98						182	127.50	22.62
2 hr 50 min	100			99						174	124.33	30.42
2 hrs 55 min				98						182	140.00	59.40
3 hrs				92						187	139.50	67.18
3 hrs 5 min				92						197	144.50	74.25
3 hr 10 min				89						202	145.50	79.90
3 hrs 15 min				89							89.00	
3 hr 20 min				80							80.00	
3 hrs 25 min				82							82.00	
3 hr 30 min												

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the pulse readings
SEM = Standard error of means
min = minute
pulse = beats/minute
hr = hour

Table A5 : Respiratory rates +/-SEM, in breaths/minute, of the individual dogs in group A, taken every 5 minutes throughout anaesthesia.
Dogs trial numbers 1-10 (group A), received flunixin meglumine, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

Respiratory rates in breaths/minute

Trial No-	1	2	3	4	5	6	7	8	9	10	Mean	SEM
Time												
Pre			64		28		24	32		28	35.20	8.17
0 min	6		15	20			16	36	30	50	24.71	6.10
5 min	6	10	25	20	30	12	12	28	16	32	19.10	3.07
10 min	6	25	25	10	28	12	8	20	16	12	16.20	2.61
15 min	10	15	20	10	15	16	16	16	24	40	18.20	2.90
20 min	10	20	20	15	15	16	16	20	8	20	16.00	1.43
25 min	34	15	25	10	25	24	12	20	12	16	19.30	2.55
30 min	6	20	20	10	30	24	12	20	10	16	16.80	2.46
35 min	6	20	20	10	30	24	8	20	12	15	16.50	2.54
40 min	20	25	25	10	20	24	12	24	12	20	19.20	1.94
45 min	25	20	20	15	20	24	12	20	12	16	18.40	1.51
50 min	20	20	25	15	28	24	16	20	24	24	21.60	1.37
55 min	10	25	25	20	25	24	12	24	12		19.67	2.28
1 hr	44	20	25	22	25	24	12	24	30		25.11	3.04
1 hr 5 min	50	20	27	22	20	24	12	28	35		26.44	3.85
1 hr 10 min	30	20	25	12	20	22	12	20	40		22.33	3.08
1 hr 15 min	20	35	25	12	20	20	12	30	30		22.67	2.83
1 hr 20 min	20	30	25	12	25	12	20		40		23.00	3.52
1 hr 25 min		29	25	15	25	12	22		40		24.00	3.77
1 hr 30 min		30	25	16	25		10		50		26.00	6.16
1 hr 35 min		35	30	12	25		10		40		25.33	5.45
1 hr 40 min		30	25	12	28		20		40		25.83	4.24
1 hr 45 min		30	30		29		20		40		29.80	3.54
1 hr 50 min		28	35		30		18		35		29.20	3.49
1 hr 55 min		30	35		25		18		40		29.60	4.28
2 hrs		30	30		29		15				26.00	4.24
2 hr 5 min		30	30		25		15				25.00	4.08
2 hr 10 min		30	30		25		15				25.00	4.08
2 hrs 15 min		28	30		28		12				24.50	4.84
2 hr 20 min		28	30		24		16				24.50	3.57
2 hrs 25 min		24	30		25		12				22.75	4.41
2 hr 30 min		30	35		25		10				25.00	6.24
2 hrs 35 min		60	30		28		20				34.50	10.13
2 hr 40 min		40	28		20		15				25.75	6.30
2 hrs 45 min		20	20		25		18				20.75	1.72
2 hr 50 min		40	20		25		18				25.75	5.74
2 hrs 55 min							20					
3 hrs							20					
3 hrs 5 min							20					
3 hr 10 min							20					
3 hrs 15 min							20					
3 hr 20 min							20					
3 hrs 25 min							20					
3 hr 30 min							20					

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the respiratory rate readings
SEM = Standard error of means
min = minute
respiratory rate = breaths/minute
hr = hour

Table A6 : Respiratory rates +/-SEM, in breaths/minute, of the individual dogs in group B, taken every 5 minutes throughout anaesthesia.
Dogs trial numbers 11-20 (group B), received flunixin meglumine, 1.1 mg/kg, i.v., immediately after anaesthesia had terminated.

Respiratory rates in breaths/minute

Trial No-	11	12	13	14	15	16	17	18	19	20	Mean	SEM
Time												
Pre	20	64	36		20						35.00	11.98
0 min		25			26	52	36	12	36		31.17	6.04
5 min	12	20	12	24	8	52	24	20	6		19.78	4.88
10 min	16	25	12	18	8	30	20	16	12	26	18.30	2.33
15 min	16	30	20	18	12	16	20	16	16	32	19.60	2.15
20 min	12	35	12	16	16	15	16	20	20	32	19.40	2.64
25 min	16	50	12	18		20	20	12	12	28	18.80	4.39
30 min	16	50	20	20		24	24	16	28	24	24.67	3.64
35 min	20	43	16	20		20	32	22	24	28	25.00	2.93
40 min	20	35	16	30		21	20	22	24	22	23.33	2.04
45 min	20	35	16	60		28	26	20	20	12	26.33	5.07
50 min	20	25	18	60		20	20	16	32	20	25.67	4.84
55 min	16	30	16	64		22	20	24	28	24	27.11	5.17
1 hr	24	30	16	26		26	20	24	32	20	24.22	1.78
1 hr 5 min	16	30	12	20		20	16	36	28	28	22.89	2.81
1 hr 10 min	20	37	12	26		26	36	28	24	28	26.33	2.69
1 hr 15 min	16	35	20	60		20	30	24	28	28	29.00	4.60
1 hr 20 min	20	32	12	62		42		22	24	28	30.25	7.30
1 hr 25 min	22	40	16	50		36		24	24	28	30.00	4.22
1 hr 30 min	30	40	16	32		36		22	76	28	35.00	6.88
1 hr 35 min	20	30	16	28		30		22	40	28	26.75	2.80
1 hr 40 min	20	35	16	30		24		20	80	16	30.13	8.02
1 hr 45 min	16	30	14	28		32		20		20	22.86	2.90
1 hr 50 min	20	44	14	24		32		20		24	25.43	4.02
1 hr 55 min	20	45	16	20		22		16		24	23.29	4.09
2 hrs	20	45	15	16		22		16		24	22.57	4.27
2 hr 5 min	24	40	12	20		12				28	22.67	4.76
2 hr 10 min	20	30	12	16						30	21.60	4.09
2 hrs 15 min	24	30	12	24						30	24.00	3.67
2 hr 20 min	24	30	12	20						32	23.60	4.02
2 hrs 25 min	24	35	12	16						42	25.80	6.31
2 hr 30 min	24	32	12	18						40	25.20	5.55
2 hrs 35 min	20	32		18						34	26.00	4.71
2 hr 40 min	20	30		18						36	26.00	4.90
2 hrs 45 min	20	30		20						42	28.00	6.04
2 hr 50 min	20			20						50	30.00	12.25
2 hrs 55 min				20								
3 hrs				20								
3 hrs 5 min				20								
3 hr 10 min				35								
3 hrs 15 min				25								
3 hr 20 min				25								
3 hrs 25 min				25								
3 hr 30 min												

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean of the respiratory rate readings
SEM = Standard error of means
min = minute
respiratory rate = breaths/minute
hr = hour

Table A7 : End tidal carbon dioxide (ETCO2) readings +/-SEM in mm Hg, of dogs trial numbers 1, 2, 3, 8, and 9 in group A, taken every 5 minutes from the commencement of surgery, till termination of anaesthesia.
Dogs in group A, received flunixin meglumine, 1.1 mg/kg, i.v., during anaesthesia, prior to the start of surgery.

ETCO2 readings in mm Hg

Trial No-	1	2	3	8	9	Mean	SEM
Time							
15 min	37						
20 min	35			35		35.00	0.00
25 min	32			35		33.50	2.12
30 min	37			35		36.00	1.41
35 min	37			35		36.00	1.41
40 min	37			35		36.00	1.41
45 min	34			35		34.50	0.71
50 min	32			35		33.50	2.12
55 min	32			35		33.50	2.12
1 hr				35			
1 hr 5 min							
1 hr 10 min			28				
1 hr 15 min			28				
1 hr 20 min			28		38	33.00	7.07
1 hr 25 min			32		38	35.00	4.24
1 hr 30 min		34	31		38	34.50	2.48
1 hr 35 min		34	30		40	34.60	3.56
1 hr 40 min		32	33		40	35.00	3.08
1 hr 45 min		31	29		40	33.30	4.14
1 hr 50 min		32	33		40	35.00	3.08
1 hr 55 min		32	29		36	32.33	2.48
2 hrs		32	32		36	33.30	1.63
2 hr 5 min		32	34		25	30.30	2.01
2 hr 10 min		32	34			33.00	1.41
2 hrs 15 min		32	33			32.50	0.71
2 hr 20 min		30	33			31.50	2.12
2 hrs 25 min			33				
2 hr 30 min			33				
2 hrs 35 min			30				
2 hr 40 min			31				
2 hrs 45 min			30				
2 hr 50 min							
2 hrs 55 min							
3 hrs							
3 hrs 5 min							

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean end tidal carbon dioxide readings
SEM = Standard error of means
min = minute
ETCO2 = millimeters of mercury (mm Hg)
hr = hour

Table A8 : End tidal carbon dioxide (ETCO2) readings +/-SEM in mm Hg, of dogs trial numbers 11, 12, 14, 16, 17, 18, 19 and 20 in group B, taken every 5 minutes from the commencement of surgery, till termination of anaesthesia.
Dogs in group B, received flunixin meglumine, 1.1 mg/kg, i.v., immediately after anaesthesia had terminated.

ETCO2 readings in mm Hg

Trial No-	11	12	14	16	17	18	19	20	Mean	SEM
Time										
5 min					38				38.00	
10 min					38				38.00	
15 min					37				37.00	
20 min					36		40		38.00	2.83
25 min					36		48	34	39.33	5.35
30 min					36		40	34	36.67	2.16
35 min					37		34	34	35.00	1.22
40 min					36		39	35	36.67	1.47
45 min				42	35		33	45	38.75	3.28
50 min				44	35	38	32	42	38.20	2.46
55 min				38	35	38	33	37	36.20	1.08
1 hr				31	32	38	33	37	34.20	1.56
1 hr 5 min	38			40	32	38	31	36	35.83	1.61
1 hr 10 min	38			34	28	36	32	35	33.83	1.56
1 hr 15 min	38			31		40	40	36	37.00	1.87
1 hr 20 min	38			35		40	36	35	36.80	1.08
1 hr 25 min	32			32		36	38	35	34.60	1.30
1 hr 30 min	32			26		40	39	37	34.80	2.90
1 hr 35 min	38			32		40	23	35	33.60	3.33
1 hr 40 min	38	40		35		40	18	35	34.33	3.72
1 hr 45 min	38	40	36	32		38		34	36.33	1.32
1 hr 50 min	38	40	42	36		36		36	38.00	1.13
1 hr 55 min	40	40	45	34		35		36	38.33	1.85
2 hrs	40	42	44	35		34		36	38.50	1.83
2 hr 5 min	40	45	41					36	40.50	2.13
2 hr 10 min	40	42	43					36	40.25	1.79
2 hrs 15 min	40	42	46					34	40.50	2.89
2 hr 20 min	40	42	46					32	40.00	3.40
2 hrs 25 min	40	42	45					34	40.25	2.68
2 hr 30 min		40	47					34	40.33	4.60
2 hrs 35 min		39	48					38	41.67	3.89
2 hr 40 min		39	47					32	39.33	5.31
2 hrs 45 min		35	48					32	38.33	6.01
2 hr 50 min									35.00	15.56
2 hrs 55 min			48					20	32.50	17.68
3 hrs										
3 hrs 5 min			39							

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
Mean = Mean end tidal carbon dioxide readings
SEM = Standard error of means
min = minute
ETCO2 = millimeters of mercury (mm Hg)
hr = hour

Table A8 : End tidal carbon dioxide (ETCO2) readings +/-SEM in mm Hg, of dogs trial numbers 11, 12, 14, 16, 17, 18, 19 and 20 in group B, taken every 5 minutes from the commencement of surgery, till termination of anaesthesia.
Dogs in group B, received flunixin meglumine, 1.1 mg/kg, i.v., immediately after anaesthesia had terminated.

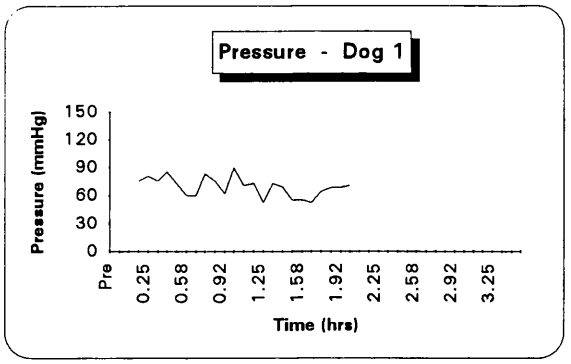
ETCO2 readings in mm Hg

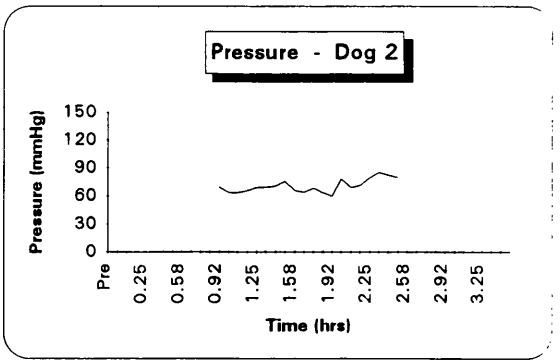
Trial No-	11	12	14	16	17	18	19	20	Mean	SEM
Time										
5 min					38				38.00	
10 min					38				38.00	
15 min					37				37.00	
20 min					36		40		38.00	2.83
25 min					36		48	34	39.33	5.35
30 min					36		40	34	36.67	2.16
35 min					37		34	34	35.00	1.22
40 min					36		39	35	36.67	1.47
45 min				42	35		33	45	38.75	3.28
50 min				44	35	38	32	42	38.20	2.46
55 min				38	35	38	33	37	36.20	1.08
1 hr				31	32	38	33	37	34.20	1.56
1 hr 5 min	38			40	32	38	31	36	35.83	1.61
1 hr 10 min	38			34	28	36	32	35	33.83	1.56
1 hr 15 min	38			31		40	40	36	37.00	1.87
1 hr 20 min	38			35		40	36	35	36.80	1.08
1 hr 25 min	32			32		36	38	35	34.60	1.30
1 hr 30 min	32			26		40	39	37	34.80	2.90
1 hr 35 min	38			32		40	23	35	33.60	3.33
1 hr 40 min	38	40		35		40	18	35	34.33	3.72
1 hr 45 min	38	40	36	32		38		34	36.33	1.32
1 hr 50 min	38	40	42	36		36		36	38.00	1.13
1 hr 55 min	40	40	45	34		35		36	38.33	1.85
2 hrs	40	42	44	35		34		36	38.50	1.83
2 hr 5 min	40	45	41					36	40.50	2.13
2 hr 10 min	40	42	43					36	40.25	1.79
2 hrs 15 min	40	42	46					34	40.50	2.89
2 hr 20 min	40	42	46					32	40.00	3.40
2 hrs 25 min	40	42	45					34	40.25	2.68
2 hr 30 min		40	47					34	40.33	4.60
2 hrs 35 min		39	48					38	41.67	3.89
2 hr 40 min		39	47					32	39.33	5.31
2 hrs 45 min		35	48					32	38.33	6.01
2 hr 50 min									35.00	15.56
2 hrs 55 min			48					20	32.50	17.68
3 hrs										
3 hrs 5 min			39							

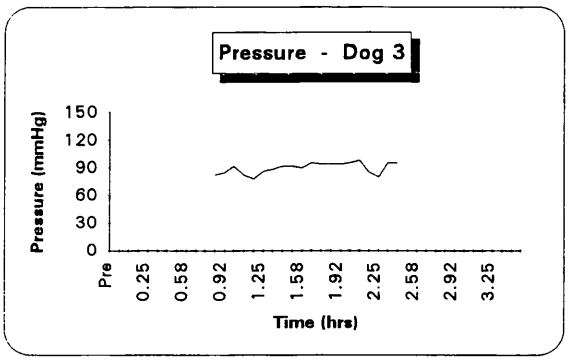
ABBREVIATIONS

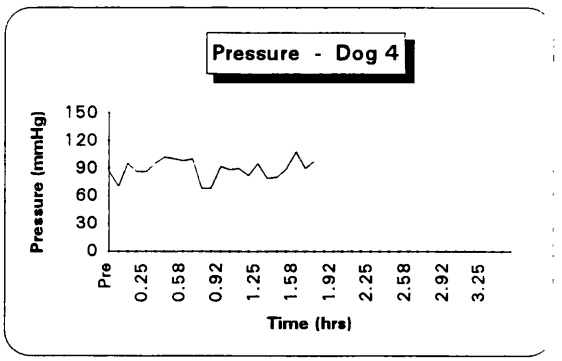
Pre = Prior to induction of anaesthesia
Mean = Mean end tidal carbon dioxide readings
SEM = Standard error of means
min = minute
ETCO2 = millimeters of mercury (mm Hg)
hr = hour

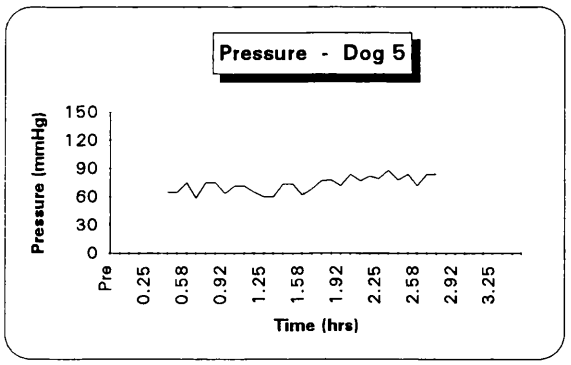
Fig. A1: Individual mean blood pressure (mmHg) readings of dogs in Group A (No 1-5) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







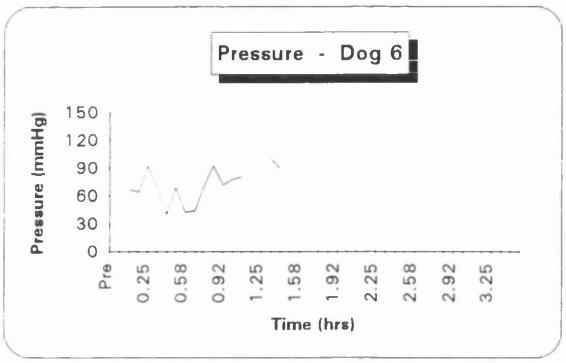


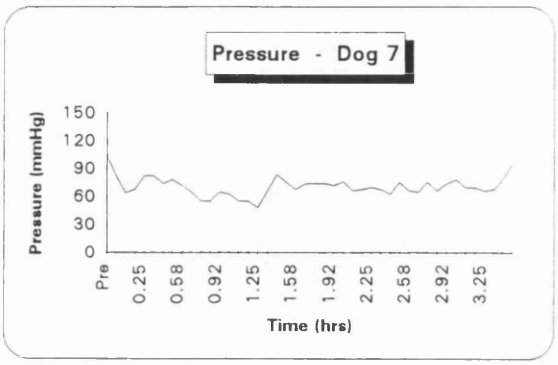


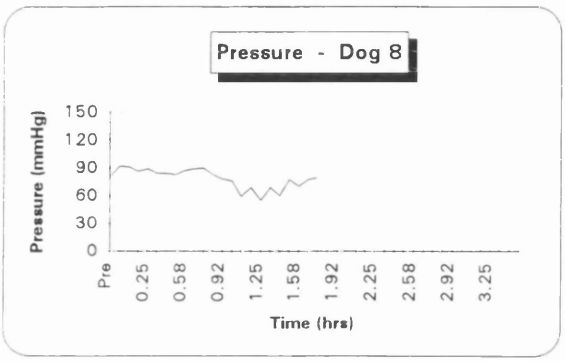
ABBREVIATIONS

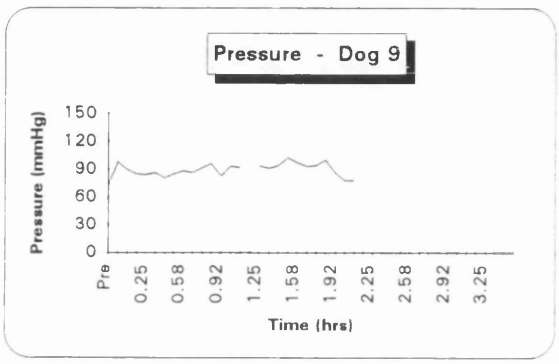
mmHg	= millimetres of mercury
hrs	= hours
Pre	= Prior to flunixin administration

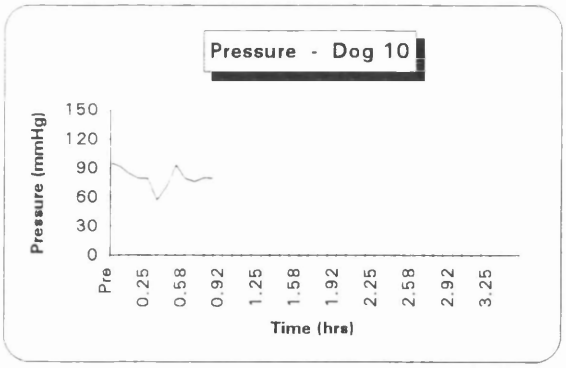
Fig. A2: Individual mean blood pressure (mmHg) readings of dogs in Group A (No 6-10) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







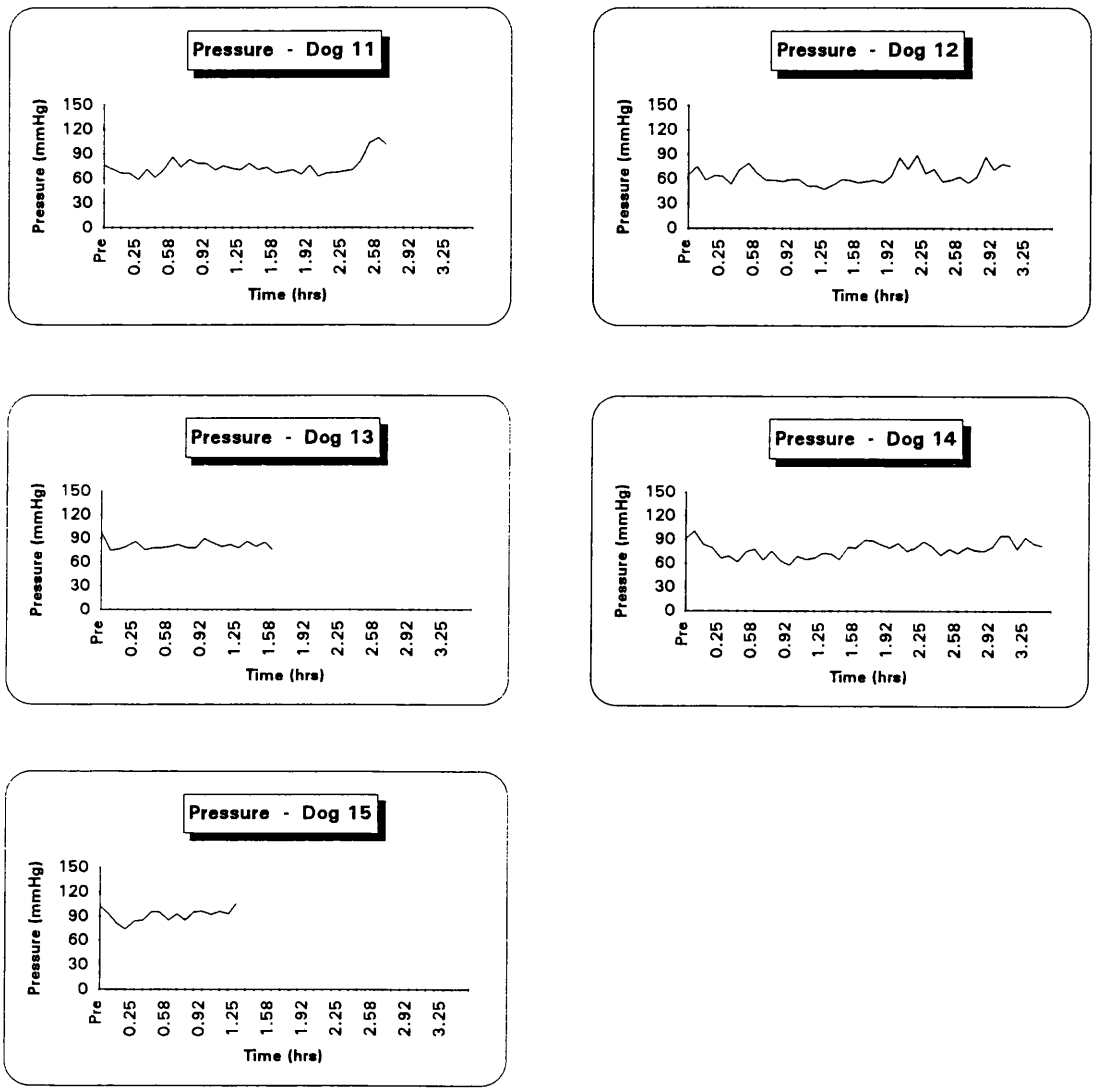




ABBREVIATIONS

mmHg	= millimetres of mercury
hrs	= hours
Pre	= Prior to flunixin administration

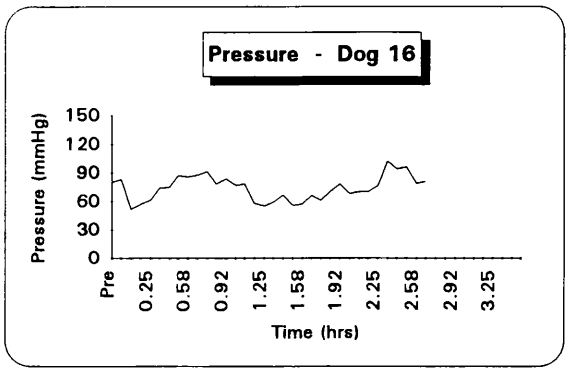
Fig. A3: Individual mean blood pressure (mmHg) readings of dogs in Group B (No 11-15) versus time. Group B (No 11-20) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.

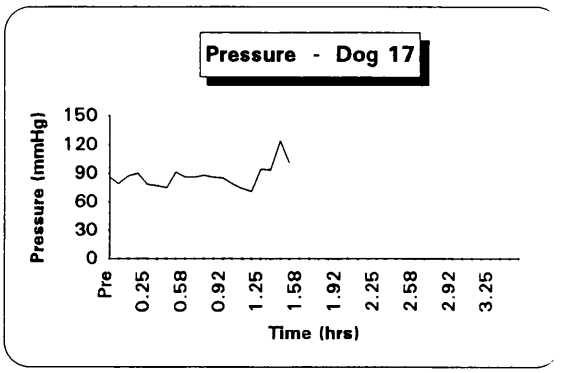


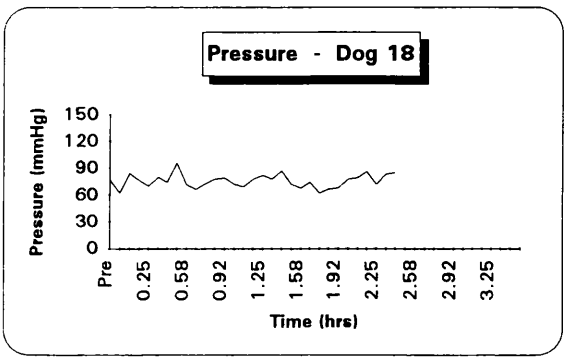
ABBREVIATIONS

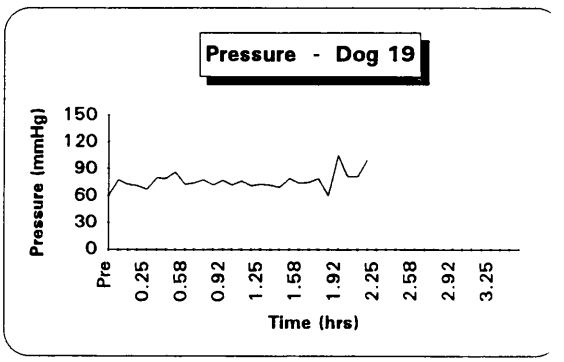
mmHg	= millimetres of mercury
hrs	= hours
Pre	= Prior to flunixin administration

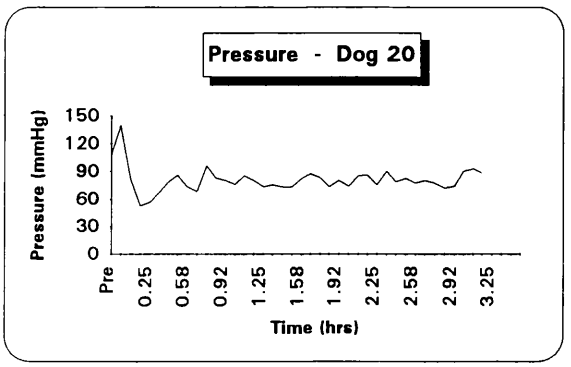
Fig. A4: Individual mean blood pressure (mmHg) readings of dogs in Group B (No 16-20) versus time. Group B (No 11-20) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.







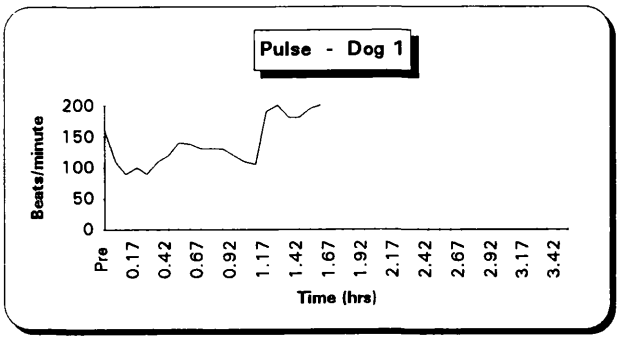


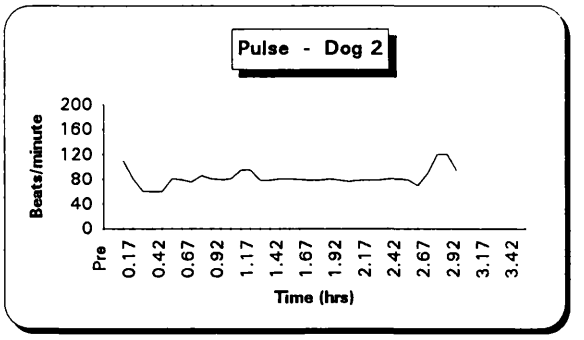


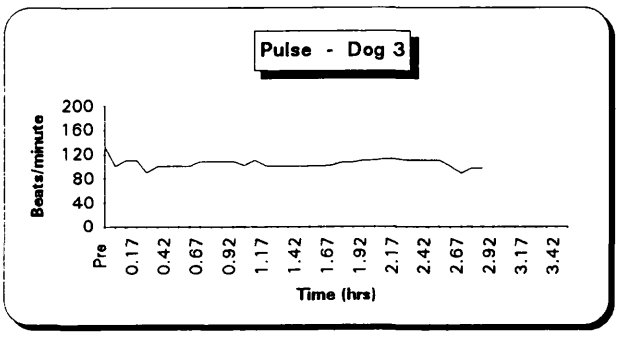
ABBREVIATIONS

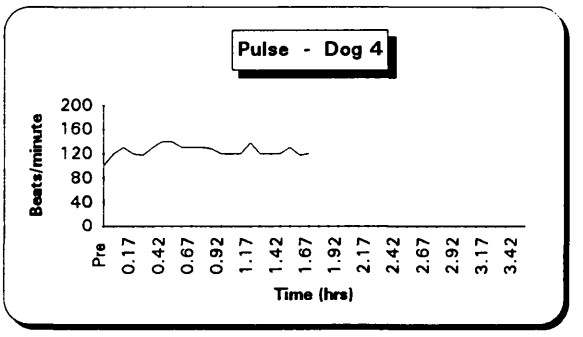
mmHg	= millimetres of mercury
hrs	= hours
Pre	= Prior to flunixin administration

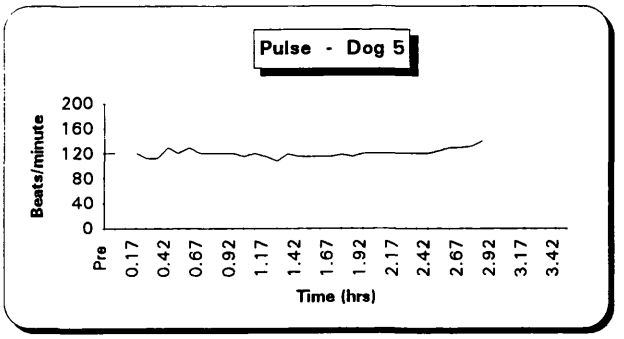
Fig. A5: Individual pulse readings (beats/min) of dogs in Group A (No 1-5) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







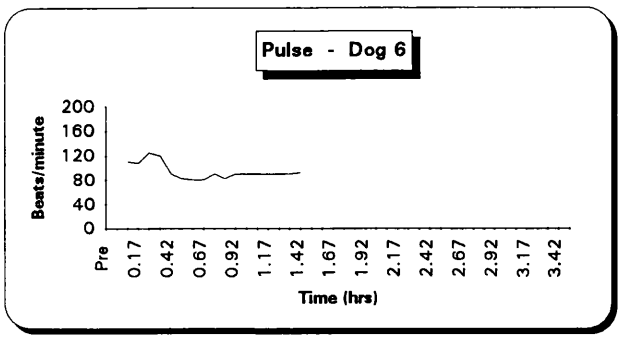


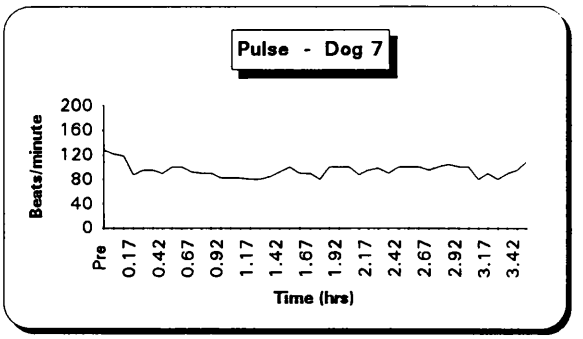


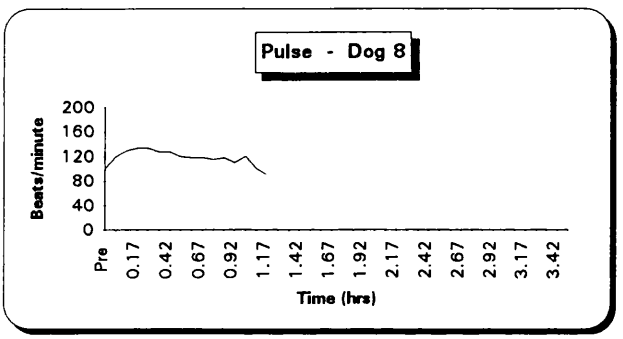
ABBREVIATIONS

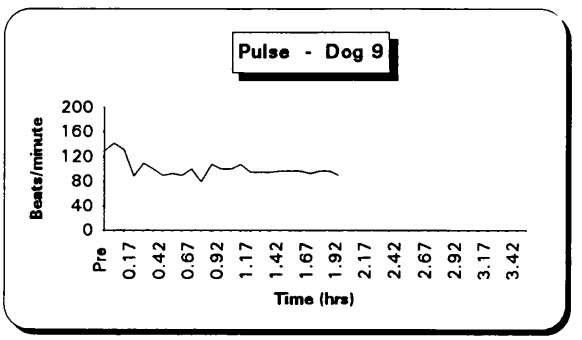
hrs = hours
beats/min = beats per minute
Pre = Prior to flunixin administration

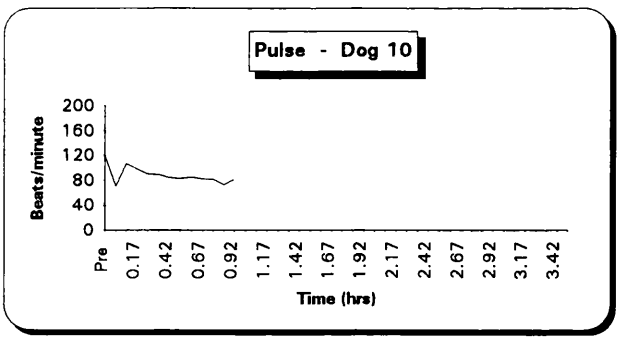
Fig. A6: Individual pulse readings (beats/min) of dogs in Group A (No 6-10) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







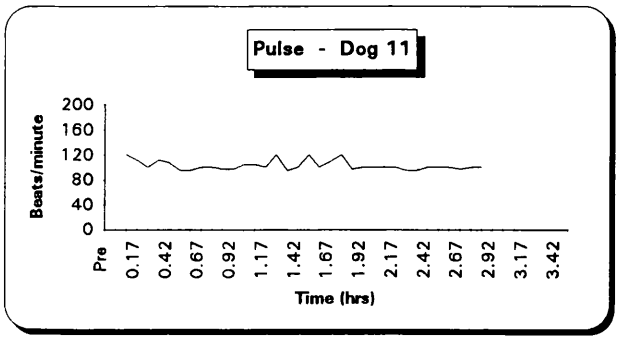


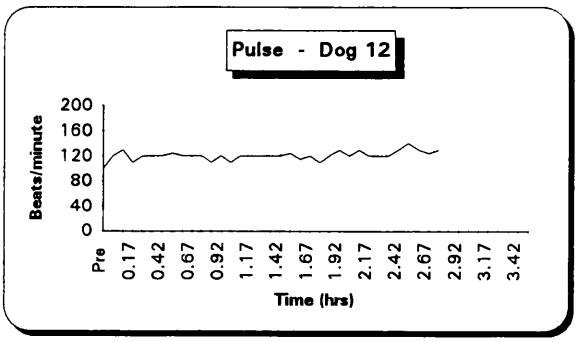


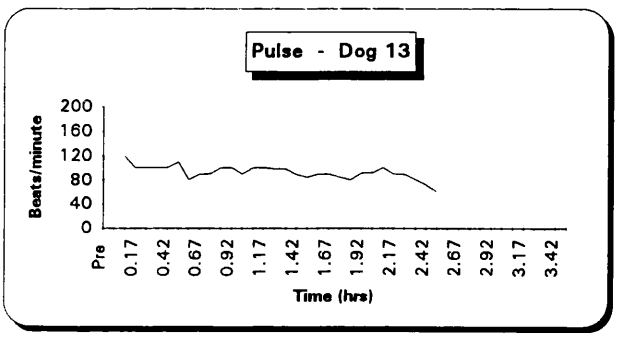
ABBREVIATIONS

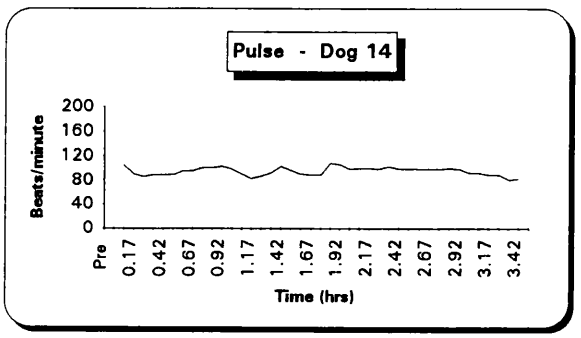
hrs	= hours
beats/min	= beats per minute
Pre	= Prior to flunixin administration

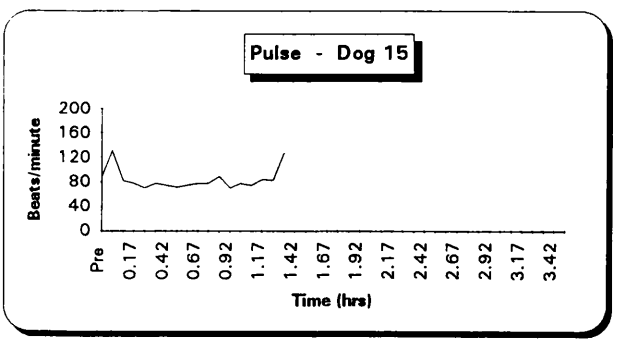
Fig. A7: Individual pulse readings (beats/min) of dogs in Group B (No 11-15) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.







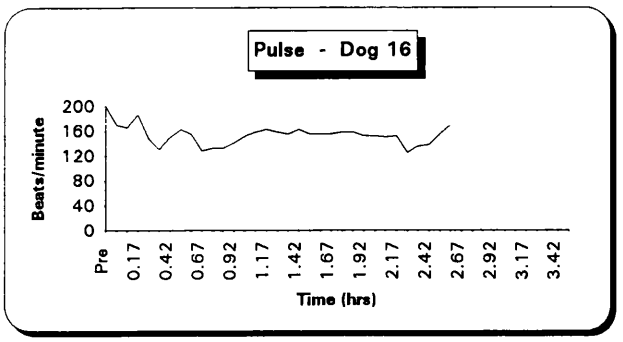


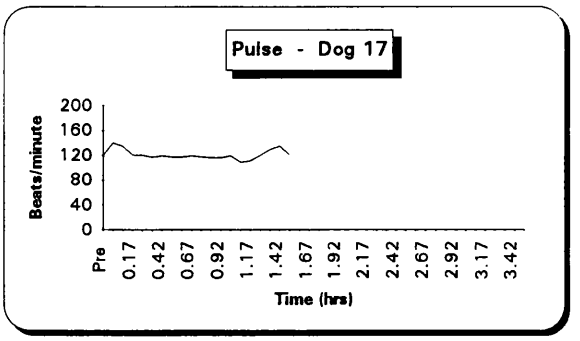


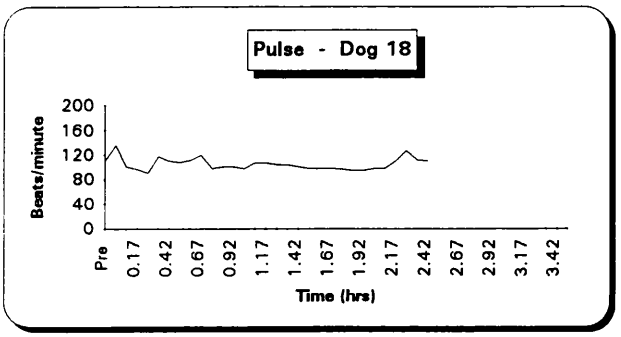
ABBREVIATIONS

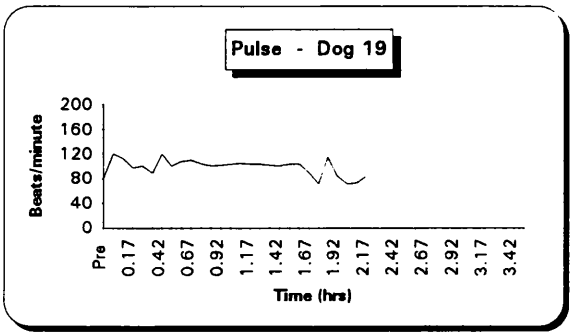
hrs	= hours
beats/min	= beats per minute
Pre	= Prior to flunixin administration

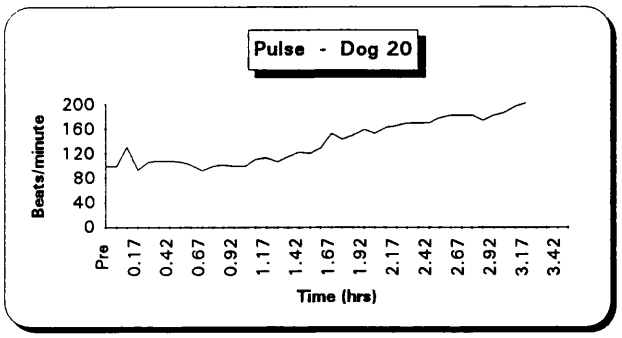
Fig. A8: Individual pulse readings (beats/min) of dogs in Group B (No 16-20) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.







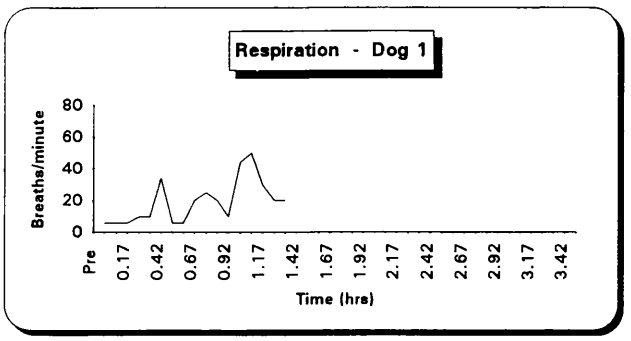


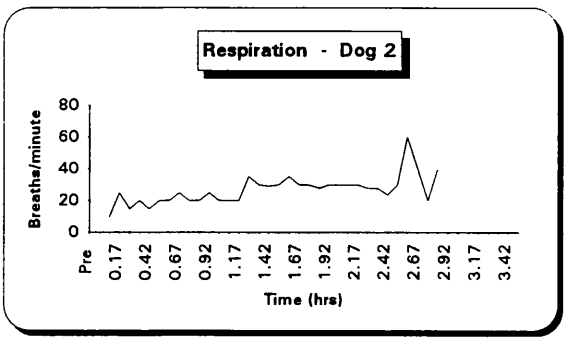


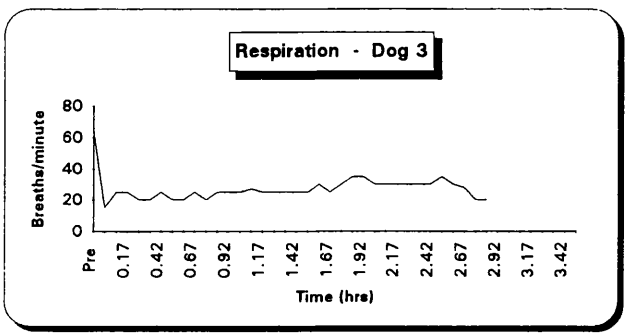
ABBREVIATIONS

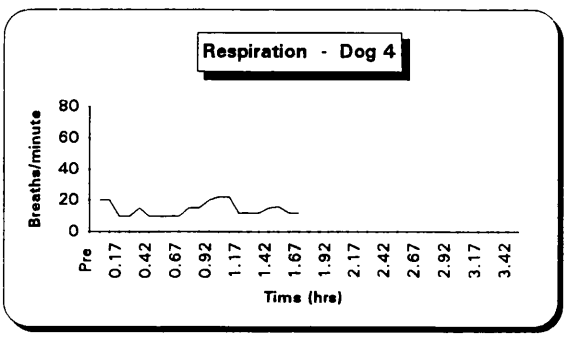
hrs	= hours
beats/min	= beats per minute
Pre	= Prior to flunixin administration

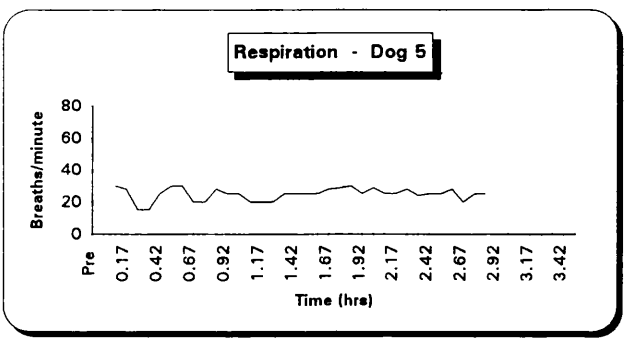
Fig. A9: Individual respiratory readings (breaths/min) of dogs in Group A (No 1-5) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







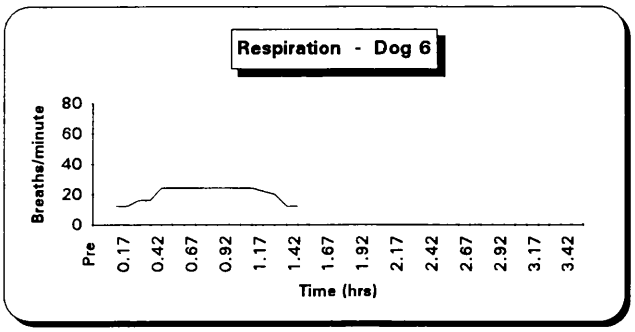


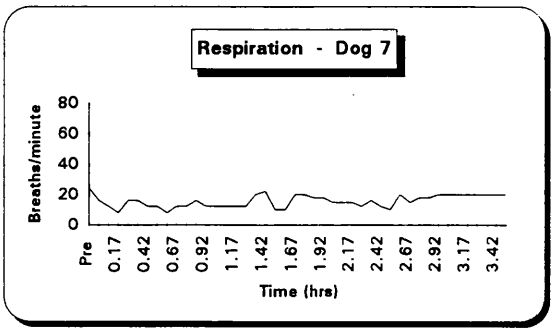


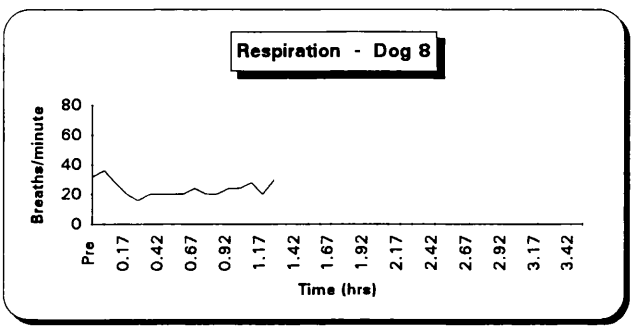
ABBREVIATIONS

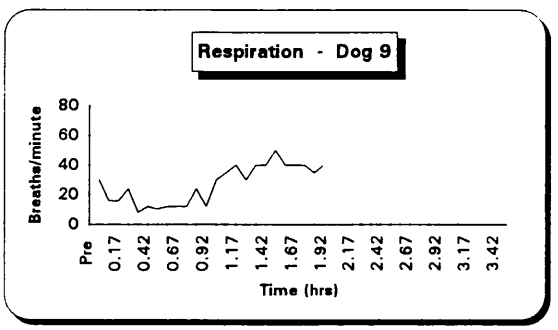
hrs	= hours
breaths/min	= breaths per minute
Pre	= Prior to flunixin administration

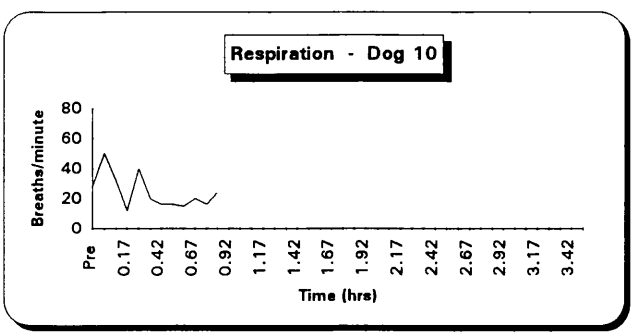
Fig. A10: Individual respiratory readings (breaths/min) of dogs in Group A (No 6-10) versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







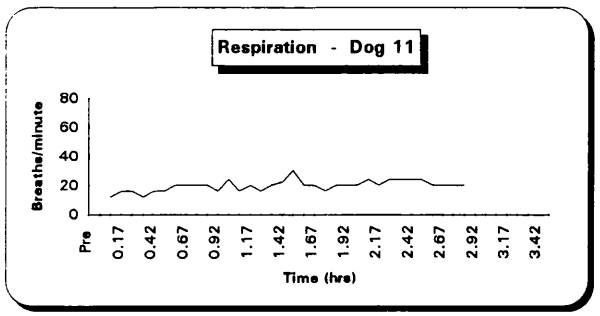


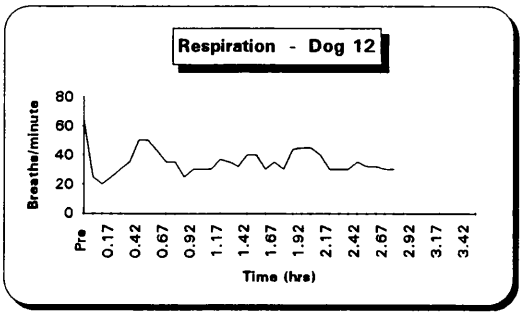


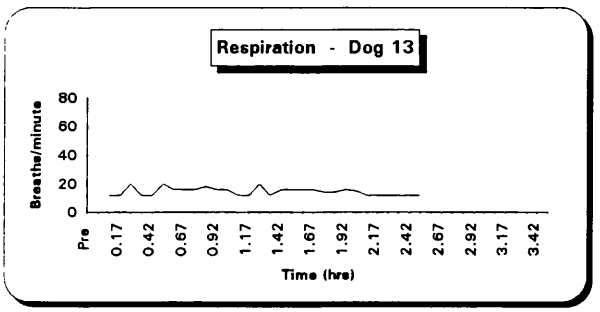
ABBREVIATIONS

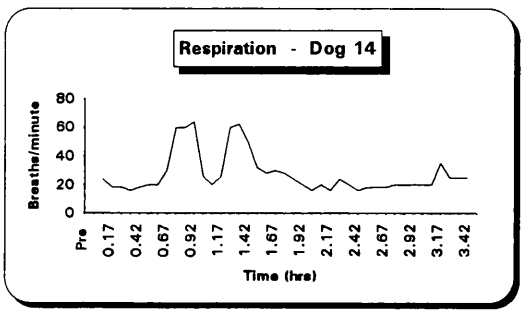
hrs	= hours
breaths/min	= breaths per minute
Pre	= Prior to flunixin administration

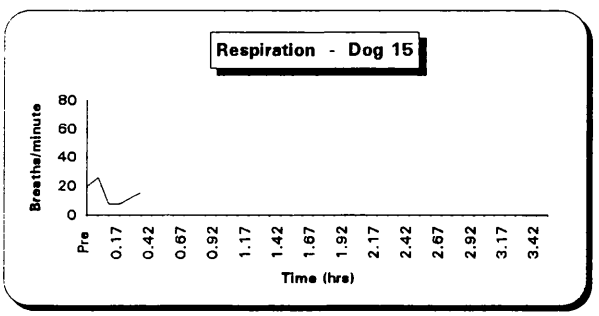
Fig. A11: Individual respiratory readings (breaths/min) of dogs in Group B (No 11-15) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.







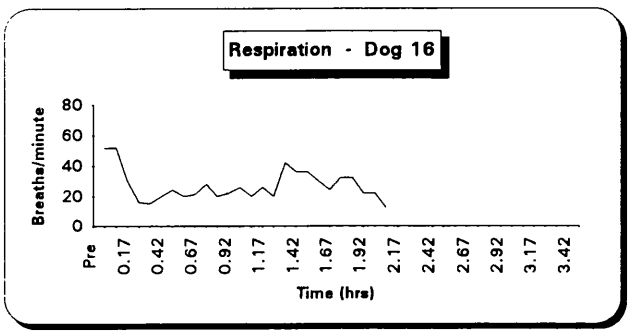


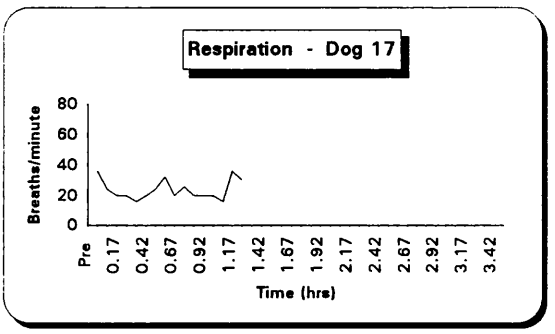


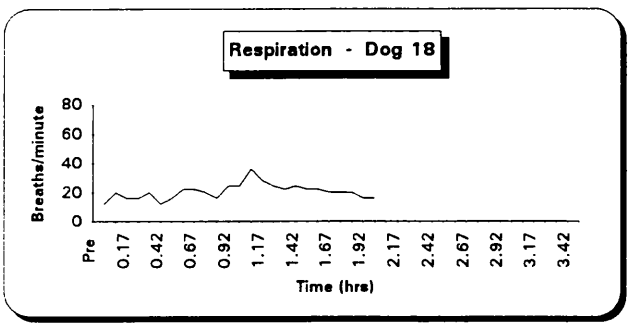
ABBREVIATIONS

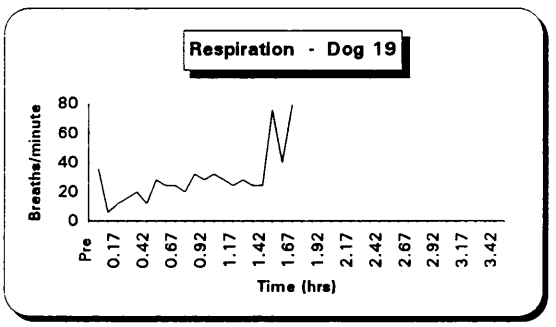
hrs	= hours
breaths/min	= breaths per minute
Pre	= Prior to flunixin administration

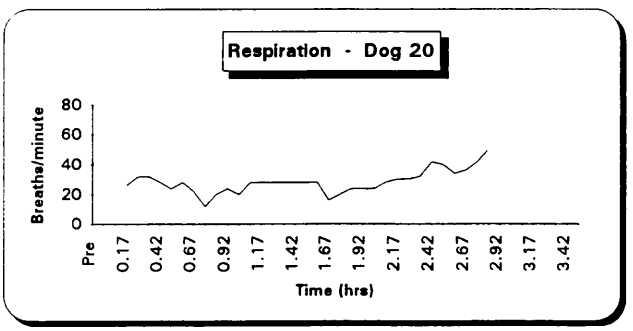
Fig. A12: Individual respiratory readings (breaths/min) of dogs in Group B (No 16-20) versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.







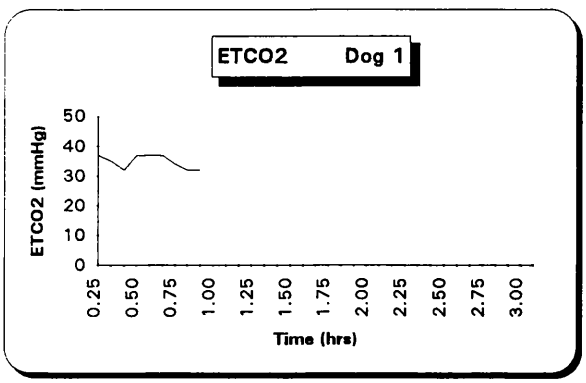


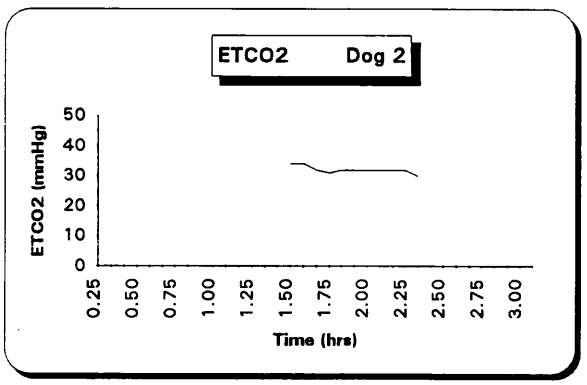


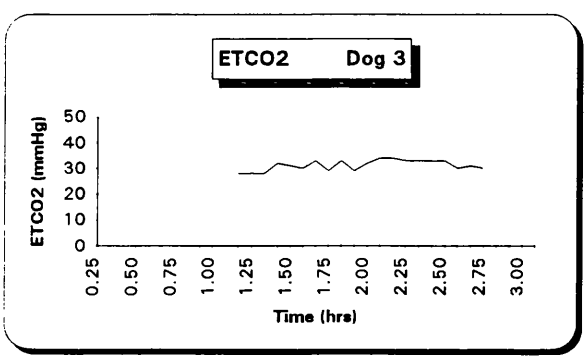
ABBREVIATIONS

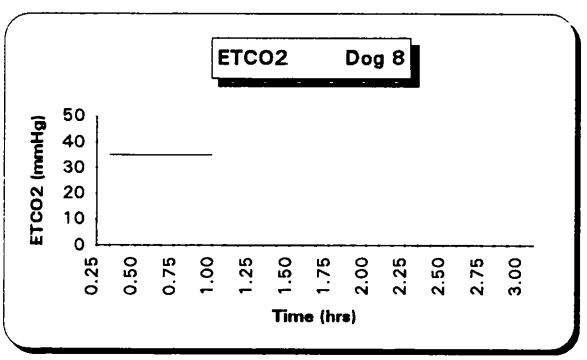
hrs = hours
breaths/min = breaths per minute
Pre = Prior to flunixin administration

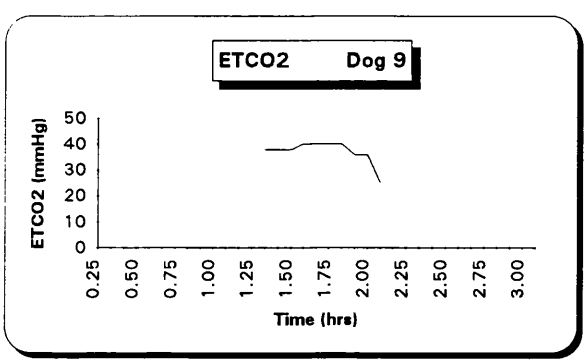
Fig. A13: Individual End tidal carbon dioxide (ETCO2) readings (mmHg) of dogs No 1, 2, 3, 8 and 9 in Group A versus time. Group A dogs received flunixin, 1.1mg/kg, i.v., during anaesthesia, prior to the start of surgery.







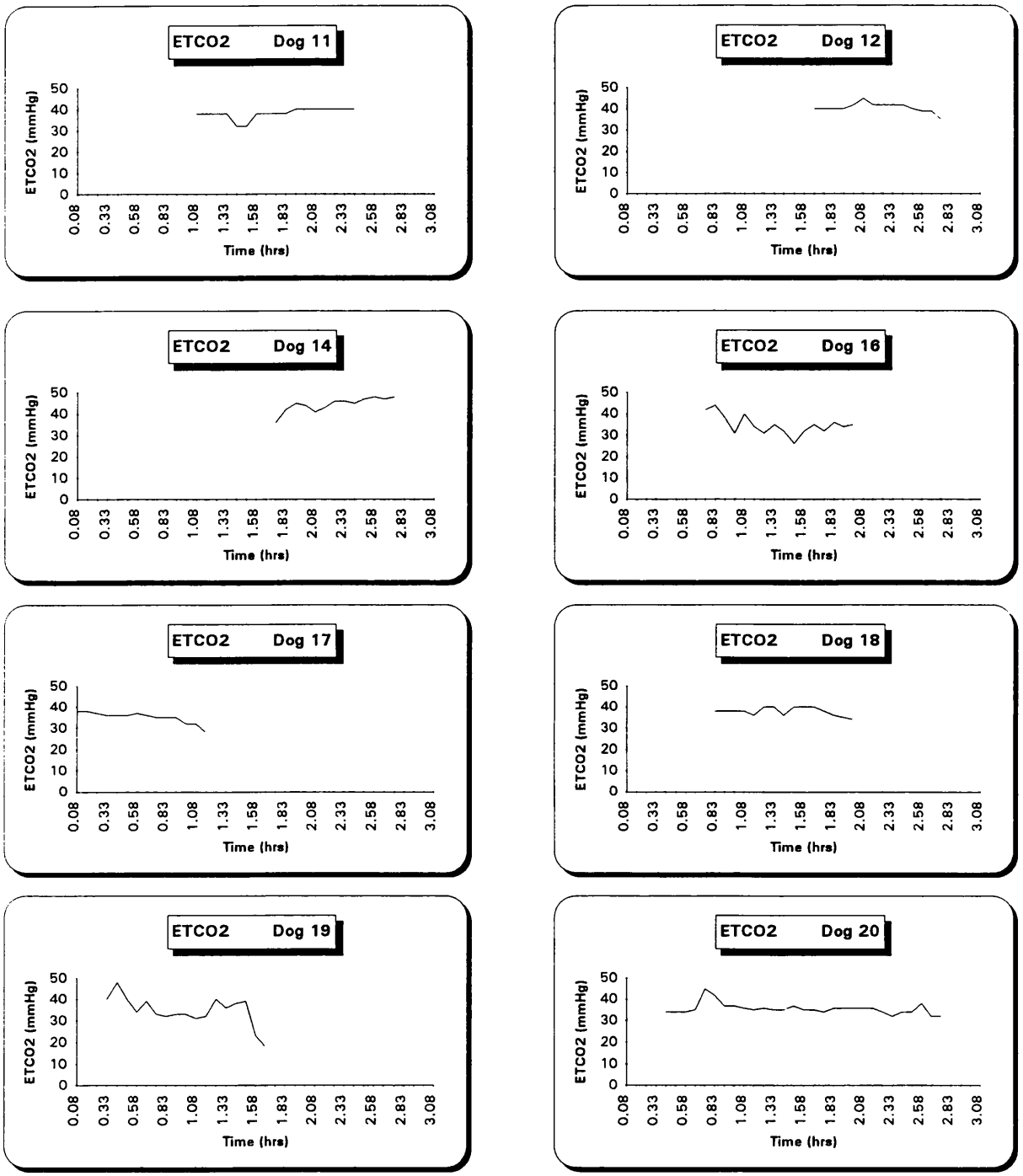




ABBREVIATIONS

ETCO2 = End-tidal carbon dioxide
mmHg = millimeters of mercury
hrs = hours

Fig. A14: Individual End tidal carbon dioxide (ETCO2) readings (mmHg) of dogs No 11, 12, 14, 16, 17, 18, 19 and 20 in Group B versus time. Group B dogs received flunixin, 1.1mg/kg, i.v., immediately after surgery and anaesthesia had been terminated.



ABBREVIATIONS

ETCO2 = End-tidal carbon dioxide
mmHg = millimeters of mercury
hrs = hours

APPENDIX B

TABLES

Table B1: Normal canine biochemistry values.
(Glasgow University Veterinary Hospital, Biochemistry Department)

TEST	NORMAL CANINE VALUES	S.I. UNITS
UREA	2 - 8	millimol/litre (mmol/l)
CREATININE	44 - 135	micromol/litre (umol/l)
PHOSPHATE	1 - 3	millimol/litre (mmol/l)
TOTAL PROTEIN	50 - 70	grams/litre (g/l)
ALBUMIN	30 - 40	grams/litre (g/l)
GLOBULIN	20 - 30	grams/litre (g/l)
SODIUM	135 - 160	millimol/litre (mmol/l)
POTASSIUM	3 - 6	millimol/litre (mmol/l)
CHLORIDE	95 - 115	millimol/litre (mmol/l)

Table B2: Kidney biochemical profile, of a group of 10 control dogs (C1 - C10), who underwent routine anaesthesia (ACP- 0.05 mg/kg i.m, Thio - 10 mg/kg i.v., halothane in $N_20/0_2$) and surgery. Blood was taken for analysis prior to induction of anaesthesia, 12 and 30 hours after commencement of anaesthesia.

B2.1. BIOCHEMICAL PROFILE:- Prior to induction of anaesthesia

Dog No →	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Urea (mmol/l)	2.9	4.4	5.4	5.9	7.8	6.1	4	3.6	4.8	7.7
Creatinine (umol/l)	106	70	118	95	85	127	90	92	80	75
Phosphate (mmol/l)	1.41	1.17	1.02	2.08	1.64	1.49	1	1.4	1.57	1.85
Total protein (g/l)	56	66	63	68	68	60	64	66	60	56
Albumin (g/l)	32	33	33	40	37	26	29	32	33	31
Globulin (g/l)	24	33	29	28	31	34	35	34	27	25
Sodium (mmol/l)	151	148	151	150	149	148	146	149	148	149
Potassium (mmol/l)	4	4.3	3.7	3.4	3.4	4	3.9	3.8	4.4	4.3
Chloride (mmol/l)	108	109	114	118	118	107	108	116	109	110

B2.2 BIOCHEMICAL PROFILE:- 12 hours after termination of anaesthesia

Dog No →	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Urea (mmol/l)	3.6	5.3	4.6	6	6.2	6.5	2.9	2.7	3.6	4.1
Creatinine (umol/l)	88	84	78	96	115	109	84	83	66	93
Phosphate (mmol/l)	1.39	1.57	2.55	1.31	1.48	1.24	1.02	1.37	1.39	1.27
Total protein (g/l)	63	66	55	62	62	52	60	61	60	60
Albumin (g/l)	31	29	33	37	35	23	27	32	32	33
Globulin (g/l)	32	37	22	25	27	29	33	29	28	27
Sodium (mmol/l)	149	149	150	148	149	146	136	149	143	148
Potassium (mmol/l)	3.7	5.6	5.3	3.6	4.2	4.2	4.5	4.4	4.7	4.3
Chloride (mmol/l)	111	111	109	115	114	109	103	113	105	110

B2. 3 BIOCHEMICAL PROFILE:- 30 hours after termination of anaesthesia

Dog No →	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Urea (mmol/l)	2.7	5.4	5.9	6.5	7.6	4.7	4.3	4.9	3.5	7.2
Creatinine (umol/l)	89	87	81	110	99	109	110	82	70	107
Phosphate (mmol/l)	1.46	1.26	2.72	1.83	1.64	1.7	1.12	1.43	1.01	1.16
Total protein (g/l)	59	72	53	65	66	52	64	64	67	59
Albumin (g/l)	27	30	33	37	38	24	28	34	34	31
Globulin (g/l)	32	42	20	28	28	28	36	30	33	28
Sodium (mmol/l)	147	144	145	146	146	148	144	147	148	143
Potassium (mmol/l)	4.2	5.4	5.6	3.8	4.5	4.8	4.3	4.9	4.2	3.9
Chloride (mmol/l)	106	103	105	114	121	108	110	107	106	108

Table B3: Kidney biochemical profiles of dogs in group A (1 - 10), who received flunixin meglumine, 1.1 mg/kg i.v. during anaesthesia, prior to the start of surgery. Blood was taken for analysis prior to the administration of flunixin, and 12 and 30 hours after its administration.

B3.1. BIOCHEMICAL PROFILE:- Prior to flunixin administration.

Dog No →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Urea (mmol/l)	NS	4.8	NS	2.8	4.3	6.3	3.5	6.3	4.6	3.6
Creatinine (umol/l)	NS	117	NS	68	101	74	79	85	93	127
Phosphate (mmol/l)	NS	1.23	NS	1.41	2.43	1.24	1.93	1.45	0.91	1.29
Total protein (g/l)	NS	53	NS	61	50	64	56	56	61	NS
Albumin (g/l)	NS	34	NS	24	28	27	33	26	29	NS
Globulin (g/l)	NS	19	NS	37	22	37	23	30	32	NS
Sodium (mmol/l)	NS	146	NS	145	147	149	146	148	148	148
Potassium (mmol/l)	NS	4.2	NS	3.8	5	4.6	4.7	4.4	4.6	4.1
Chloride (mmol/l)	NS	115	NS	114	110	118	116	113	111	119

B3.2 BIOCHEMICAL PROFILE:- 12 hours after flunixin administration.

Dog No →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Urea (mmol/l)	8.4	10.2	NS	7.8	5.9	5.4	6.4	8.7	6.2	6.2
Creatinine (umol/l)	113	192	NS	81	112	75	98	112	121	125
Phosphate (mmol/l)	1.58	1.51	NS	1.15	2.21	1.29	2.32	1.24	1.67	1.63
Total protein (g/l)	62	64	NS	58	52	66	52	57	61	47
Albumin (g/l)	29	36	NS	22	30	27	21	27	29	24
Globulin (g/l)	33	28	NS	36	22	39	31	30	32	23
Sodium (mmol/l)	150	145	NS	140	147	147	147	146	150	150
Potassium (mmol/l)	4	4.1	NS	4.1	4.8	5	5.1	4.8	4.7	5.2
Chloride (mmol/l)	115	109	NS	111	112	114	116	114	109	119

B3. 3 BIOCHEMICAL PROFILE:- 30 hours after flunixin administration.

Dog No →	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Urea (mmol/l)	6.2	NS	NS	5.6	5.5	5.7	5.1	8.1	6.6	6.8
Creatinine (umol/l)	101	NS	NS	78	100	82	98	112	119	100
Phosphate (mmol/l)	1.07	NS	NS	1.58	2.09	1.26	2.11	1.36	1.38	1.7
Total protein (g/l)	50	NS	NS	62	44	62	53	62	49	NS
Albumin (g/l)	32	NS	NS	24	25	25	32	29	23	NS
Globulin (g/l)	18	NS	NS	38	19	37	21	33	26	NS
Sodium (mmol/l)	151	NS	NS	142	149	145	149	146	151	149
Potassium (mmol/l)	4	NS	NS	4.1	4.8	4.7	4.4	4.7	3.4	4.1
Chloride (mmol/l)	114	NS	NS	106	115	117	119	117	NS	122

NS = Not sampled

B3. 4 BIOCHEMICAL PROFILES: -of dog 8 taken 60 days after flunixin administration.
-of dog 10 taken 15, 60 and 150 days after flunixin administration.

Parameters	Dog 8 (60 days)	Dog 10 (15 days)	Dog 10 (60 days)	Dog 10 (150 days)
Urea (mmol/l)	4.1	6.6	7.9	7.4
Creatinine (umol/l)	88	147	100	113
Phosphate (mmol/l)	1.06	1.21	1.39	1.2
Total protein (g/l)	64	57	50	56
Albumin (g/l)	27	30	34	34
Globulin (g/l)	37	27	16	22
Sodium (mmol/l)	142	148	151	146
Potassium (mmol/l)	4.4	3.8	3.9	4.5
Chloride (mmol/l)	110	118	112	116

Table B4: Kidney biochemical profiles of trial dogs in group B (Trial No : 11 - 20), who received flunixin meglumine, 1.1 mg/kg i.v. immediately after surgery and anaesthesia had been terminated. Blood was taken for analysis prior to the administration of flunixin, and 12 and 30 hours after its administration.

B4. 1. BIOCHEMICAL PROFILE:- Prior to flunixin administration

Dog No →	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Urea (mmol/l)	4.4	4.7	2.9	5.4	4.2	4.7	3.8	4	4.5	4.3
Creatinine (umol/l)	72	69	77	91	83	119	73	71	79	115
Phosphate (mmol/l)	1.98	1.45	1.06	2	1.6	1.62	1.69	1.47	2.19	1.21
Total protein (g/l)	49	50	54	57	48	53	67	50	55	51
Albumin (g/l)	26	26	26	28	23	28	28	27	26	25
Globulin (g/l)	23	24	28	29	25	25	39	23	29	26
Sodium (mmol/l)	147	147	149	146	147	147	145	150	149	146
Potassium (mmol/l)	4.5	4.7	4.5	4.8	4.7	4	4.5	4.2	4.3	4.4.
Chloride (mmol/l)	112	115	115	115	113	111	110	112	111	115

B4. 2 BIOCHEMICAL PROFILE:- 12 hours after flunixin administration

Dog No →	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Urea (mmol/l)	5.6	5.1	5.2	5.6	4.4	5.1	3.9	5.6	7.4	5.5
Creatinine (umol/l)	74	69	87	103	78	113	60	79	88	127
Phosphate (mmol/l)	1.81	2.05	1.4	1.6	1.26	1.44	1.24	1.26	1.27	1.42
Total protein (g/l)	52	55	52	56	48	NS[1]	63	51	53	43
Albumin (g/l)	29	28	25	29	24	NS	27	27	26	23
Globulin (g/l)	23	27	27	27	24	NS	36	24	27	20
Sodium (mmol/l)	148	147	144	148	149	146	148	150	151	139
Potassium (mmol/l)	5.4	4.7	4.4	4.2	4.6	5.2	4.8	5	5	4.6
Chloride (mmol/l)	113	111	110	119	116	113	114	113	113	111

B4. 3 BIOCHEMICAL PROFILE:- 30 hours after flunixin administration

Dog No →	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Urea (mmol/l)	2	5.9	4.3	5	2.2	5.1	3.2	4.7	5.1	10.1
Creatinine (umol/l)	68	74	88	114	66	110	64	85	90	134
Phosphate (mmol/l)	1.52	2.12	1.54	1.5	1.33	1.74	1.51	1.24	1.46	1.46
Total protein (g/l)	48	54	56	60	50	61	67	54	58	52
Albumin (g/l)	28	27	29	30	24	32	31	30	28	27
Globulin (g/l)	20	27	27	30	26	29	40	24	30	25
Sodium (mmol/l)	148	145	148	147	147	147	148	149	148	144
Potassium (mmol/l)	4.7	5.6	4.5	4.6	4.8	4.8	4.6	4.5	4.5	4.3
Chloride (mmol/l)	109	106	NS	4	116	113	111	106	107	116

[1] NS = Not sampled

B4. 4 BIOCHEMICAL PROFILE of dog No 15 taken 15, 30 and 60 days after flunixin administration.

Parameters	15 days	30 days	60 days
Urea (mmol/l)	3.7	5.2	4.2
Creatinine (umol/l)	97	84	61
Phosphate (mmol/l)	1.08	1.64	1.75
Total protein (g/l)	54	55	55
Albumin (g/l)	28	25	26
Globulin (g/l)	26	30	29
Sodium (mmol/l)	148	149	148
Potassium (mmol/l)	4.1	4.6	5.4
Chloride (mmol/l)	112	117	112

APPENDIX C

TABLES

TABLE C1 - Intra-assay coefficient of variation for flunixin analysis.

TABLE C2 - Inter-assay coefficient of variation for flunixin analysis.

TABLE C3 - Plasma concentrations of flunixin (μg/ml), together with mean concentrations ± SEM[48], measured using HPLC, following intravenous administration of a single dose of 1.1 mg/kg flunixin, to dogs in group A (Trial numbers 1 - 10).

TABLE C4 - Plasma concentrations of flunixin (μg/ml) together with mean concentrations ± SEM, measured using HPLC, following intravenous administration of a single dose of 1.1 mg/kg flunixin, to dogs in group B (Trial numbers 11 - 20).

[48]SEM = Standard error of means

Table C1: Intra-assay coefficient of variation of the HPLC technique used for flunixin analysis, in this study

This table gives the coefficient of variation of replicated plasma samples, to which known concentrations of the drug flunixin has been added (spike samples), and analysed in a single assay. In this assay, 0.25 mls of canine plasma was used initially for the extraction procedure (plasma volume), but only 0.15 mls of the extracted mixture was analysed by the HPLC machine (residual volume). The % recovery of the drug by this method was 66.66%.

S. No	Conc of sample	Peak height of sample	Peak height of standard	Std conc	% recovery of flunixin	Mean % recovery	Sample std. dev	Sample std. error	Coefficient of variation (%)
S1	0.25	15.25	64.30	1.00	85.46				
S2	0.25	12.75	65.50	1.00	70.08	76.5	6.59	3.29	8.61
S3	0.25	14.00	65.50	1.00	76.95				
S4	0.25	14.00	68.50	1.00	73.58				
S5	1.00	61.50	68.50	1.00	80.81				
S6	1.00	66.00	68.00	1.00	87.36	83.8	5.92	2.96	7.06
S7	1.00	58.25	68.00	1.00	77.10				
S8	1.00	67.00	68.50	1.00	90.01				
S9	2.00	44.50	54.50	2.00	73.49				
S10	2.00	47.50	53.80	2.00	79.54	80.2	5.17	2.59	6.45
S11	2.00	51.25	53.80	2.00	85.82				
S12	2.00	48.50	53.30	2.00	81.98				
S13	5.00	72.75	68.50	5.00	95.59				
S14	5.00	64.50	68.50	5.00	84.75	83.5	8.95	4.47	10.72
S15	5.00	54.50	63.00	5.00	77.86				
S16	5.00	53.00	63.00	5.00	75.72				
S17	10.00	59.75	61.30	10.00	87.80				
S18	10.00	57.50	61.30	10.00	84.50	84.3	2.53	1.26	3.00
S19	10.00	54.25	58.80	10.00	83.11				
S20	10.00	53.50	58.80	10.00	81.97				
S21	25.00	56.75	46.00	25.00	88.83				
S22	25.00	48.75	46.00	25.00	76.31	80.5	6.70	3.35	8.32
S23	25.00	45.75	44.50	25.00	74.03				
S24	25.00	51.25	44.50	25.00	82.93				
S25	0.00	0.00	53.30	2.00	0.00				
S26	0.00	0.00	68.50	1.00	0.00				
					Recovery =	81.5%			

ABBREVIATIONS

S.No = Sample number or spike number

Conc of sample = Concentrationof the drug flunixin in the plasma sample in ug/ml

Std conc = Concentration of standard in ug/ml

Mean % recovery = It is the mean of the percentage recovery of flunixin for each set of spiked samples

Sample std. dev = Sample standard deviation

Sample std. error = Sample standard error of the mean % recovery

% = Percentage

Table C2: Inter-assay coefficient of variation, in the HPLC techniques used for flunixin analysis, in the 20 trial dogs in the study

This table shows the variation in the % recoveries of the same concentration of spiked samples of flunixin, in the 20 different assays performed on the 20 trial dogs, on 20 different days. An inter-assay coefficient of variation was performed to determine the degree of variation in the % recoveries of the spikes, between the 20 different assays performed.
Dogs no 1 - 10 (group A) received flunixin, 1.1 mg/kg iv, during anaesthesia, prior to the start of surgery
Dogs no 11 - 20 (group B) received flunixin, 1.1 mg/kg iv, immediately after anaesthesia terminated

% recovery of each spike, for the individual trial dogs, are filled in the given table

Spike conc	0.25 ug/ml	1 ug/ml	2 ug/ml	5 ug/ml	10 ug/ml	25 ug/ml
Dog 1	73.7	65.5	83.8	87.5	84.7	92.3
Dog 2	86.1	71.3	83.2	78.7	88.7	*
Dog 3	63.9	62.4	61.6	65.2	84.5	79.7
Dog 4	72.3	71.0	68.3	78.2	75.7	85.5
Dog 5	79.1	67.6	75.4	69.8	*	60.2
Dog 6	91.0	83.9	91.3	90.4	79.1	95.9
Dog 7	60.0	73.2	84.9	84.4	95.4	86.3
Dog 8	88.7	90.7	78.4	88.2	95.0	89.5
Dog 9	111.6	94.6	96.3	93.8	*	88.7
Dog 10	64.5	65.6	78.5	80.0	*	78.8
Dog 11	78.1	87.5	75.6	92.0	98.3	93.1
Dog 12	67.9	72.9	76.1	80.2	*	83.3
Dog 13	86.6	*	72.4	89.4	84.8	67.2
Dog 14	119.0	89.3	81.7	86.8	106.9	90.4
Dog 15	98.5	81.1	76.5	88.2	86.3	79.3
Dog 16	73.1	81.6	83.9	91.2	*	94.5
Dog 17	66.7	65.7	82.6	98.3	86.5	77.5
Dog 18	80.3	*	86.1	74.4	80.2	92.2
Dog 19	73.0	89.5	83.8	95.6	86.1	92.0
Dog 20	64.7	69.2	67.5	*	74.6	93.5
Mean % recovery	79.9	76.8	79.4	84.9	87.1	85.3
Sample std dev	15.9	10.4	8.2	8.8	8.7	9.6
Sample std error	3.6	2.5	1.8	2.0	2.3	2.2
Coeff of var (%)	19.9	13.6	10.3	10.4	10.0	11.2

ABBREVIATIONS

Mean % recovery = Mean percentage recovery of drug flunixin for each spike, in the 20 different assays performed (Dogs trial No 1 - 20)
Sample std dev = Sample standard deviation
Sample std error = Sample standard error
Coeff of var (%) = Coefficient of variance , expressed as a percentage
* = Missing value

Table C3: Concentration of flunixin in plasma (ug/ml), together with mean concentrations +/- SEM , measured following intravenous administration of a single dose of 1.1 mg/kg flunixin, to dogs in group A (trial No 1 - 10).
Group A dogs (trial no 1- 10), received flunixin during anaesthesia, prior to the start of surgery.

Plasma Flunixin concentration (ug/ml)

Time (hrs)	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9	Dog 10	Mean conc	SEM
Pre	0	0	0	0	0	0	0	0	0	0	0	0
(2 min) 0.03	25.34	26.94	25.56	22.22	18.81	21.58	23.33	18.14	38.57	27.77	24.48	1.84
(5 min) 0.08	17.82	18.67	18.01	14.23	12.78	16.24	19.36	13.26	28.16	21.50	18.00	1.43
(10 min) 0.17	13.59	13.68	13.74	11.46	9.31	13.83	14.44	10.39	17.41	16.20	13.36	0.78
(15 min) 0.25	11.40	12.16	12.46	11.28	7.27	10.49	12.51	9.11	16.61	14.80	11.81	0.84
(20 min) 0.33	12.83	10.54	12.81	9.77	6.68	8.85	11.71	8.82	15.30	14.31	11.16	0.86
(30 min) 0.50	12.83	10.17	12.28	8.62	4.67	6.48	12.03	6.45	13.15	13.88	10.06	1.04
(45 min) 0.75	10.44	9.54	10.72	7.49	4.29	6.40	10.12	5.74	10.70	11.88	8.73	0.81
1	10.08	7.72	7.88	7.23	3.61	5.62	9.01	4.38	8.52	11.47	7.55	0.78
1.5	*	*	*	5.78	2.57	4.07	7.80	3.67	6.47	8.58	5.56	0.84
2	5.48	4.45	4.28	4.57	2.14	2.46	5.70	2.58	5.90	5.59	4.32	0.46
4	1.70	1.92	1.62	2.52	0.39	0.58	2.79	0.54	5.39	3.20	2.07	0.48
6	0.83	1.44	0.48	1.64	0.21	0.39	0.99	0.16	4.96	1.16	1.23	0.45
8	0.70	1.13	0.21	1.15	0.16	0.26	0.94	0.15	2.71	1.16	0.86	0.25
10	*	*	*	1.04	0.14	0.21	0.93	0.13	1.37	0.88	0.67	0.19
12	0.32	0.71	0.14	0.96	0.11	0.19	0.46	0.09	1.10	0.64	0.47	0.12
20	*	*	*	0.42	0.07	0.19	0.37	0.08	*	0.22	0.23	0.06
24	0.10	0.26	0.12	0.37	0.07	0.17	0.20	0.07	0.63	0.08	0.21	0.06
30	0.10	*	0.00	0.04	0.06	*	0.16	0.00	0.16	0.05	0.07	0.02

ABBREVIATIONS

Pre = Prior to induction of anaesthesia
* = Not sampled
Mean conc = Mean concentration of plasma flunixin in the 10 trial dogs (ug/ml)
SEM = Standard error of the means

Table C4: Concentration of flunixin in plasma (ug/ml), together with mean concentrations +/- SEM , measured following intravenous administration of a single dose of 1.1 mg/kg flunixin, to dogs in group B (trial No 11 - 20). Group B dogs (trial no 11 - 20), received flunixin at the termination of anaesthesia.

Plasma Flunixin concentration (ug/ml)

Time (hours)		Dog 11	Dog 12	Dog 13	Dog 14	Dog 15	Dog 16	Dog 17	Dog 18	Dog19	Dog 20	Mean conc	SEM
	Pre	0	0	0	0	0	0	0	0	0	0	0	0
(2 min)	0.03	28.18	26.87	30.39	27.99	28.63	16.77	26.64	36.87	23.56	41.16	28.71	2.11
(5 min)	0.08	19.24	24.13	24.39	20.49	20.69	14.62	18.91	28.49	15.34	27.09	21.34	1.47
(10 min)	0.17	17.02	19.16	15.84	14.38	14.99	13.11	14.86	23.16	12.32	21.70	16.65	1.14
(15 min)	0.25	15.23	17.43	16.55	12.63	11.54	12.23	13.20	18.28	9.77	18.82	14.57	0.99
(20 min)	0.33	13.22	16.69	16.52	11.74	12.38	12.83	11.06	17.62	8.88	15.21	13.62	0.89
(30 min)	0.5	12.24	13.28	16.01	11.19	10.46	12.24	8.81	17.25	7.96	12.56	12.20	0.91
(45 min)	0.75	8.48	12.39	11.39	8.84	8.17	11.27	5.94	14.91	6.86	10.67	9.89	0.86
	1	8.39	9.04	9.55	8.45	6.75	9.77	4.86	11.74	5.31	10.09	8.40	0.69
	1.5	5.52	6.21	8.39	5.65	4.70	8.39	1.87	8.41	3.36	6.84	5.93	0.70
	2	4.35	4.08	4.71	5.04	2.61	5.02	1.54	6.49	2.22	5.07	4.11	0.48
	4	1.41	0.84	2.73	4.46	2.33	1.83	0.38	1.91	0.36	1.09	1.73	0.39
	6	0.75	0.44	1.25	1.54	1.55	0.85	0.21	1.08	0.30	0.47	0.84	0.16
	8	0.46	0.40	0.74	1.38	0.87	0.61	0.15	0.61	0.21	0.30	0.57	0.12
	10	0.46	0.32	0.46	0.80	0.56	0.35	0.10	0.59	0.18	0.23	0.41	0.07
	12	0.31	0.24	0.30	0.66	0.48	0.27	0.08	0.49	0.18	0.18	0.32	0.06
	20	*	0.12	0.30	0.34	0.14	0.16	*	*	0.08	0.17	0.19	0.04
	24	0.07	0.09	0.23	0.20	0.13	0.09	0.00	0.10	0.07	0.13	0.11	0.02
	30	0.00	0.06	0.15	0.20	0.10	0.04	0.00	0.05	0.01	0.11	0.07	0.02

ABBREVIATIONS

Pre = Prior to induction of anaesthesia

NS = Not sampled

Mean conc = Mean concentration of plasma flunixin in the 10 trial dogs (ug/ml)

SEM = Standard error of the means

APPENDIX D

TABLES

TABLE D1 - Pharmacokinetic parameters of flunixin, in dogs in group A, obtained after compartmental analysis of data.

TABLE D2 - Pharmacokinetic parameters of flunixin, in dogs in group B, obtained after compartmental analysis of data.

TABLE D3 - Pharmacokinetic parameters of flunixin, in dogs in group A, obtained after non-compartmental analysis of data.

TABLE D4 - Pharmacokinetic parameters of flunixin, in dogs in group B, obtained after non-compartmental analysis of data.

Table D1: Pharmacokinetic parameters of flunixin, obtained after compartmental analysis of data, in dogs in group A (Trial No 1- 10)

Trial No	UNITS	1	2	3	4	5	6	7	8	9	10	MEAN	SEM
EXPONENTIAL		3	3	3	3	3	2	3	3	3	3		
1/2 LIFE P (distribution)	hours	0.031	0.038	0.032	0.019	0.053	0.179	0.048	0.039	0.045	0.042	0.05	0.01
1/2 LIFE A (distribution)	hours	1.291	0.909	1.16	0.418	0.818		1.376	0.784	0.353	1.011	0.90	0.12
1/2 LIFE B (elimination)	hours	9.704	7.727	11.855	4.75	15.398	3.834	9.482	5.763	5.64	4.474	7.86	1.18
CPO	ug/ml	35.558	36.614	35.639	39.61	24.098	25.541	29.8	23.6	49.388	34.69	33.45	2.52
AUC	ug.hr/ml	37.144	41.39	32.794	44.256	15.361	26.643	47.673	18.38	69.868	48.481	38.20	5.08
AUC (observed)	ug.hr/ml	36.244	38.723	29.293	41.631	14.27	20.31	43.999	16.64	69.628	46.254	35.65	5.24
Vc	ml/kg	30.94	30.04	30.87	27.77	45.65	43.07	36.91	46.62	22.27	31.71	34.58	2.58
Vd (ss)	ml/kg	148.8	188.8	168.8	150.3	528.9	189.2	166.6	208	111.5	98	195.89	38.5
CL(b)	ml/kg.hr	29.6	26.6	33.5	24.9	71.6	41.3	23.1	59.8	15.7	22.7	34.88	5.64
K el	/hr	0.957	0.885	1.087	0.895	1.569	0.846	0.625	1.284	0.707	0.716	0.96	0.09

Table D2: Pharmacokinetic parameter of flunixin, obtained after compartmental analysis of data, in dogs in group B (Trial No 11- 20)

Trial No	UNITS	11	12	13	14	15	16	17	18	19	20	MEAN	SEM
EXPONENTIAL		3	3	3	3	3	2	3	3	3	3		
1/2 LIFE P (distribution)	hours	0.02	0.07	0.06	0.04	0.04	1.22	0.03	0.04	0.02	0.06	0.16	0.12
1/2 LIFE A (distribution)	hours	0.59	0.74	1.16	0.80	0.62		0.46	0.90	0.57	1.03	0.76	0.08
1/2 LIFE B (elimination)	hours	3.76	8.29	9.53	5.64	5.48	5.37	3.59	5.12	4.66	9.58	6.10	0.74
CPO	ug/ml	47.43	30.27	36.88	38.52	36.90	15.60	37.27	45.95	35.47	49.55	37.38	3.08
AUC	ug.hr/ml	33.52	30.95	46.51	49.97	34.98	38.40	16.13	47.01	21.52	38.23	35.72	3.45
AUC (observed)	ug.hr/ml	31.06	32.22	42.39	46.05	33.14	35.00	15.46	46.27	18.45	33.98	33.40	3.27
Vc	ml/kg	23.19	36.34	29.83	28.55	29.81	70.50	29.52	23.94	31.01	22.20	32.49	4.43
Vd (ss)	ml/kg	114.90	142.40	141.50	138.60	165.40	113.80	115.90	84.70	180.70	128.40	132.63	8.73
CL(b)	ml/kg.hr	32.80	35.50	23.70	22.00	31.40	28.60	68.20	23.40	51.10	28.80	34.55	4.58
K el	/hr	1.42	0.98	0.79	0.77	1.06	0.41	2.31	0.98	1.65	1.30	1.16	0.17

ABBREVIATIONS

SEM = Standard error of means
1/2 LIFE P (distribution) = Distribution half life
1/2 LIFE A (distribution) = Distribution half life
1/2 LIFE B (elimination) = Elimination half life
CPO = Initial concentration of drug in plasma, following an intravenous injection
AUC = Area under zero moment curve
AUC (observed) = Area under the curve (observed values)
Vc = Apparent volume of central compartment
Vd (ss) = Apparent volume of distribution at steady state
CL(b) = Body clearance of drug
K el = Elimination rate constant

Table D3: Flunixin pharmacokinetic variables obtained after non-compartmental analysis of data, in dogs in group A (trial no 1-10)

TRIAL NO	UNITS	1	2	3	4	5	6	7	8	9	10	MEAN	SEM
AUC (observed)	ug.hr/ml	37.59	41.57	31.29	41.86	15.57	21.20	59.68	18.04	78.11	42.20	38.71	6.10
AUMC (observed)	ug.hr/ml	168.68	288.29	951.08	266.69	120.04	102.42	737.46	85.22	493.41	134.57	334.79	94.50
MRT	hours	4.49	6.94	30.40	6.37	7.71	4.83	12.36	4.72	6.32	3.19	8.73	2.53
Vd (ss)	ml/kg	131.31	183.51	1068.56	167.42	544.68	250.67	227.76	288.05	88.96	83.12	303.40	94.80
CL(b)	ml/kg.hr	29.26	26.46	35.16	26.28	70.65	51.89	18.43	60.98	14.08	26.07	35.93	5.96

Table D4: Flunixin pharmacokinetic variables obtained after non-compartmental analysis of data, in dogs in group B (trial no 11- 20)

TRIAL NO	UNITS	11	12	13	14	15	16	17	18	19	20	MEAN	SEM
AUC (observed)	ug.hr/ml	31.38	32.86	44.38	47.62	33.87	35.27	20.07	46.55	18.47	35.62	34.61	3.15
AUMC (observed)	ug.hr/ml	104.14	126.65	270.35	302.24	179.32	130.30	100.94	163.77	60.19	173.57	161.15	23.90
MRT	hours	3.32	3.85	6.09	6.35	5.29	3.69	4.98	3.52	3.26	4.87	4.52	0.36
Vd (ss)	ml/kg	116.33	129.02	150.99	146.61	171.86	115.22	270.24	83.14	194.08	150.48	152.80	16.40
CL(b)	ml/kg.hr	35.05	33.48	24.79	23.10	32.48	31.19	54.27	23.63	59.56	30.88	34.84	3.93

ABBREVIATION

SEM = Standard error of mean
AUC (observed) = Area under the zero moment curve (observed)
AUMC (observed) = Area under the first moment curve (observed)
MRT = Mean residence time
Vd (ss) = Apparent volume of distribution at steady state
CL(b) = Body clearance of drug