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INVESTIGATIONS OF ETOMIDATE AND PROPOFOL
FOR THE INDUCTION AND MAINTENANCE OF ANAESTHESIA

NORMAN WATSON LEES

M.B. Ch.B., F.F.A.R.C.S.

Thesis submitted for the Degree of
Doctor of Medicine
University of Glasgow.

Department of Anaesthesia
Victoria Infirmary

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STATEMENT OF COLLABORATION

I initiated and participated in all the studies. The initial supplies of etomidate for the induction studies were obtained by Dr. J.G.B. Hendry. Further supplies of etomidate, and all the supplies of alfentanil and propofol were obtained by myself. During different studies I received valuable help from:

Dr. J.G.B. Hendry, Consultant Anaesthetist, Victoria Infirmary, Glasgow, without whom these studies would not have been undertaken.

Drs. W.R.A. Antonios, J. Glasser, T. Houston, M.D. Inglis, M.J. McCulloch, F.J. McGroarty, W.B. Mair and B.M. Miller. All were junior members of the Department of Anaesthesia, Victoria Infirmary, Glasgow at the time of their participation in these studies.

The members of staff of the Department of Biochemistry, Victoria Infirmary carried out the biochemical analyses described in this thesis. In particular, these included the measurements of pH and osmolality described in Chapter Four, the analysis of the arterial blood samples described in Chapter Seven and the measurements of liver function tests and serum electrolytes described in Chapter Eight.

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DECLARATION OF WORK PUBLISHED

The following publications are based on material presented in this thesis:

- 1: Lees, N.W., and Hendry, J.G.B. (1977). Etomidate in urological outpatient anaesthesia: a clinical evaluation.
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- 2: Hendry, J.G.B., Miller B.M. and Lees N.W. (1977).
Etomidate in a new solvent: a clinical evaluation.
Anaesthesia, 32, 996 - 999.
- 3: Miller B.M., Hendry J.G.B. and Lees N.W. (1978)
Etomidate and methohexitone: a comparative clinical study in outpatient anaesthesia. Anaesthesia, 33, 450 - 453.
- 4: Lees N.W. (1981). Etomidate and fentanyl infusions for anaesthesia. Clinical Research Reviews, 1, 111 - 113.
- 5: Lees N.W., Glasser J., McGroarty F.J. and Miller B.M. (1981). Etomidate and fentanyl for maintenance of anaesthesia. British Journal of Anaesthesia, 53, 959 - 961 .
- 6: Lees N.W. (1983). Experience with etomidate as part of a total anaesthetic technique. Anaesthesia, 38, Suppl. 70 - 73.

- 7: Lees N.W. and Antonios W.R.A. (1984). Two-stage infusion of etomidate for the induction and maintenance of anaesthesia. British Journal of Anaesthesia, 56, 1239 - 1242.
- 8: Antonios W.R.A., Inglis M.D. and Lees N.W. (1984). Alfentanil in minor gynaecological surgery: use with etomidate and a comparison with halothane. Anaesthesia, 39: 812 - 815.
- 9: McCulloch M.J. and Lees N.W. (1985). Assessment and modification of pain on induction with propofol. Anaesthesia, 40, 1117 - 1120.
- 10: Lees N.W., McCulloch, M.J. and Mair W.B. (1985). Propofol (Diprivan) for induction and maintenance of anaesthesia. Postgraduate Medical Journal, 61, Suppl. 3, 86 - 89.

ABSTRACT

Because of the hazards of inhalational agents to both patients and theatre staff, investigations of the hypothesis that total intravenous anaesthetic techniques might provide equally satisfactory anaesthesia for patients either breathing spontaneously or requiring mechanical ventilation compared with conventional inhalational based techniques were carried out. A review of the literature suggested that etomidate and later propofol might be suitable agents for this purpose.

The investigations were carried out in two stages. Firstly their properties as induction agents were investigated to determine their potential suitability for infusion. After these studies were completed, the infusion studies were carried out. Supplementary analgesia was provided by the infusion of fentanyl.

SUMMARY

INVESTIGATIONS OF ETOMIDATE AND PROPOFOL FOR THE INDUCTION AND MAINTENANCE OF ANAESTHESIA

This thesis investigates the hypothesis that total intravenous anaesthetic techniques involving the infusion of etomidate or propofol could provide adequate anaesthesia for fit patients undergoing a variety of routine operations requiring either spontaneous or assisted ventilation.

The initial studies of the bolus administration of etomidate for the induction of anaesthesia were carried out in outpatients undergoing cystoscopy premedicated only with atropine. The first two studies of etomidate with sodium phosphate/biphosphate dissolved in sterile water as diluent showed it to be a potent, short acting hypnotic with cardiovascular and respiratory stability, superior to that of propanidid. A high incidence of pain on injection and muscle movement was found.

Reformulation in polyethylene glycol (Study Three) and propylene glycol (Study Four) did not appear to alter its potency or physiological characteristics. In both formulations the incidence of pain on injection, but not muscle movement, was reduced.

Alfentanil given intravenously immediately before an induction dose of etomidate was found to reduce the incidence of pain on injection and muscle movement without affecting the speed of recovery (Study Five).

Investigation of propofol in Study Six as an induction agent in patients undergoing minor general and gynaecological surgery showed it to have similar cardiovascular properties to thiopentone, but with a higher incidence of apnoea and pain on injection. The incidence of pain on injection was reduced when administered via a vein in the antecubital fossa, but not by the prior intravenous injection of lignocaine.

The continuous infusion of etomidate and fentanyl was found to provide adequate anaesthesia for most patients in all the etomidate studies. Cardiovascular and respiratory stability was well maintained. Induction of anaesthesia using a bolus of etomidate (Study Seven) was found to be unsatisfactory due to pain on injection and muscle movement. The substitution of thiopentone (Study Eight) provided an excellent induction of anaesthesia but was associated with a prolonged recovery time. The use of a pre-determined two stage infusion scheme of etomidate with a separate variable infusion of fentanyl (Study Nine) was found to give a smoother induction compared with Study Seven, faster recovery than that found in Study Eight, and reduced the amount of etomidate infused over a period of time. A wide variation in infusion rates for fentanyl was found in all the studies.

The effects of these infusion techniques on hepatic and renal function (Study Ten) in patients undergoing simple abdominal hysterectomy were found to be similar to those of a standard inhalational based anaesthetic technique.

Using a predetermined infusion scheme with a separate variable

infusion of fentanyl as analgesic (Study Eleven), propofol provided a smooth induction of anaesthesia following an opiate premedication. Maintenance of anaesthesia was satisfactory in ventilated patients, but spontaneously breathing patients became apnoeic. Although arterial blood systolic and diastolic pressures and heart rate tended to fall during induction, this was not clinically significant and soon returned to pre-induction levels. Recovery was rapid and the incidence of side effects was low. Administration over two to three hours (Study Twelve) was associated with progressive prolongation of the duration of action of bolus increments of vecuronium, but not atracurium. The variability of the fentanyl infusion rates were found to be similar to those of the etomidate studies.

The conclusions of these studies were that etomidate and propofol offer advantages of rapid recovery and (for etomidate) cardiovascular stability. For general use, their side-effects reduce their potential advantages over other currently available induction agents. Total intravenous anaesthetic techniques are possible with both etomidate and propofol supplemented with fentanyl, but better methods of assessing the requirements of individual patients are required before such techniques are suitable for widespread use in clinical anaesthesia.

The conclusions of this thesis do not fully support the hypothesis.

CHAPTER ONE

INTRODUCTION

Hypothesis

This thesis explores the hypothesis that total intravenous anaesthetic techniques could provide equally satisfactory anaesthesia for patients either breathing spontaneously or requiring mechanical ventilation, compared with inhalational agents.

Hazards of Inhalational Agents to Patients

Although in widespread use for many years, problems have recently been attributed to the use of the inhalational agents. With the exception of carbon tetrachloride (Powell, 1945) the concept that anaesthetic agents such as ether (Haggard, 1924) were eliminated unchanged was not challenged until the 1960's. Using radio-isotopes, chloroform and carbon tetrachloride (Paul and Rubenstein, 1963), ether, halothane and methoxyflurane (Van Dyke, Chenoweth and Van Poznack, 1964) were found to be metabolised. During the late 1960's and 70's these findings took on greater significance when a series of clinical reports appeared, implicating inhalational anaesthetic agents as posing potential hazards both to patients and to theatre personnel.

Methoxyflurane is metabolised to oxalic acid and fluoride ions, which can cause nephrotoxicity and renal failure (Panner et al, 1970; Taves et al, 1970; Mazze, Trudell and Cousins, 1971). Halothane hepatotoxicity has been a controversial issue but appears to be a complex clinical entity (Van Dyke, 1983; Cousins, Plummer and Hall, 1984; Neuberger and Williams, 1984) This topic has recently been reviewed again when further problems

associated with its use have been described (Blogg, 1986; Brown and Gandolfi, 1987).

Nitrous oxide can cause problems by diffusion into gas loculi. This may occur in intestinal obstruction, pneumothorax (Eger, 1980) or middle ear surgery (Mann, Woodsford and Jones, 1985). Nitrous oxide can also affect the haematological system causing leucopenia, acute aplasia (Lassen et al, 1956), megaloblastic haemopoiesis (Amess et al, 1978) and myeloneuropathy (Layser, 1978) resulting from the inhibition of the production of methionine synthetase (Koblin et al, 1982; Nunn, 1987). The time of exposure required may be as short as two hours in seriously ill patients (Amos et al, 1982). Nitrous oxide may also affect cell mediated immunity (Nunn and O'Morain, 1982). The degree of liver damage associated with hypoxia (Fassoulaki et al, 1984) may be increased by nitrous oxide and it may also affect metabolic pathways in the liver (Black, Virayotha and Tephily, 1984).

Hazards of Inhalational Agents to Theatre Staff

The chronic inhalation of volatile and gaseous anaesthetic agents may reduce psychomotor performance (Bruce and Bach, 1976) but such effects have not been found by other investigators (Smith and Shirley, 1977; Frankhuizen et al, 1978). Higher sub-anaesthetic levels found in patients after operation (Cook et al, 1978) have been shown to cause impairment of psychological function and decision making (Bentin, Collins and Adam, 1978).

Early concern about the effect of theatre pollution on staff

was expressed by Werthmann (1949) who found haematological changes in theatre personnel chronically exposed to ether. He suggested the venting of gases out of the operating theatre and the filtering of theatre air. Later studies suggested that there was an increased incidence of miscarriage and congenital abnormality in theatre personnel (Cohen, Belville and Brown, 1971; Knill-Jones et al 1972) although not in the wives of exposed males (Knill-Jones, Newman and Spence, 1975).

Other suggested hazards have been an increase in carcinoma (Bruce et al, 1968; Corbett et al, 1973), and altered drug metabolism in anaesthetists (Harman et al, 1978; Duvaldestine et al, 1981). Jaundice attributable to halothane sensitivity has been described (Klatskin and Kimberg, 1969).

The amount of disease potential has been widely discussed and the consensus of opinion would appear to be that there is an increased risk of abortion in theatre staff (Vessey and Nunn, 1980; Mazze, 1983; Buring et al, 1985) possibly due to nitrous oxide (Lane et al, 1979; Cohen et al, 1980; Brodsky, 1983). This has been supported by animal studies which have shown that nitrous oxide may be foetotoxic (Vieira, 1979; Vieira, Cleaton-Jones and Moyes, 1983) and that the administration of folinic acid partially reduced this teratogenic effect (Keeling et al, 1986). In contrast, prolonged exposure to volatile anaesthetic agents has been shown to be without adverse effect on rats (Plummer et al, 1986). Reduction of theatre pollution has become official policy of the Association of Anaesthetists of Great Britain and Ireland (Association of Anaesthetists, 1978). A recent review has suggested

that these environmental problems may not be as significant as previously suggested (Spence, 1987).

Possible Solutions

Scavenging Systems

The most common solution has been the introduction of scavenging systems, both active and passive. Such systems are not always efficient (Railton and Fisher, 1984) and cannot compensate for ill fitting face masks (Torda, Jones and Englert, 1978). Closed circuit anaesthesia using oxygen and halothane without nitrous oxide has been advocated (Burns, 1980; Hughes, 1980). Nitrous oxide, in particular, can cause problems of gaseous homeostasis and gas uptake (Conway, 1982), with the accumulation of nitrogen (Barton and Nunn, 1975).

At best, these solutions reduce the dangers of pollution to the theatre staff, but not to the patients. Apart from the pharmacological dangers described earlier, hazards may arise from anaesthetic equipment (Ward, 1985) often attributable to inconvenient or poorly designed equipment (Rendell-Baker, 1982). Bulk storage supplies of oxygen and nitrous oxide may be mis-connected with potentially fatal results (Feeley and Hedley-Whyte, 1976; Carley, Houghton and Park, 1984). Vapourizers (Kelly, 1985; Hogan, 1985) and scavenging systems (Tavakoli and Habeeb, 1978; Seymour, 1982) can also give rise to unexpected hazards.

Total Intravenous Anaesthesia

Total intravenous anaesthetic techniques offer potential advantages of non-hypoxic oxygen and air mixtures combined with a total absence of the hazards of inhalational agents to both patients and theatre staff. Such techniques require the provision of hypnosis and analgesia and the ability to infuse small volumes of drugs, with a high degree of accuracy.

Historical Survey of Total Intravenous Anaesthesia

The technique was first described by Ore' in 1874. He administered two bolus injections of 9 gm. of chloral hydrate intravenously on February 9th 1874 to anaesthetise a 52 year old male for exploration of a crushed finger which had caused tetanus (Ore', 1874, a). A similar anaesthetic for the removal of a testicular tumour was carried out in August of that year (Ore', 1874, b). The technique failed to find general acceptance. In the early 1900's the use of I.V. ether (Burkhardt, 1909; Kummel, 1912) and hedonal (Federoff, 1912) was described. The techniques were difficult and time consuming, although shocked patients seemed to benefit from the administration of large amounts of fluid (Rood, 1911). Intravenous paraldehyde (Noel and Souttar, 1913) and magnesium sulphate (Peck and Meltzer, 1916) were also investigated. Later alcohol (Constantine, 1929; 1930) and intravenous tribromoethanol (avertin), (Kirschner, 1930) were also investigated as potential intravenous anaesthetics, but again without success.

Intratracheal anaesthesia was developing at the same time

(Cotton and Boothby, 1913; Kelly, 1913) based on the work of Meltzer and Auer (1909). These techniques soon became superior to intravenous techniques (Shipway, 1913).

Review of Intravenous Hypnotic Agents

One of the major advances in anaesthesia was the introduction of the intravenous hypnotic agents. They provide a rapid, smooth induction of anaesthesia compared with the prolonged and sometimes stormy inhalation inductions associated with the use of ether or chloroform. The first drugs used in this way were the barbiturates of which thiopentone, pioneered by Lundy (1936; 1942) and later methohexitone, remain in everyday use in Britain. The introduction of thiopentone allowed minor operations to be done with intravenous anaesthesia alone (Lundy, 1942), but this was soon superseded by the use of a combination of thiopentone, nitrous oxide and oxygen (Organe and Broad, 1938).

The barbiturates have disadvantages of cardiovascular and respiratory depression. Recovery is due principally to redistribution (Dundee and Clarke, 1980) and cumulation occurs on repeated injection (Dundee, 1955). Methohexitone is more rapidly metabolised than thiopentone (Vickers, Wood-Smith and Stewart, 1978).

Both thiopentone and methohexitone have been used as infusions during neurosurgical operations (Hunter, 1972, a; b). However the problems of cumulation, and delayed recovery have meant that these techniques have also not become widely used.

During the last twenty years various induction agents have been introduced which are metabolised more rapidly than the barbiturates. None of these has been entirely successful. Ketamine has an effect described as "dissociative anaesthesia" (Corssen and Domino, 1966) but has been found to be associated with a high incidence of hypertension, delirium and hallucinations during the recovery period (Knox et al, 1970). Alcohol has been investigated but has not been found to be as reliable for induction as the barbiturates or eugenols (Dundee et al, 1970). Minaxolone has been shown to be a satisfactory induction agent (Punchihewa et al, 1980) but has been withdrawn due to toxicological findings (Morgan and Dawson, 1984). Benzodiazepines have also been used but they have a marked variability in effect and delay in hypnotic action (Dundee et al, 1985).

Several intravenous induction agents are highly lipophilic and virtually insoluble in water. A polyoxyethylated castor oil, Cremophor E.L. is a detergent which until recently was commonly used as a solubilising agent. Although the mechanisms are not clear (Watkins et al, 1976; Glen et al, 1979; Benoit et al, 1983) anaphylactic reactions to propanidid, althesin and di-isopropyl phenol (Briggs, Clarke and Watkins, 1982) have been associated with the use of Cremophor. As a result of these problems propanidid (Pharmaceutical Journal, 1983) and althesin (Lancet, 1984) have been withdrawn from use. Di-isopropyl phenol has been reformulated in a soya bean emulsion formulation, now re-released as propofol.

Etomidate and Propofol

Etomidate

Early animal work (Janssen et al, 1971; 1975) suggested that etomidate (R-(1)-ethyl-1-(a methyl-benzyl) imidazole-5 carboxylate) was a potent hypnotic of rapid onset, with a high safety margin. Metabolism was mainly by hydrolysis in the liver (Meuldermans, Lauwers and Heykants, 1976) and over seventy six per cent was protein bound (Meuldermans and Heykants, 1976). Much of the early clinical work on etomidate was reported by Doenecke and his group. Reviewing his experience he concluded (Doenecke, 1974) that an induction dose of 0.15 mg.kg.^{-1} was inadequate, but that 0.3 mg.kg.^{-1} of etomidate was better than 5 mg.kg.^{-1} of thiopentone, and that etomidate possessed marked cardiovascular and respiratory stability with few side-effects and no serious complications. The capacity of etomidate to release histamine was found to be very much less than that of althesin or propanidid (Doenecke et al, 1973).

Other clinical studies confirmed its properties of cardiovascular stability (Brückner et al, 1974; Kettler et al, 1974; Hemplemann et al, 1974, a), and respiratory stability (Hemplemann et al, 1974, b). All these studies described a lack of analgesia, pain on injection and myoclonic movements as significant disadvantages.

Propofol

2,6 di-isopropylphenol is one of a series of alkylphenols. Early animal work in several species showed it to be a potent hypnotic (James and Glen, 1980). Being insoluble in water, Cremophor E.L. was used as a solvent and the compound was investigated as disoprofol. Although found to be a satisfactory induction agent (Kay and Rolly, 1977, b); Briggs et al, 1981), concern over possible anaphylactic responses to Cremophor E.L. (Briggs, Clarke and Watkins, 1982) led to reformulation in an emulsion formulation - Propofol. This consists of di-isopropylphenol 1% w/v. in an aqueous emulsion containing 10% w/v. soya bean oil, 1.2% w/v. egg phosphatide and 2.25% w/v. glycerol. No adverse effects were produced when repeatedly injected into mini-pigs and no evidence of histamine release has been demonstrated (Glen and Hunter, 1984; Doenecke et al, 1985). The most important change clinically was an increase in the required induction dose to 2.5 mg.kg.^{-1} (Cummings et al, 1984).

Scope of the Thesis

The hazards of inhalational agents to both patients and theatre staff have been outlined. Reviewing the properties of etomidate and propofol suggested that these drugs could possibly be used as the hypnotic component of a total intravenous anaesthetic technique.

This thesis describes several studies designed to evaluate the potential of etomidate and propofol to provide hypnosis by

infusion. The studies were carried out in two stages. The first stage was their administration as a single bolus for the induction of anaesthesia. Studies One and Two investigated the use of etomidate when dissolved in sodium phosphate/biphosphate in sterile water as diluent. Study Three assessed its use when reformulated in polyethylene glycol. Study Four investigated its use when formulated in propylene glycol and Study Five investigated the effect of alfentanil on the induction characteristics of etomidate. Study Six investigated the effects of the administration of propofol. These studies allowed an assessment of the cardiovascular and respiratory stability, rapidity and quality of induction and recovery and the presence of any side-effects of the two drugs.

The second stage evaluated their infusion as the hypnotic component of a total intravenous technique. Study Seven investigated the effect of a bolus injection of etomidate followed by a combined infusion of etomidate and fentanyl. In Study Eight, anaesthesia was induced with thiopentone, then maintained by an infusion of etomidate and fentanyl. In Study Nine the effect of a predetermined infusion rate of etomidate combined with a variable infusion rate of fentanyl was investigated. Study Ten described an investigation of the effects of the infusion techniques of Studies Eight and Nine on hepatic and renal function. Study Eleven described the initial infusion study of propofol and fentanyl and Study Twelve described the effects of their infusion over a longer (2 - 3 hours) period of time. These studies were particularly concerned with the safety of the technique, the rates of infusion, any effects on cardiovascular and respiratory stability and the quality of

anaesthesia both for patients and theatre staff.

The results are discussed, and conclusions drawn.

CHAPTER TWO

METHODOLOGY OF THE INDUCTION

AND INFUSION STUDIES

Patient Selection

All the etomidate induction and infusion studies were granted Clinical Trial Certificates before being carried out. The licencing system was then changed slightly and the alfentanil study and the propofol induction and infusion studies were carried out after having been granted Clinical Trial Exemption Certificates. All studies also had prior approval from the Victoria Infirmary Ethical Committee.

All patients in the studies were A.S.A. Grade One or Two. All patients were weighed pre-operatively. Patients were excluded from any study who gave a history of previous adverse reaction to anaesthesia, who were possibly pregnant, or who were greater than 10% over their expected body weight. Before taking part, the study was discussed in detail with each patient. Their right to refuse to participate was specifically pointed out before their final agreement was obtained. Oral consent was obtained for all the etomidate studies and written consent obtained for all the propofol studies. Separate oral consent was obtained for taking blood for arterial blood gas measurements or for liver function tests. Oral confirmation of the patient's willingness to participate in a study was obtained immediately before the induction of anaesthesia.

Organisation of the Investigating Teams

All drugs were given by a member of the investigating team for that particular study. A senior member of the team (a Consultant or Senior Registrar) was always present and was the anaesthetist with full clinical responsibility for that patient. It was their

responsibility to obtain valid patient consent, to prepare and to administer the anaesthetic. The anaesthetist was allowed to make any decision that was clinically necessary. The anaesthetist also supervised the patient's recovery and measured the time to early recovery when this measurement was required. The anaesthetist was also responsible for visiting the patient in the ward, or before they left hospital, and recording any complications which occurred in the post-operative period.

There was always a second anaesthetist present who was also a member of the investigating team. Their function was to record all complications and when necessary, their duration, which occurred during the induction and maintenance of anaesthesia, to make and record all measurements of pulse rate and systolic and diastolic blood pressures, to take all arterial blood gas samples when required, to record the times of starting and ending anaesthesia and to record all changes in infusion rates.

Methodology

The studies described in this thesis fall into two distinct groups. The studies described in Chapters Three to Six are concerned with the investigation of etomidate and propofol as induction agents only. The later chapters, Seven to Nine, describe their use by infusion to produce hypnosis. For clarity, the methodology of each group of studies will be described separately.

Methodology of the Induction Studies

Groups of Patients Studied

The groups of patients investigated varied from study to study. Studies One to Four (the initial etomidate induction studies) were carried out in day stay patients undergoing cystoscopy. This procedure was chosen because it represents a relatively uniform surgical procedure of short duration. Study Five (etomidate and alfentanil) was carried out in patients undergoing diagnostic dilatation and curettage, or termination of pregnancy of less than ten weeks duration. This group of patients was chosen because the procedures also represent a short, relatively uniform surgical stimulus, but unlike patients undergoing cystoscopy patients undergoing minor gynaecological surgery in this hospital remain overnight in the ward after surgery. Study Six (induction with propofol) was carried out on in-patients undergoing a range of minor surgical and gynaecological procedures.

Allocation of Patients to Groups within each Study

In the etomidate induction studies (Studies One - Five) patients were randomly allocated to different groups. A table of random numbers was used to produce a code by which patients were randomly assigned to one group in each study. In Study Six, patients were randomly allocated according to a code supplied by I.C.I. Plc.

Anaesthetic Techniques

All patients received atropine 0.6mg. I.M. as premedication, except for forty nine patients in the second study who received no premedication. All patients in Studies One to Four were placed supine on the cystoscopy operating table before any preparation for anaesthesia was carried out. In Studies Five and Six, patients were anaesthetised in the anaesthetic room and not transferred into theatre until anaesthesia had been satisfactorily established.

After the attachment of a blood pressure cuff, the arterial systolic and diastolic blood pressures and the pulse rate were measured. Once the intravenous injection of the appropriate hypnotic induction agent had been completed, patients received oxygen 33% and nitrous oxide 67% via a Mapleson "A" circuit. Manual ventilation was carried out on all patients who remained apnoeic for 60 seconds or longer. Any supplementary volatile or intravenous anaesthetic agent required, was added after a minute had elapsed in the etomidate studies. This was extended to two minutes in the propofol study.

Anaesthesia was supplemented with halothane 0.5 - 2% as required (except in the alfentanil group in Study Six) to provide satisfactory induction of anaesthesia. The induction of anaesthesia was judged to be satisfactory when the patient was lying still with all cardiovascular parameters within 20% of their pre-induction values, breathing adequately with a quiet, unobstructed respiratory pattern and an absent eye-lash reflex. Thereafter the patients were transferred on to the operating table unless they were already lying there and then positioned as required for surgery.

During maintenance anaesthesia the inspired concentration of halothane was set at 1% and was maintained at this level throughout the operation. This level was increased up to a level of 4% if the patient moved during surgery, the arterial systolic blood pressure or the pulse rate rose to a level 20% or higher compared with the pre-induction levels, or if the respiratory rate rose above a rate of 20 breaths per minute. The inspired concentration of halothane was reduced or switched off if the arterial systolic blood pressure or the pulse rate fell to a level 20% or lower compared with the pre-induction levels, or if the respiratory rate fell to a rate lower than 10 breaths per minute.

Observations Made

The following observations were made in all patients in the induction studies.

Quality of Induction and Maintenance of Anaesthesia

The quality of anaesthesia during the induction and maintenance of anaesthesia was observed. Of particular interest during the induction period was the presence or absence of pain on injection or muscle movement. Patients were not specifically asked about the presence of pain during injection, but only whether their hand and arm remained comfortable. If a patient complained of pain or discomfort they were asked to describe the sensation more fully. Muscle movement was classified as severe (generalised muscle spasm), moderate (contraction of a group of muscles), or mild (slight twitching of one or more limbs).

The ease of transition from the induction of anaesthesia to the maintenance of anaesthesia was noted. In particular, the response of the patients to the insertion of the cystoscope, the cervix being dilated, or the skin being incised (as appropriate) was observed.

The presence or absence of cutaneous flushing, peripheral vasodilatation, angioneurotic oedema, or other manifestations of histamine release, such as bronchospasm, were looked for and their occurrence noted.

Cardiovascular System

The arterial systolic and diastolic blood pressures and the pulse rate were measured immediately before induction and one minute afterwards, before the introduction of halothane. Further measurements were made during and after the operations at times which are described in detail in the specific studies. In Studies One to Four the pulse rate was counted by palpation of the radial pulse. In the later induction studies (Five and Six) a continuous E.C.G. and heart rate monitor (Diascope D.S. 521, Simonsen and Weel, Denmark) was used to provide a continuous display of the E.C.G. throughout the induction and maintenance of anaesthesia. The arterial systolic and diastolic blood pressures were measured using an oscillotonometer in Studies One to Five. A Dinamap 845 (Criticon Inc.) was used to measure systolic and diastolic arterial blood pressures and pulse rate in Study Six.

Respiratory System

The presence or absence of respiratory upsets such as cough, hiccough, bronchospasm, or laryngospasm were noted. Apnoea was defined as the absence of respiration and its duration was timed. Manual assistance of ventilation was carried out, if required, after the elapse of 60 seconds. Apnoea lasting 60 seconds or longer was defined as being prolonged.

Recovery

Once surgery had ended, the nitrous oxide and halothane were switched off and the patients breathed 100% oxygen. This point was taken to be the end of anaesthesia and the start of the recovery period. The time was recorded. The patients were then taken down from the lithotomy position when this was necessary and transferred by trolley to the recovery area. Transfer of the patients was complete within 1 - 2 minutes. A nurse was allocated to supervise the recovery of each patient until they had fully recovered consciousness. All patients in Studies Five and Six breathed air enriched with 4.1 min.⁻¹ of oxygen via a Hudson mask until they were about to be sent back to the ward.

All patients in Studies One to Five were asked to open their eyes, raise their head on command and move their left thumb at thirty second intervals after the end of anaesthesia by the anaesthetist. The time when the patient could achieve all three of these objectives was taken to be the time of early recovery and was recorded. Patients undergoing cystoscopy remained lying

on their trolley until they could stand unaided. The time taken to achieve this was recorded in Study Two by the attendant nurse and was taken to be the time to achieve late recovery. Patients in Studies Five and Six were returned to the ward after the anaesthetist had seen them and had judged them to be fit to do so.

All patients in Studies One to Four were seen by the anaesthetist before they were allowed to leave the hospital. Patients remaining in hospital overnight (Studies Five and Six) were visited several hours after their operation and revisited 24 hours after operation by the anaesthetist. The patients were asked about the presence or absence of nausea, vomiting or headache, and their opinion of the anaesthetic they had received. In particular, the presence of pain on injection or other unpleasant sensation was asked about. During this visit, the injection site was inspected for signs of venous damage. Redness and tenderness over the injection site was defined as phlebitis. The presence of hardness alone was defined as thrombosis and the combination of both was defined as thrombophlebitis.

Methodology for the Infusion Studies

Groups of Patients Studied

Studies Seven, Eight, Nine (infusion of etomidate and fentanyl) and Eleven (infusion of propofol) were carried out on in-patients undergoing a range of common surgical and major gynaecological procedures. A range of procedures was chosen so that the advantages and disadvantages of such techniques when used in routine clinical practice could be assessed. Study Ten (effect of etomidate on hepatic and renal function) was carried out in

patients undergoing simple abdominal hysterectomy. Study Twelve (longer infusion of propofol) was undertaken in patients undergoing peripheral vascular or surgery for the correction of Dupuytren's contracture of the hand.

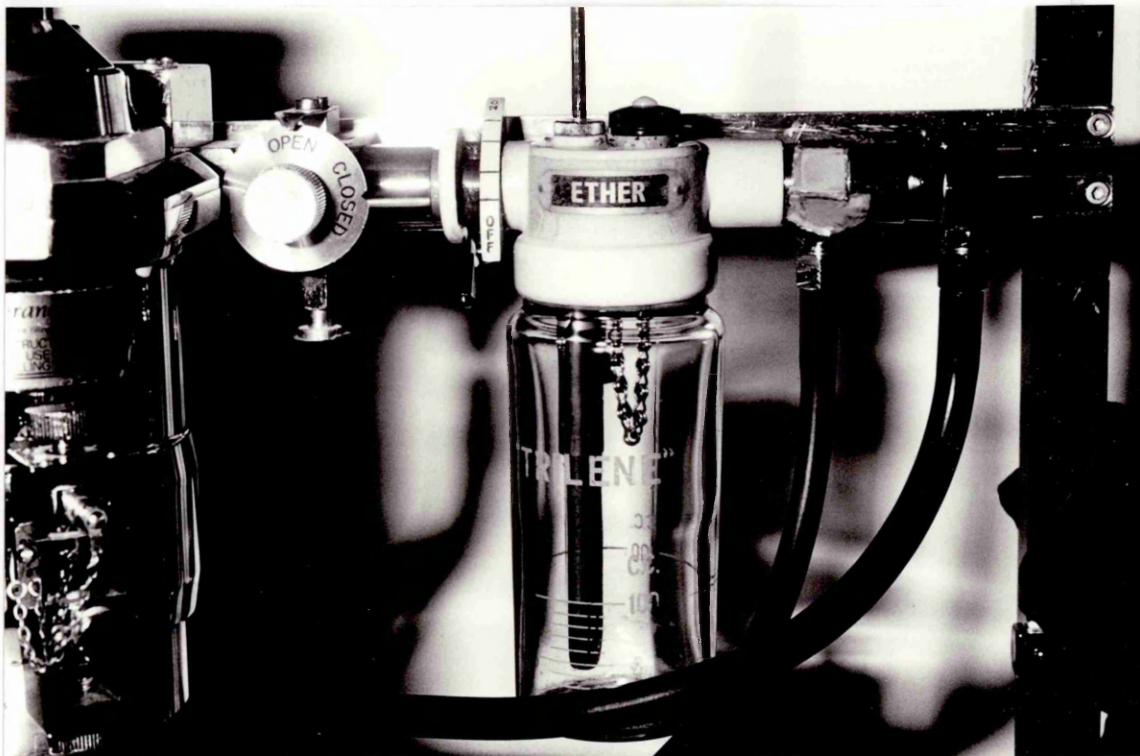
Allocation of Patients to Groups within Each Study

In Studies Eight and Nine, patients were not randomly allocated to control or infusion groups. A deliberate attempt was made to reduce the number of possible confounding variables by matching patients in the infusion and control groups for age, weight, sex and operation undergone. In all the studies the operations were carried out whenever possible, by the same surgeons. In Study Ten, patients were randomly allocated to one of the three groups using a code derived from a random number table similar to that used to allocate patients in the induction studies. In Study Twelve, patients were randomly allocated to one of two groups according to a code supplied by I.C.I. Plc.

Administration of Oxygen and Air

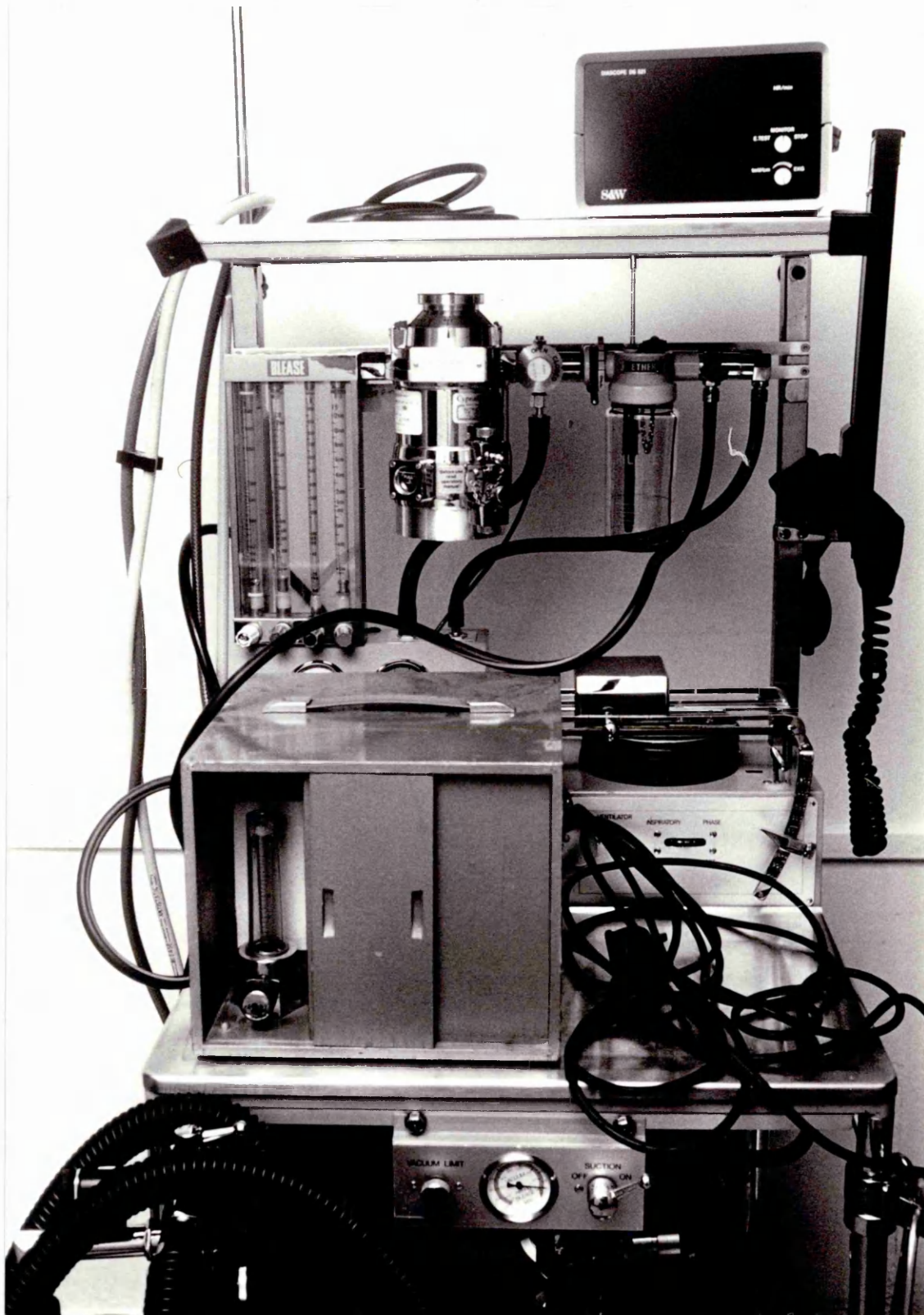
To allow the administration of an oxygen/air mixture using the available anaesthetic equipment, a Barnett air compressor was connected by a T piece to the back bar of a standard Northwick Park anaesthetic machine, as shown in Figure One. By this means an infinitely variable oxygen/air mixture could be administered to patients either breathing spontaneously or being ventilated without further modification of the anaesthetic equipment. An overall view of the equipment used is shown in Figure Two. The

FIGURE ONE



INSERTION OF THE T PIECE FROM THE AIR COMPRESSOR
INTO THE BACK BAR OF THE ANAESTHETIC MACHINE.

FIGURE TWO



GENERAL VIEW OF THE ANAESTHETIC EQUIPMENT
INCLUDING THE AIR COMPRESSOR.

flows of oxygen and air were adjusted to provide a concentration of 40% oxygen in the inspiratory limb of the breathing circuit throughout these studies. This concentration was periodically checked during the studies using a mass spectrometer (Medishield Multi-gas Monitor M.S.2).

Preparation of the Infusion Solutions

Because of the concern about the amount of propylene glycol solvent which would have to be infused with the etomidate, a specially concentrated solution of etomidate (125 mg. of etomidate dissolved in 1 ml. of absolute alcohol, Janssen Pharmaceutical) was used. This was diluted with normal saline to provide a 2.5 mg.ml.^{-1} solution of etomidate. In Studies Seven, Eight and in one group of Study Ten, a combined solution of 2.5 mg.ml.^{-1} etomidate and 7 mcg.ml.^{-1} of fentanyl was prepared by removing 16 ml. of fluid from a 100 ml. bag of normal saline (Viaflex, Travenol). This volume of fluid was replaced by 2 ml. (250 mg.) of concentrated etomidate and 14 ml. (700 mcg.) of fentanyl. In Study Nine and in another group in Study Ten, when fentanyl was infused separately, etomidate was diluted to a 2.5 mg.ml.^{-1} solution by removing 2 ml. of fluid from a 100 ml. bag of normal saline and adding 2 mls. of concentrated etomidate solution.

When infused separately, fentanyl was diluted to a 30 mcg.ml.^{-1} solution by the addition of 20 cc. of normal saline to 30 ccs. (1500 mcg) of fentanyl which had been drawn up in a 50 cc. syringe (Plastipak, Becton Dickinson). The formulation of propofol used for infusion in Studies Eleven and Twelve has

already been described on page 38 and was identical to that used in the induction study. This was drawn up undiluted in a 50 cc. syringe.

Administration of the Infusion Solutions

The combined etomidate and fentanyl solutions used in Studies Seven, Eight and Ten and the etomidate solutions used in Studies Nine and Ten were administered via a Treonic D.C.2 rotary pump. A special administration set (A 27, Avon Medical) designed for use with this rotary pump was used. This administration set has a portion of soft plastic which is intermittently compressed by the roller, thus injecting small frequent boluses of fluid.

Fentanyl was infused separately in Studies 9 - 12 from a 50 cc. syringe attached to a 100 cm. manometer line (Portex) using a Treonic I.P.3 volumetric syringe pump to drive the syringe. Propofol was infused in Studies Eleven and Twelve from a 50 cc. syringe connected to a 100 cm. manometer line using an Injectomat Syringe Pump (Dylade Medical, Runcorn, Cheshire) which is also a volumetric pump. The precise means of connecting the infusion sets to the intravenous cannulae varied in different studies and are described in detail in each study.

Calibration of the Infusion Pumps

The Treonic D.C.2 rotary pump is essentially a drop counter, As drop size, and therefore the volume of fluid infused, may be altered by the surface tension of the solution, the pump was

calibrated before each study. Solutions of normal saline (the control solution), etomidate in normal saline and a mixture of etomidate and fentanyl in normal saline, in the volumes and concentration which were to be used clinically, were prepared. The infusion sets and the infusion pump were set up as if in clinical use. The pump was set to deliver fluid at different drop rates and for different lengths of time so that the total volume delivered should have been 10 mls. The volumes were measured in a dry test tube calibrated to 0.1 ml. Each combination of drop rate and time was repeated twenty five times. The results are shown in Table One. The mean volume of the control solution (saline) delivered was 10.0 ± 0.03 ml. For etomidate in saline the mean volume delivered was 9.0 ± 0.03 ml. and for etomidate, fentanyl and saline the mean volume delivered was 8.5 ± 0.03 ml. These results are highly significantly different from each other ($p < 0.001$). The amounts of etomidate and fentanyl quoted in the chapters describing the infusion studies have been corrected to take account of these calibration results.

The Treonic I.P.3 and Injectomat Syringe Pumps are volumetric pumps. Similar calibration studies to those described for the Treonic D.C.2 pump showed that using 50 cc. syringes and 100 cm. manometer lines, both pumps were accurate to $\pm 2\%$ when infusing either fentanyl or propofol over the rates of infusion used in these studies.

Anaesthetic Technique for the Infusion Groups

All patients received intramuscular premedication sixty minutes before operation. All patients over sixty years of age received

TABLE ONE

CALIBRATION OF THE TREONIC INFUSION PUMP

| DURATION OF INFUSION (MINS.) | DROPS MIN. ⁻¹ | VOLUME INFUSED \pm S.E.M. | | |
|---------------------------------|--------------------------|-----------------------------|----------------|----------------------|
| | | CONTROL | ETOMIDATE | ETOMIDATE & FENTANYL |
| 2.5 | 60 | 10.1 ± 0.11 | 9.1 ± 0.08 | 8.4 ± 0.04 |
| 7.5 | 20 | 10.0 ± 0.15 | 8.9 ± 0.09 | 8.6 ± 0.12 |
| 15 | 10 | 10.0 ± 0.09 | 8.9 ± 0.05 | 8.5 ± 0.06 |
| 25 | 6 | 10.0 ± 0.06 | 9.1 ± 0.04 | 8.5 ± 0.08 |
| 50 | 3 | 10.0 ± 0.13 | 9.1 ± 0.08 | 8.5 ± 0.12 |

morphine 10mg. and atropine 0.6 mg. Male patients under sixty years of age received omnopon 20 mg. and hyoscine 0.4 mg. and female patients under sixty years of age received omnopon 15 mg. and hyoscine 0.3 mg. Patients were brought to the anaesthetic room 10 - 20 minutes before the induction of anaesthesia. A continuous E.C.G. and heart rate monitor (Diascope D.S. 521, Simonsen and Weel, Denmark) and a blood pressure cuff were attached. At this time, the patient's agreement to take part in any study was finally confirmed.

Immediately before the induction of anaesthesia, venous access was established via a vein in the dorsum of the non-dominant hand under local analgesia, through which all injections and infusions of hypnotics and analgesics were administered. Local analgesia for the venepuncture was provided by the subcutaneous injection of 1 ml. of 1% lignocaine without adrenaline over the proposed puncture site. Induction began with the injection of $1.3 \text{ mcg. kg.}^{-1}$ of fentanyl intravenously. After the elapse of 1 - 2 minutes, the hypnotic appropriate to that particular study was injected or infused. Once the eyelash reflex had disappeared, intubation of the trachea, if required, was facilitated with 100 mg. of succinylcholine except in Studies Eleven and Twelve, when a dose of 1 mg.kg.^{-1} of succinylcholine was used. The position of the endotracheal tube was confirmed by observation of the movement of the patient's chest wall and by auscultation of their chest and abdomen. The infusion of the hypnotic under study was commenced immediately thereafter. All patients breathed 100% oxygen during the induction of anaesthesia. If apnoea occurred in patients who were to breathe spontaneously, manual ventilation was carried out until spontaneous respiration returned.

The induction of anaesthesia was judged to be satisfactory

when the patient was lying still with all cardiovascular parameters within 20% of their pre-induction values and either breathing adequately with a quiet, unobstructed respiratory pattern, or being adequately ventilated after a satisfactory intubation, and an absent eye-lash reflex.

Once the induction of anaesthesia had been satisfactorily completed, the patients were moved from the anaesthetic room and transferred to the operating theatre. At this point the patients had to be disconnected from the anaesthetic equipment for a period of 30 - 60 seconds. The Treonic D.C.2 infusion pump was connected to an electrical socket in the operating theatre by an extension cable, and the Injectomat Syringe Pump was both battery and electrically powered. This meant that neither the infusion of etomidate nor of propofol was interrupted during transfer of the patients.

The patients were then connected to the modified anaesthetic machine and the correct functioning of the monitors and the infusion pumps was rechecked. At this point, the infusion of analgesia was commenced (unless it had been combined with the etomidate). The initial infusion rates of the hypnotics and analgesics were three to four times the estimated maintenance infusion rates. The aim was to gradually reduce these rates during surgery unless the protocol for a particular study required a fixed rate of infusion.

If the systolic arterial blood pressure and the pulse rate remained within a range of 20% above and below the pre-operative values and the respiratory rate remained between 10 - 20 breaths per minute (in spontaneously breathing patients), then the rate of

infusion of etomidate and fentanyl or fentanyl alone was gradually reduced throughout the operation to as low a rate as possible.

If the systolic arterial pressure and the pulse rate rose above the upper limit, or if the patient began to sweat or to lachrymate then the rate of infusion of etomidate and fentanyl or fentanyl alone (depending on the protocol) was increased until these variables had returned to within the desired range. Other indications for increasing the rate of infusion in spontaneously breathing patients were a respiratory rate greater than 20 breaths per minute, or if the patient began to move during surgery. If increasing the infusion rate did not produce an adequate response, then 33% oxygen in nitrous oxide was substituted for the inspired oxygen/air mixture, halothane was added and the total intravenous anaesthetic technique was abandoned. Other measures which were thought to be clinically necessary could be carried out at the discretion of the anaesthetist in charge of the case.

If the systolic arterial pressure, pulse rate or respiratory rate fell below the lower limit, the rate of infusion of etomidate and fentanyl or fentanyl alone (depending on the protocol) was decreased until an adequate response was obtained. If decreasing the rate of infusion did not produce an adequate response then the protocol could be broken and other measures be taken at the discretion of the anaesthetist in charge of the case.

When mechanical ventilation was required, the ventilator was adjusted to produce an expired tidal volume of $8 - 9 \text{ ml.kg.}^{-1}$.

This was checked by a Wright's respirometer inserted into the expiratory limb of the ventilatory circuit. The minute volume flow was adjusted to produce a respiratory rate of 12 - 15 breaths per minute. Neuromuscular blockade was continued in Studies 7 - 10 with tubocurarine 0.5 mg.kg.^{-1} administered intravenously. This was administered after the return of diaphragmatic movement had been observed and confirmed by movement of the reservoir bag of the anesthetic machine. Further increments of tubocurarine 0.25 mg.kg.^{-1} were given in response to muscle movement during surgery. In Studies Eleven and Twelve, bolus doses of atracurium or vecuronium were administered intravenously as required to provide neuromuscular blockade. In Study Eleven an initial dose of 400 mcg.kg.^{-1} of atracurium was given with further increments of 200 mcg.kg.^{-1} given in response to patient movement or tightening of the abdominal muscles during surgery. In Study Twelve bolus increments of atracurium 190 mcg.kg.^{-1} or vecuronium 45 mcg.kg.^{-1} were administered when there was a palpable response to the second stimulus of a "train of four" series of supramaximal stimuli delivered to the ulnar nerve in the forearm delivered from a Myotest Mark 2 peripheral nerve stimulator.

Anaesthetic Technique for the Control Groups

Anaesthesia for the control groups in Studies Eight, Nine and Ten was kept as similar to that of the infusion groups as possible. The important differences were that for all patients in the control groups anaesthesia was induced with thiopentone 5 mg.kg.^{-1} and maintained by the inhalation of 33% oxygen in nitrous oxide. This was supplemented with halothane in the spontaneously breathing

groups, or morphine 0.7 mg.kg.^{-1} in the ventilated groups. The inspired concentration of halothane varied from 0.5 - 2% and was altered using the same criteria as described for the infusion groups. Halothane 0.5% was administered to the ventilated patients if increases in systolic arterial blood pressure or pulse rate occurred which were greater than 20% above the pre-induction levels, or if sweating or lachrymation was observed.

Observations Made

Quality of Induction and Maintenance of Anaesthesia

Observations were made of the presence or absence of pain on injection or infusion and muscle movement. Patients were not specifically asked about the presence of pain during injection, but only whether the hand and arm were comfortable. The extent of muscle movement was classified as described for the induction studies on page 46 . The quality of the maintenance of anaesthesia, particularly in response to surgical incision and the ease of maintenance of anaesthesia was noted.

The presence or absence of cutaneous flushing, peripheral vasodilatation, angioneurotic oedema, or other manifestations of histamine release, such as bronchospasm, were looked for and their occurrence noted.

Cardiovascular System

The E.C.G. was continuously monitored from before induction

until the end of anaesthesia, using a Diascope D.S. 521. Measurements of arterial systolic and diastolic blood pressures were made immediately before induction, one minute after induction, and at various intervals as described in each study until anaesthesia and surgery were satisfactorily established. Thereafter, measurements were made at five minute intervals until the end of surgery, unless more frequent measurements were clinically required. In the etomidate studies, arterial systolic and diastolic blood pressures were measured using an oscillotonometer and the pulse rate was measured by palpation. In the propofol studies, a Dinamap 845 (Criticon Inc.) was used to measure the arterial systolic and diastolic blood pressures and the heart rate.

Respiratory System

Every five to ten minutes, measurements of the respiratory rate were made visually over a two minute period in all the spontaneously breathing patients. Severe respiratory depression was defined as a respiratory rate of less than six breaths per minute. In these circumstances, ventilation was manually assisted and the infusion rate reduced until adequate spontaneous respiration was re-established. Complications such as cough, hiccough, laryngospasm and bronchospasm were looked for and their occurrence noted.

In all the etomidate infusion studies which involved patients being allowed to breathe spontaneously, arterial blood samples, using a heparinised syringe connected to a 23 S.W.G. needle, were taken from the radial artery at the wrist of the non-dominant arm of

twenty suitable patients in both infusion and control groups for the measurement of arterial carbon dioxide tension. Samples were not taken from any patient if Allen's test suggested that the collateral circulation was inadequate. The control sample was taken under local analgesia, after the patient had been in the anaesthetic room for 10 minutes and after the attachment of any monitoring equipment, but before the insertion of an intravenous cannula. Local analgesia for the arterial puncture was provided by the subcutaneous injection of 1 ml. of 1% lignocaine without adrenaline over the proposed puncture site. A further sample was taken once a steady state of anaesthesia had been achieved for at least 20 minutes. The third sample was taken under local analgesia in the recovery area, 15 minutes after the end of anaesthesia. Samples were not taken from any patient during anaesthesia or during the recovery period if a steady respiratory state was not achieved during anaesthesia. If a complete set of results was not obtained from any patient the patient was withdrawn from this part of the study and the next suitable patient was substituted.

Recovery

The hypnotic agents (infused or inhaled) were switched off when wound closure was complete. This point was taken to be the end of the operation and the start of the recovery period. The time was noted. In the ventilated patients, residual neuromuscular blockade was antagonised with neostigmine 2.5 mg. (combined with atropine 1.2 mg.). The patients were extubated once adequate spontaneous respiration had been re-established.

The patients were then transferred to a trolley and returned to the recovery area. Transfer of all patients was completed within two minutes. Their recovery was supervised by a nurse whose sole responsibility was the care of that patient. All patients breathed air enriched with 4.1 min^{-1} of oxygen via a Hudson mask throughout their stay in the recovery area. At thirty second intervals after the end of anaesthesia, patients were asked by the anaesthetist to open their eyes, raise their head on command and move their left thumb. The time when the patients could achieve these three objectives was taken to be the time of early recovery and was recorded. In the propofol infusion studies, patients were also asked their name and address. Patients remained in the recovery area until they had fully recovered consciousness for at least fifteen minutes. They were then reassessed by the anaesthetist who decided whether they should return to the ward, or remain for a longer period of time in the recovery area.

Patients were visited in the ward by the anaesthetist several hours after their operation and revisited 24 - 48 hours after operation. As in the induction studies, the patients were asked about the presence or absence of pain on injection, nausea, vomiting or headache, and their opinion of the anaesthetic they had received. Particular attention was paid to trying to determine whether any episodes of awareness had occurred during anaesthesia. This was done by asking specific questions as to what patients remembered from leaving the ward until their post-operative visit by the anaesthetist. Patients were also asked whether they had had any dreams or other memories associated with this period. During this visit, the infusion site was inspected for signs of venous damage.

The extent of venous damage was classified as described on page 48

Analysis of Data

One of the major statistical problems of the infusion studies was how to quantify the changes in infusion rates and cardiovascular parameters. This was done by calculating the coefficient of variation. The coefficient of variation is defined as the standard deviation of a series of numbers divided by their mean, expressed as a percentage. In the infusion studies, changes in infusion rates and cardiovascular parameters occurring during the course of an individual anaesthetic were quantified by calculating the appropriate coefficient of variation for each parameter. The variation of the infusion rates and the cardiovascular parameters for each group was estimated by calculating from the values obtained from each patient, the mean coefficient of variation and the standard error of the mean for each variable.

Statistical Analysis

Data such as patient's age and weight, arterial systolic and diastolic blood pressures, pulse rate, arterial carbon dioxide tension, infusion rates and duration of action of neuromuscular blocking agents were regarded as being normally distributed. If three or more groups were being compared, then the one-way F test was used; otherwise Student's t test, either paired or unpaired as appropriate, was used.

The time to recovery, urea and electrolytes and liver function

test results were regarded as being non parametric in distribution. For paired data the Wilcoxon matched pairs signed-ranks test was used, if unpaired, the Mann-Whitney U test.

The incidence of pain on injection, apnoea and muscle movement were regarded as binomial data. The Chi squared test with the Yates correction for small numbers was used with the appropriate degrees of freedom.

The following statistical text books were consulted.

Haber A. and Runyon R.P. (1973) General Statistics. Second Edition. Pub. Addison Welsey Company.

Siegel S. (1956) Nonparametric Statistics for the Behavioural Sciences. Pub. McGraw-Hill.

CHAPTER THREE

STUDIES ONE AND TWO

ETOMIDATE IN PHOSPHATE BUFFER FOR
THE INDUCTION OF ANAESTHESIA

Study One

Effects of Different Rates of Injection

Introduction

Etomidate was first supplied for intravenous administration in a vial of 20 mgs. of etomidate powder with a separate vial of sodium phosphate 27 mgs. and sodium biphosphate 44 mgs. also in powder form, as diluent. This second vial was made up to a 20 ml. solution with sterile water and added to the vial of etomidate to produce a 1 mg.kg.^{-1} solution of etomidate. The solution was used as soon as possible after preparation. The aim of this study was to assess the effects of different rates of injection of etomidate in this solvent on the quality of induction and maintenance of anaesthesia.

Patients and Methods

Ninety eligible patients were randomly allocated to one of three groups. Each group was to be induced with etomidate 0.3 mg.kg.^{-1} administered over 15, 30 or 60 seconds. Due to a misunderstanding of the protocol, two patients received etomidate over 60 seconds instead of the intended 30 seconds. Premedication and preparation of patients for the induction of anaesthesia was carried out as described in Chapter Two. After the measurement of pulse rate and arterial systolic and diastolic blood pressures, etomidate was injected via a 21 S.W.G. needle inserted into a vein in the antecubital fossa or in the dorsum of the non-dominant hand. Maintenance

anaesthesia and recovery of the patients, as well as observations of the quality of induction and maintenance of anaesthesia were carried out as described in Chapter Two. Measurements of arterial systolic and diastolic blood pressures and pulse rate were made immediately before the induction of anaesthesia, at one minute after induction, before the administration of halothane and again five minutes after induction. In this study, the times to early and late recovery were not recorded.

Results

Composition of the Groups

Patient details are shown in Table Two. The groups were very similar in weight and sex distribution. These differences were not statistically significant. However the group receiving etomidate over 30 seconds was younger than the other two groups. This difference was statistically significant ($p < 0.02$).

Quality of Induction and Maintenance

Anaesthesia was successfully induced in all patients. Induction was rapid and without apnoea, laryngospasm or bronchospasm. There was no evidence of histamine release in any patient. Maintenance of anaesthesia was satisfactory in all patients in each group. The complications found are discussed later in the chapter.

TABLE TWO

DETAILS OF PATIENTS

IN THE FIRST ETOMIDATE INDUCTION STUDY

| INJECTION RATE | NO. OF PATIENTS | MEAN AGE (YRS) \pm S.E.M. | MEAN WT. (Kg.) \pm S.E.M. |
|-------------------|--------------------|-----------------------------------|-----------------------------------|
| 60 SECS. | 21M 32 11F | 60 ± 3 | 61 ± 1 |
| 30 SECS. | 17M 28 11F | $52 \pm 3 *$ | 60 ± 1 |
| 15 SECS. | 23M 30 7F | 61 ± 2 | 59 ± 1 |

* SIGNIFICANTLY ($P < 0.02$) LOWER THAN THE OTHER TWO GROUPS.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates in each group with their associated standard errors of the mean are shown in Figure Three. There were no statistically significant changes in arterial systolic and diastolic pressures in any group during the induction of anaesthesia. There was a rise in pulse rate in all three groups during the induction of anaesthesia, but this was not clinically or statistically significant.

Study Two

Comparison with Propanidid

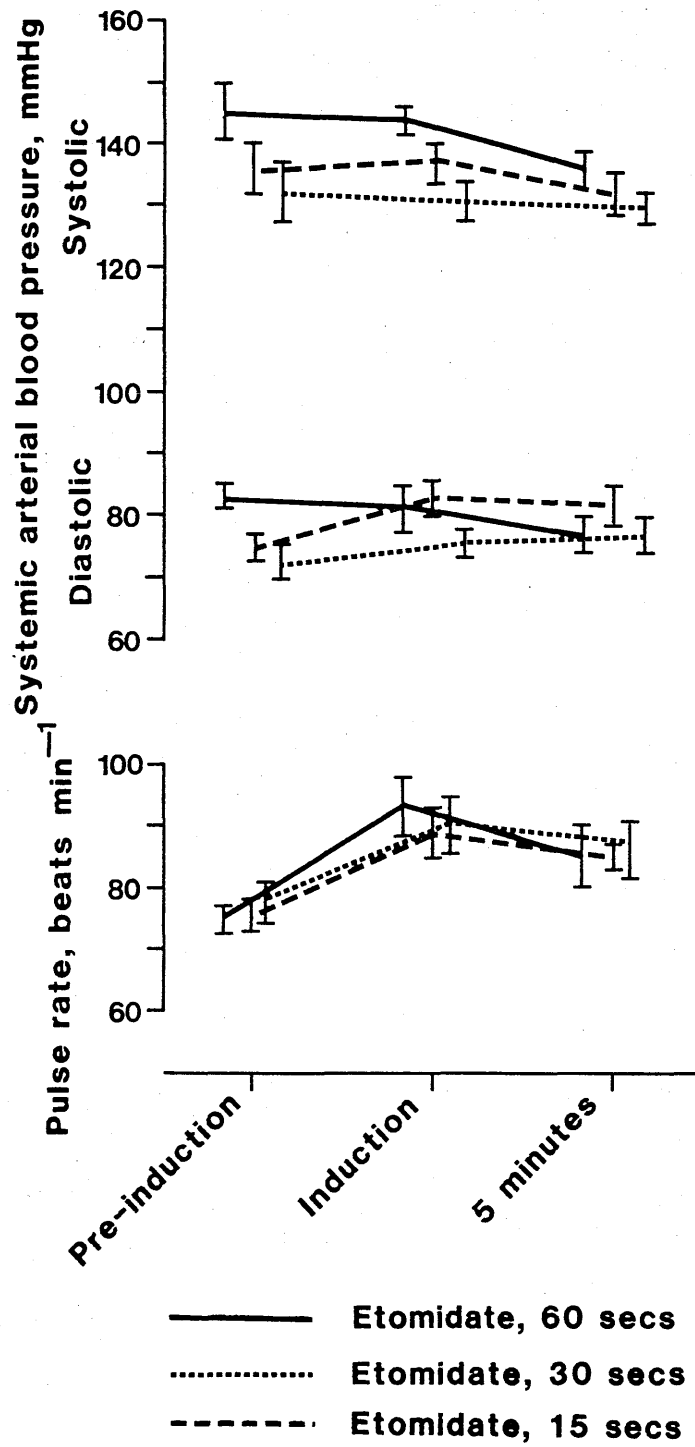
The aim of this study was to compare the cardiovascular effects and quality of anaesthesia of different rates of injection of etomidate with a fixed rate of injection of propanidid.

Patients and Methods

One hundred and sixty eligible patients were randomly allocated to one of four groups. The preparation of etomidate used was the same as that used in the first study. One group was to receive propanidid 7 mg.kg.^{-1} over 30 seconds. The other groups were to receive etomidate 0.3 mg.kg.^{-1} administered over 15 or 30 seconds. In one group who was to receive etomidate 0.3 mg.kg.^{-1} over 15 seconds, atropine premedication was omitted.

Fig. 3

**CARDIOVASCULAR CHANGES DURING THE FIRST
ETOMIDATE INDUCTION STUDY**



Due to a misunderstanding of the protocol by one of the investigators, nine patients received fentanyl immediately before induction and were eliminated from the trial. Another nine patients were allocated to the wrong group. The final number of patients in each group is shown in Table Three.

Premedication and preparation of patients for the induction of anaesthesia was carried out as described in Chapter Two. After the measurement of pulse rate and arterial systolic and diastolic blood pressures, etomidate or propanidid was injected via a 21 S.W.G. needle inserted into a vein in the antecubital fossa or in the dorsum of the non-dominant hand. Maintenance of anaesthesia and recovery of the patients as well as observations of the quality of induction and maintenance of anaesthesia and the time to early and late recovery were carried out as described in Chapter Two. Measurements of arterial systolic and diastolic blood pressures and pulse rate were made immediately before the induction of anaesthesia, at one minute after induction, before the administration of halothane, again on insertion of the cystoscope and also at the end of anaesthesia. The time to achieve early recovery was noted and further measurements of arterial systolic and diastolic blood pressures and pulse rate were made at that time. The time to late recovery was also noted.

Results

Composition of the Groups

The composition of the groups is shown in Table Three.

TABLE THREE

DETAILS OF PATIENTS

IN THE SECOND ETOMIDATE INDUCTION STUDY

| | NO. OF PATIENTS | MEAN AGE (YRS.) \pm S.E.M. | MEAN WT. (Kg.) \pm S.E.M. |
|--|--------------------|------------------------------------|-----------------------------------|
| PROPANIDID | 24M 40 16F | 58 ± 2 | 64 ± 22 |
| ETOMIDATE (30 SECS.) | 20M 30 10F | 55 ± 2 | 62 ± 2 |
| ETOMIDATE (15 SECS.) | 22M 32 10F | 61 ± 3 | 63 ± 2 |
| ETOMIDATE (15 SECS.) (ATROPINE OMITTED) | 37M 49 12F | 53 ± 2 | 69 ± 2 |

There were no statistically significant differences between the groups.

Quality of Induction and Maintenance

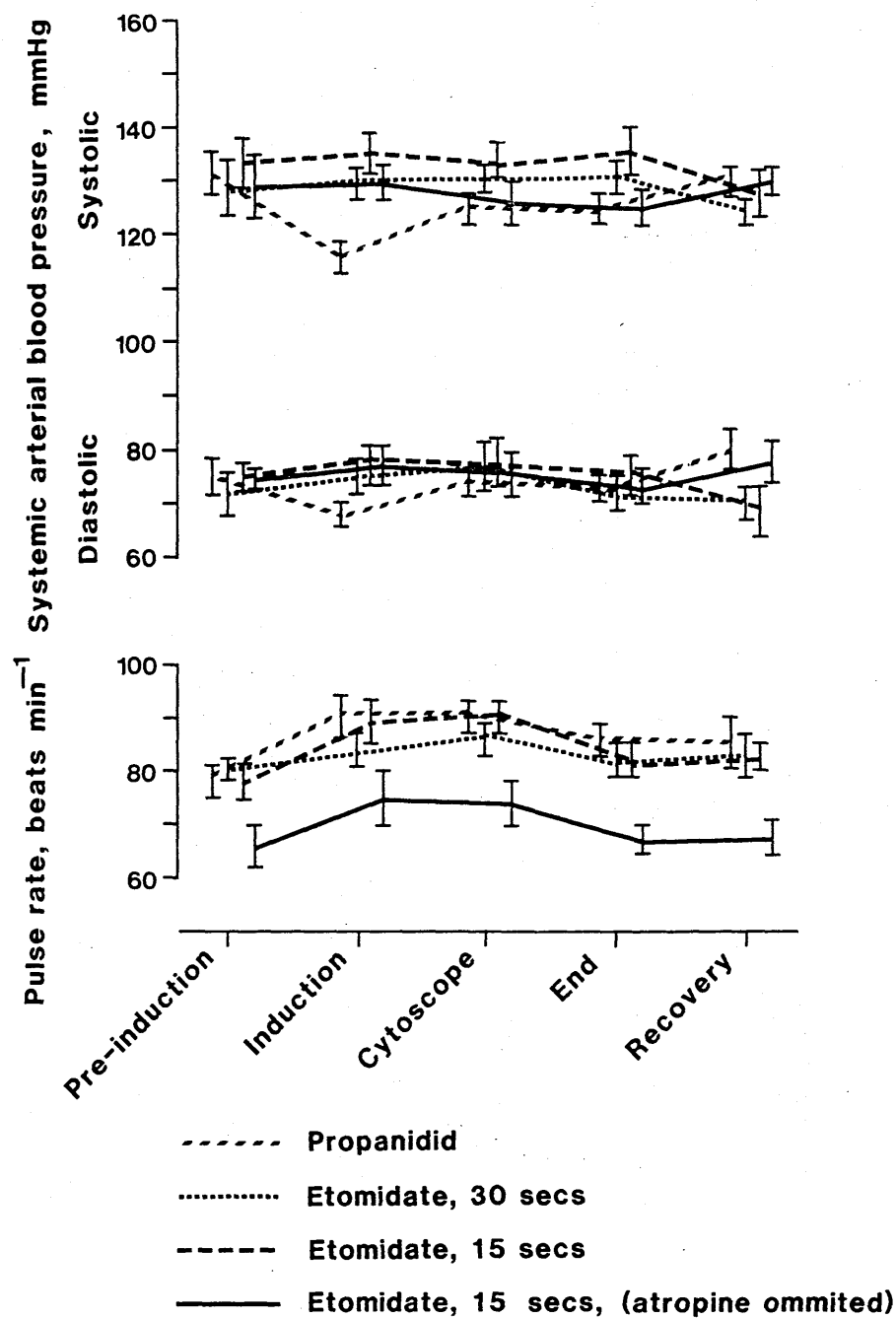
Anaesthesia was successfully induced in all patients. The induction of anaesthesia was rapid without apnoea, laryngospasm or bronchospasm. There was no evidence of histamine release in any patient. Maintenance of anaesthesia was satisfactory in all patients in each group. The complications found are discussed later in the chapter.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates in each group with their associated standard errors of the mean are shown in Figure Four. There were no statistically significant changes in the arterial systolic and diastolic pressures or pulse rates in the two groups receiving etomidate and atropine. There was a statistically significant fall ($p < 0.01$) in the mean arterial systolic pressure during induction in the control group receiving propanidid which rapidly returned to control levels. There were no statistically significant changes in the mean arterial diastolic pressures and pulse rates in any group during the induction and maintenance of anaesthesia. The omission of atropine resulted in a lower mean pulse rate in that etomidate group prior to induction. The mean pulse rate rose after induction but remained lower than the corresponding group which had received atropine premedication. These differences

Fig. 4

CARDIOVASCULAR CHANGES DURING THE SECOND ETOMIDATE INDUCTION STUDY



were all statistically significant ($p < 0.01$).

Recovery

The times of early and late recovery were comparable in the four groups as shown in Table Four. There were no statistically significant differences between the groups, except that the mean time to respond was faster when etomidate (with atropine premedication) was administered over 15 seconds compared with its administration over 30 seconds. This difference was statistically significant ($p < 0.05$). The overall incidence of nausea and vomiting was 7.5%. Two patients had hallucinations, another, a known epileptic, suffered an epileptiform fit.

Complications

The incidence and severity of pain on injection and muscle movement of all patients receiving etomidate and atropine were pooled and compared with those found with propanidid. The results are shown in Table Five. The overall incidence of pain with etomidate (24%) was greater than that of propanidid (0%). This difference was statistically significant ($p < 0.0001$). Increasing the rate of injection to 15 seconds from 30 or 60 seconds reduced the incidence of pain from 32% to 13%. This difference was statistically significant ($p < 0.025$). The pain could be extreme and three patients refused to be re-anaesthetized with etomidate as a result of their experience.

The overall incidence of muscle movement with etomidate (29%)

TABLE FOUR

DETAILS OF RECOVERY TIMES
IN THE SECOND ETOMIDATE INDUCTION STUDY

| | PATIENT NOS. | MEAN TIME TO RESPOND (MINS.) \pm S.E.M. | MEAN TIME TO STAND (MINS.) \pm S.E.M. |
|--|-----------------|---|---|
| PROPANIDID | 40 | 7 \pm 0.1 | 17 \pm 0.6 |
| ETOMIDATE (30 SECS.) | 30 | 8 \pm 0.8 | 19 \pm 1.2 |
| ETOMIDATE (15 SECS.) | 32 | 6 \pm 0.4 | 18 \pm 1.0 |
| ETOMIDATE (15 SECS.) (ATROPINE OMITTED) | 49 | 6 \pm 0.6 | 18 \pm 1.0 |

TABLE FIVE

OVERALL INCIDENCE OF PAIN ON INJECTION AND MUSCLE MOVEMENT
IN PATIENTS PREMEDICATED WITH ATROPINE
IN THE FIRST TWO ETOMIDATE INDUCTION STUDIES.

| | NO. OF PATIENTS | PAIN ON INJECTION | MUSCLE MOVEMENT | | | |
|-------------------------|--------------------|----------------------|-----------------|----------|------|-------|
| | | | SEVERE | MODERATE | MILD | TOTAL |
| PROPANIDID | 40 | 0* | 0 | 0 | 0 | 0* |
| ETOMIDATE (60 SECS.) | 32 | 10 | 2 | 4 | 4 | 10 |
| ETOMIDATE (30 SECS.) | 58 | 19 | 4 | 14 | 7 | 25 |
| ETOMIDATE (15 SECS.) | 62 | 8 | 1 | 3 | 5 | 9 |

* SIGNIFICANTLY LOWER ($P < 0.0001$)

was greater than that found with propanidid (0%). This difference was statistically significant ($p < 0.0001$). Injection of etomidate 0.3 mg.kg.^{-1} over 15 seconds reduced the incidence of involuntary muscle movements to 14.5%, compared with the 43% found when injected over 30 seconds. This difference was statistically significant ($p < 0.01$). This incidence just failed to reach statistical significance at the 0.05 level when compared with the 31% found when etomidate was injected over 60 seconds. The movements soon ceased when halothane was introduced and the time to insertion of the cystoscope was not unduly prolonged. Patients did not complain of muscular pain post-operatively.

Conclusions

The conclusions of these initial studies were that etomidate was a short acting induction agent with excellent cardiorespiratory stability. There was a high incidence of pain on injection and involuntary muscle movements, reduced by the rapid injection of etomidate. The muscle movements were easily controlled by the administration of halothane.

Compared with propanidid, etomidate produced a greater degree of cardiovascular stability; but the incidence of pain on injection and muscle movement was significantly higher.

CHAPTER FOUR

STUDIES THREE AND FOUR

ETOMIDATE IN POLYETHYLENE AND PROPYLENE GLYCOL
FOR THE INDUCTION OF ANAESTHESIA

Introduction

From the results of the studies described in Chapter Three and from other similar studies (Morgan, Lumley and Whitwam, 1975; Holdcroft et al, 1976), it became clear that the incidence of side effects with the original formulation of etomidate was unacceptably high. In an attempt to reduce these side-effects, the solvent was changed to first polyethylene glycol (P.E.G. 1000) and then to propylene glycol. Table Six shows how changing the solvent considerably raised the osmolality and pH of the etomidate preparations. The values for methohexitone and diazepam are shown for comparison. Changes in solvent can affect the potency of a drug due to changes in drug solubility or to synergistic or antagonistic effects of the solvent itself (Walsh, 1984). Studies Three and Four assessed the effects of these changes of formulation of etomidate on cardiovascular stability and the incidence of side-effects.

Study Three

Polyethylene Glycol as Solvent

Polyethylene glycol 1000 is a macrogol with an average molecular weight of 1000 (Walsh, 1984). The aim of this study was to evaluate the effects of two different rates of injection of etomidate dissolved in polyethylene glycol 1000 on potency, cardiovascular stability, and quality of anaesthesia.

TABLE SIX

EFFECT OF DIFFERENT SOLVENTS ON pH
AND OSMOLALITY OF ETOMIDATE

| | pH AT 37°C | OSMOLALITY (mOs/Kg.) |
|---------------------------------|------------|-------------------------|
| ETOMIDATE (PHOSPHATE) | 3.46 | 254 |
| ETOMIDATE (PEG) | 5.21 | 550 |
| ETOMIDATE (PROPYLENE GLYCOL) | 8.10 | 4640 |
| METHOHEXITONE | 9.94 | 78 |
| DIAZEPAM (VALIUM) INJECTION | 6.38 | 7800 |

Patients and Methods

Fifty eligible patients were randomly allocated to one of two groups. Each group was to receive etomidate 0.3 mg.kg.^{-1} with polyethylene glycol as solvent, administered over 15 or 30 seconds. Premedication and preparation of patients for the induction of anaesthesia was carried out as described in Chapter Two. After the measurement of pulse rate and arterial systolic and diastolic blood pressures, etomidate was injected via a 21 S.W.G. needle inserted into a vein in the dorsum of the non-dominant hand. Maintenance of anaesthesia and recovery of the patients as well as observations of the quality of induction and maintenance of anaesthesia and the time to early recovery were carried out as described in Chapter Two. Measurements of arterial systolic and diastolic blood pressures and pulse rate were made immediately before induction and at one minute after induction, before the administration of halothane. The time to achieve early recovery was noted and a further measurement of arterial systolic and diastolic blood pressures and pulse rate was made at that time.

Results

Composition of the Groups

The composition of the two groups is shown in Table Seven. There were no statistically significant differences between the groups.

TABLE SEVEN

DETAILS OF PATIENTS, INCIDENCE OF PAIN ON INJECTION
MUSCLE MOVEMENT, AND TIME TO RECOVERY
IN THE THIRD ETOMIDATE INDUCTION STUDY.

| | NO. OF PATIENTS | MEAN AGE (YRS.) + S.E.M. | MEAN WT. (Kg.) + S.E.M. | PAIN ON INJECTION | MUSCLE MOVEMENT | TIME TO RECOVERY (MINS.) + S.E.M. |
|-------------------------|-------------------------|--------------------------------|-------------------------------|----------------------|--------------------|---|
| ETOMIDATE (15 SECS.) | 23M 25 2F | 59 + 2 | 63 + 2 | 1 | 4 | 4.5 + 2 |
| ETOMIDATE (30 SECS.) | 17M 25 8F | 57 + 3 | 66 + 3 | 1 | 5 | 5.0 + 1 |

Quality of Induction and Maintenance

Anaesthesia was successfully induced in all patients. No respiratory upsets, apnoea, or hiccough were observed. The incidence of pain on injection and myoclonia are shown in Table Seven. The incidence of pain on injection and muscle movement was very similar in both groups. This difference did not reach statistical significance.

Maintenance of anaesthesia was satisfactory in all patients in each group. No patient in either group showed any evidence of histamine release.

Cardiovascular Changes

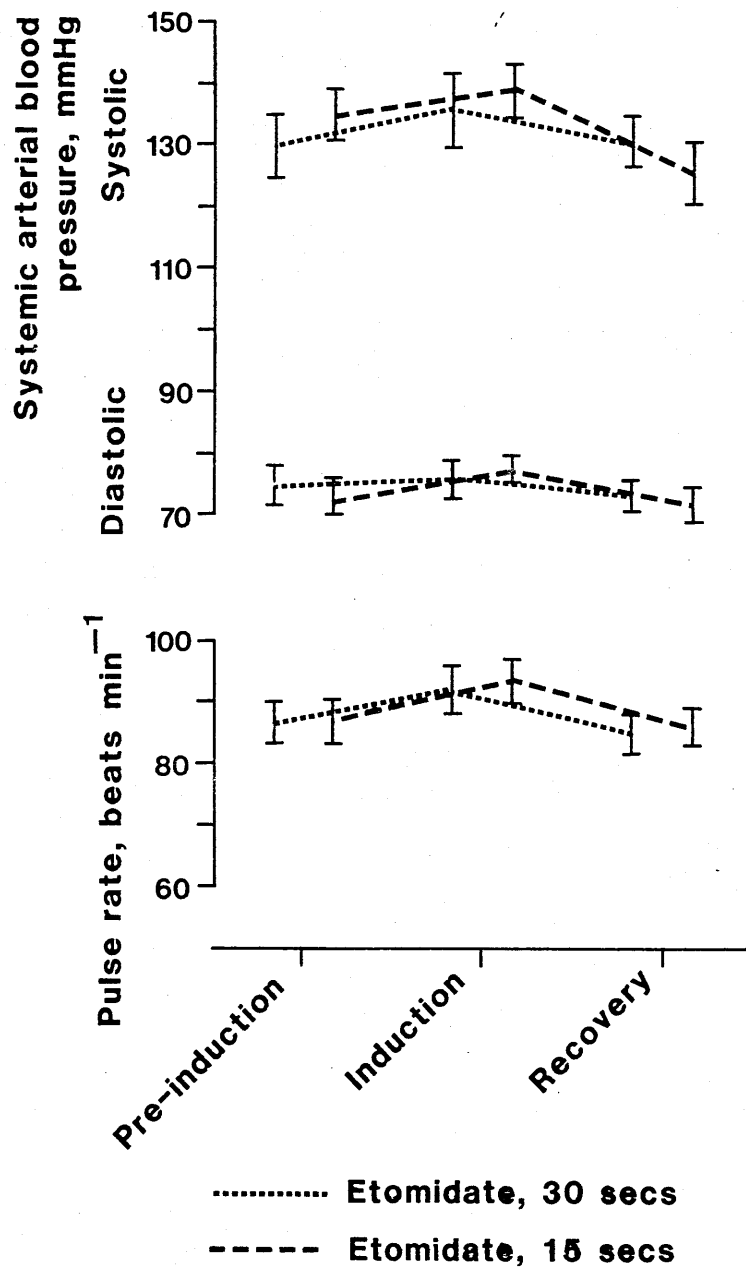
The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates in each group with their associated standard errors of the mean are shown in Figure Five. There were no statistically significant changes in the mean arterial systolic or diastolic pressures or pulse rates during the induction of anaesthesia or recovery in either group.

Recovery

Early recovery time when the etomidate was injected over 15 seconds was slightly faster when compared with its injection over 30 seconds (Table Seven). This difference was not statistically significant. Two patients in each group felt nauseated or were

Fig. 5

**CARDIOVASCULAR CHANGES DURING THE THIRD
ETOMIDATE INDUCTION STUDY**



physically sick. All patients were willing to receive etomidate again.

Potential Toxicity of Polyethylene Glycol

Polyethylene glycol is a term for a wide range of glycols with molecular weights ranging from 200 to 6000. One of their pharmaceutical uses is to solubilise poorly water soluble drugs (Walsh, 1984). For many years these substances have been regarded as being biologically unreactive (Wilson and Thomas, 1984). It was in this climate of opinion about the safety of the polyethylene glycols that the study of etomidate in polyethylene glycol 1000 was carried out in 1975 - 1976.

The pharmacological properties of the polyethylene glycols have recently been reviewed (Wilson and Thomas, 1984) and the assumptions about the biological inactivity of the glycols were questioned. The conclusions of this review were that the polyethylene glycols do show physicochemical and biochemical interactions with cells, and concluded that such interactions could be important.

These interactions could explain some isolated examples of possible toxicity associated with the use of polyethylene glycol 300. In a study of thirty two patients in which a preparation of nitrofurantoin and polyethylene glycol 300 had been infused for eight hours a day for five days, seven patients developed renal failure and two died. The histological appearances of the kidneys of the dead patients showed changes similar to those found with

ethylene glycol poisoning (McCabe, Jackson and Griebble, 1959). This suggested that the renal damage may have been linked with the use of polyethylene glycol 300.

As the low molecular weight polyethylene glycols are mainly excreted unchanged, and the remainder are not metabolised to ethylene glycol, the findings described by McCabe, Jackson and Griebble (1959) were attributed to deterioration of the polyethylene glycol 300 before infusion (Walsh, 1984). In retrospect, the review by Wilson and Thomas (1984) would suggest that this was perhaps an over simplistic explanation.

In view of the uncertainty surrounding the use of polyethylene glycols, it was decided to review all the patients who had participated in the study. Because of the length of time which had elapsed from the date of the study (ten years) and the apparent rapidity and severity of the reactions described by McCabe, Jackson and Griebble (1959), it was felt that a review of the case-sheets of the patients concerned should be carried out first. If there was any evidence that any patient had suffered from cardiac or renal illness within a six month period of the administration of the preparation then these patients would be reviewed in person, if at all possible. No such evidence was found.

If these doubts about the safety of polyethylene glycol had been appreciated at the time of the study, it would not have been carried out. The study is included in this thesis because it represented a logical step in the investigation of etomidate. At

the same time it is felt that these doubts about the safety of the study should be recorded.

Study Four

Propylene Glycol as Solvent

After the previous study had been completed, the solvent used for etomidate was changed to propylene glycol. This was done for pharmaceutical reasons as propylene glycol can be manufactured on a large scale more easily than polyethylene glycol.

This study compared the cardiovascular effects and complications of etomidate in propylene glycol with those of methohexitone. Methohexitone was chosen as the control hypnotic in preference to propanidid because of concern about the safety of Cremophor E.L. (Watkins et al, 1976).

Patients and Methods

A hundred eligible patients were randomly allocated to one of two groups. Each group was to receive either etomidate 0.3 mg.kg.^{-1} with propylene glycol as solvent or methohexitone 1.5 mg.kg.^{-1} . Both drugs were to be injected over 30 seconds. Premedication and preparation of patients for the induction of anaesthesia was carried out as described in Chapter Two. After the measurement of pulse rate and arterial systolic and diastolic blood pressures, etomidate or methohexitone was injected via a 21 S.W.G. needle inserted into a

vein in the dorsum of the non-dominant hand. Maintenance of anaesthesia and recovery of the patients as well as observations of the quality of induction, maintenance and time to early recovery were carried out as described in Chapter Two. Measurements of arterial systolic and diastolic blood pressures and pulse rate were made immediately before induction and at one minute after induction, before the administration of halothane. The time to achieve early recovery was noted and further measurements of arterial systolic and diastolic blood pressures and pulse rate were made at that time.

Results

Composition of the Groups

Patient details are shown in Table Eight. Age, weight and sex distributions were similar in both groups and were not statistically significantly different.

Quality of Induction and Maintenance

Anaesthesia was successfully induced in all patients. No respiratory upsets, apnoea, or hiccough were observed. The incidence of myoclonic movements and pain on injection are shown in Table Eight. There was no statistically significant difference in the incidence of pain between the two groups but the incidence of myoclonia was greater in the etomidate group. This difference was statistically significant ($p < 0.01$).

TABLE EIGHT

DETAILS OF PATIENTS, INCIDENCE OF PAIN ON INJECTION,
MUSCLE MOVEMENT, AND TIME TO RECOVERY
IN THE FOURTH ETOMIDATE INDUCTION STUDY.

| | NO. OF PATIENTS | MEAN AGE (YRS.) + S.E.M. | MEAN WT. (KG.) + S.E.M. | PAIN ON INJECTION | MUSCLE MOVEMENT | TIME TO RECOVERY (MINS.) + S.E.M. |
|---------------|--------------------|--------------------------------|-------------------------------|----------------------|--------------------|---|
| ETOMIDATE | 50 33M 17F | 57 + 3 | 67 + 2 | 2 | 11 | 4.5 + 0.3 |
| METHOHEXITONE | 50 32M 18F | 56 + 3 | 63 + 1 | 3 | 0 | 4.0 + 0.3 |

Maintenance of anaesthesia was satisfactory in all patients in each group. No patient in either group showed any evidence of histamine release.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates in each group with their associated standard errors of the mean are shown in Figure Six. No statistically significant differences were found between the groups, both groups showing minimal changes in their mean systemic arterial systolic and diastolic arterial pressures and pulse rates during the induction of anaesthesia and during recovery.

Recovery

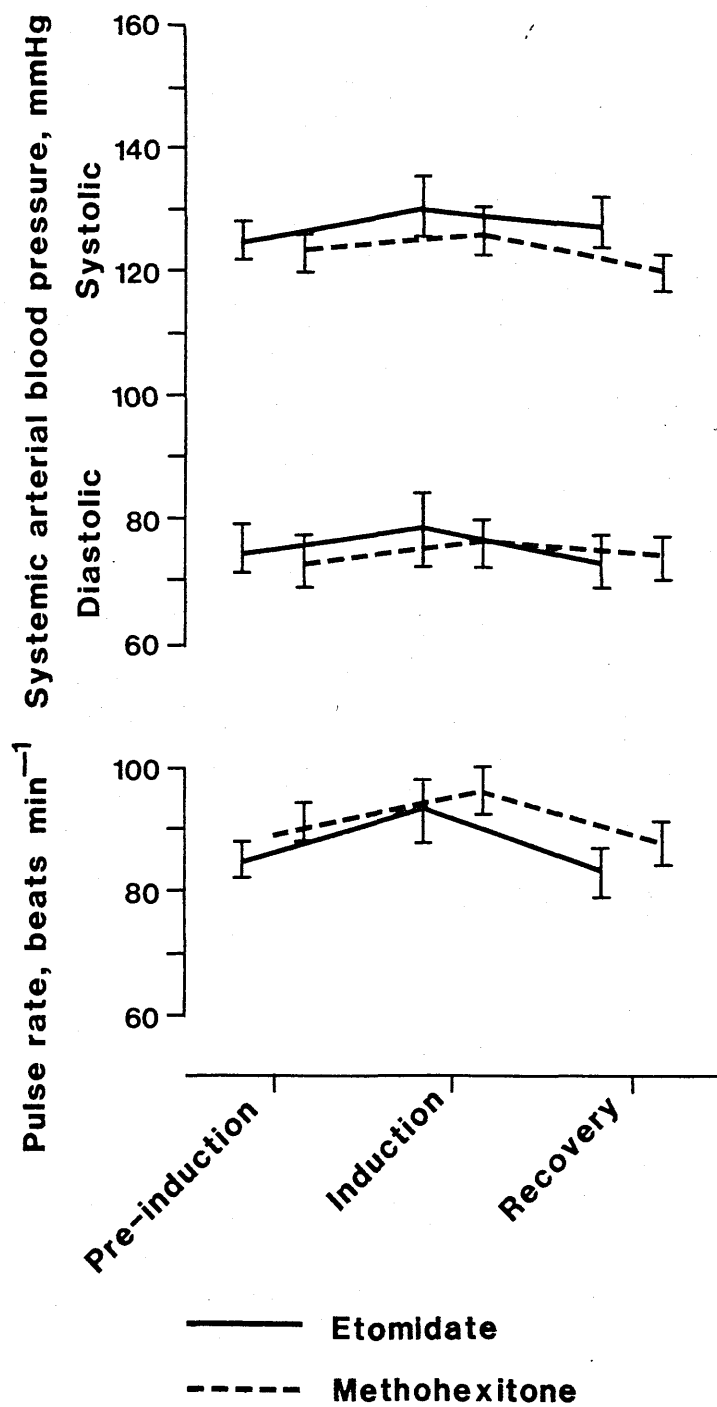
Early recovery from methohexitone was slightly faster compared with etomidate as shown in Table Eight. This difference was not statistically significant. Three patients in the etomidate group felt nauseated or were sick compared with two in the methohexitone group. All patients were willing to receive etomidate again.

Conclusions

The potency, short duration of action and the cardiovascular stability of etomidate remained unchanged despite changes of solvent. The incidence of pain on injection was greatly reduced compared with

Fig. 6

**CARDIOVASCULAR CHANGES DURING THE FOURTH
ETOMIDATE INDUCTION STUDY**



the incidence of pain in the groups receiving the original formulation of etomidate. In contrast, the incidence of myoclonic movements remained unchanged. In these two studies, no patient refused to be re-anaesthetised with etomidate as a result of their experience.

Etomidate formulated in propylene glycol was found to have a similar degree of cardiovascular and respiratory stability to that found with methohexitone. The incidence of pain on injection was similar with both drugs, but the incidence of muscle movement was much higher with etomidate.

CHAPTER FIVE

STUDY FIVE

ETOMIDATE AND FENTANYL
FOR THE INDUCTION OF ANAESTHESIA

Introduction

Chronologically this study was carried out after the etomidate infusion studies and was designed partly as a prelude to further infusion studies with etomidate. These proposed studies were abandoned after the effect of etomidate on adrenal function became known (Fellows et al, 1983). However, since the study investigated the effects of alfentanil on the induction characteristics of etomidate it is appropriate to describe it here, following the other etomidate induction studies.

Alfentanil is an intravenous narcotic closely related to fentanyl, but with a more rapid onset of action and recovery (Kay and Stephenson, 1980; Stanski and Hug, 1982; Sinclair and Cooper, 1983). The fifth etomidate induction study was carried out mainly to assess the effects of an intravenous bolus of alfentanil on the quality of induction of anaesthesia with etomidate.

Patients and Methods

Fifty women aged between 18 and 65 years old, who were to undergo minor gynaecological surgery, either dilatation and curettage, or early termination of pregnancy (of less than ten weeks duration) were randomly allocated to one of two groups. One group was to be induced with etomidate alone. The other group was to receive alfentanil prior to receiving etomidate.

Premedication and preparation of patients for anaesthesia were carried out as described in Chapter Two. In this study

continuous monitoring of the E.C.G. was carried out before and during the induction and maintenance of anaesthesia. After the measurement of pulse rate and arterial systolic and diastolic blood pressures, a 23 S.W.G. cannula (Abbott "Butterfly", No. 4871) was inserted into a vein in the dorsum of the non-dominant hand.

The control group received etomidate 0.3 mg.kg.^{-1} alone, injected over thirty seconds. Anaesthesia was maintained with 33% oxygen in nitrous oxide. After a minute, anaesthesia was supplemented with halothane 0.5 - 2%. The inspired concentration of halothane was altered according to clinical requirements as described in Chapter Two.

The alfentanil group received a bolus dose of 8 mcg.kg.^{-1} of alfentanil I.V. immediately before induction with etomidate 0.3 mg.kg.^{-1} administered over thirty seconds. Anaesthesia was maintained with 33% oxygen in nitrous oxide and supplemented with bolus increments of etomidate 6 mg. I.V. as required. All patients undergoing termination of pregnancy received 0.5 mg. of ergometrine intravenously when requested by the surgeon.

Observations of the quality of induction and maintenance of anaesthesia were carried out as described in Chapter Two.

Measurements of arterial systolic and diastolic blood pressures and pulse rate were made immediately before induction and at one, two and five minutes after induction. After being transferred to the recovery area, patients breathed air enriched with 4.1 min^{-1} of oxygen via a Hudson mask until recovery was complete. Their

recovery was supervised as described in Chapter Two. The time to early recovery was noted. Patients were seen again in the ward some hours after operation and again within the next 24 hours whenever this was possible.

Results

Composition of the Groups

Details of the patients and the duration of anaesthesia are shown in Table Nine. There were no statistically significant differences between the two groups.

Quality of Induction and Maintenance

Anaesthesia was induced successfully in both groups, without breath-holding, coughing or apnoea. The effect of alfentanil on the incidence of the side-effects of etomidate are shown in Table Nine. In particular, there was a statistically significant reduction ($p < 0.01$) in the incidence of pain on injection and myoclonic movements. However on questioning after anaesthesia, seven patients recalled having pain or being aware of venous sensation during injection of etomidate. Five had received alfentanil and two were in the control group.

Maintenance of anaesthesia was satisfactory in all patients in both groups. An average amount of $25 \text{ mcg.kg.}^{-1} \text{ min}^{-1}$ of etomidate was required to maintain anaesthesia in the patients in the alfentanil group.

TABLE NINE

DETAILS OF PATIENTS, INCIDENCE OF PAIN ON INJECTION,

MUSCLE MOVEMENT AND DURATION OF ANAESTHESIA

IN THE FIFTH ETOMIDATE INDUCTION STUDY.

| | NO. OF PATIENTS | AGE (YRS.) + S.E.M. | WT. (Kg.) + S.E.M. | PAIN ON INJECTION | MUSCLE MOVEMENT | DURATION (MINS.) + S.E.M. |
|------------|--------------------|------------------------|-----------------------|----------------------|--------------------|------------------------------|
| ALFENTANIL | 25 | 33 + 2 | 60 + 2 | 0 | 1 | 8 + 1 |
| HALOTHANE | 25 | 33 + 2 | 57 + 2 | 12 * | 20 * | 10 + 1 |

* SIGNIFICANTLY HIGHER ($P < 0.0001$)

No patient in either group showed any evidence of histamine release.

Cardiovascular Changes

The mean values of the measurements of the systemic arterial systolic and diastolic arterial pressures and pulse rates in each group with their associated standard errors of the mean are shown in Figure Seven. No statistically significant changes from the pre-operative values during the induction period were found in either group.

Recovery

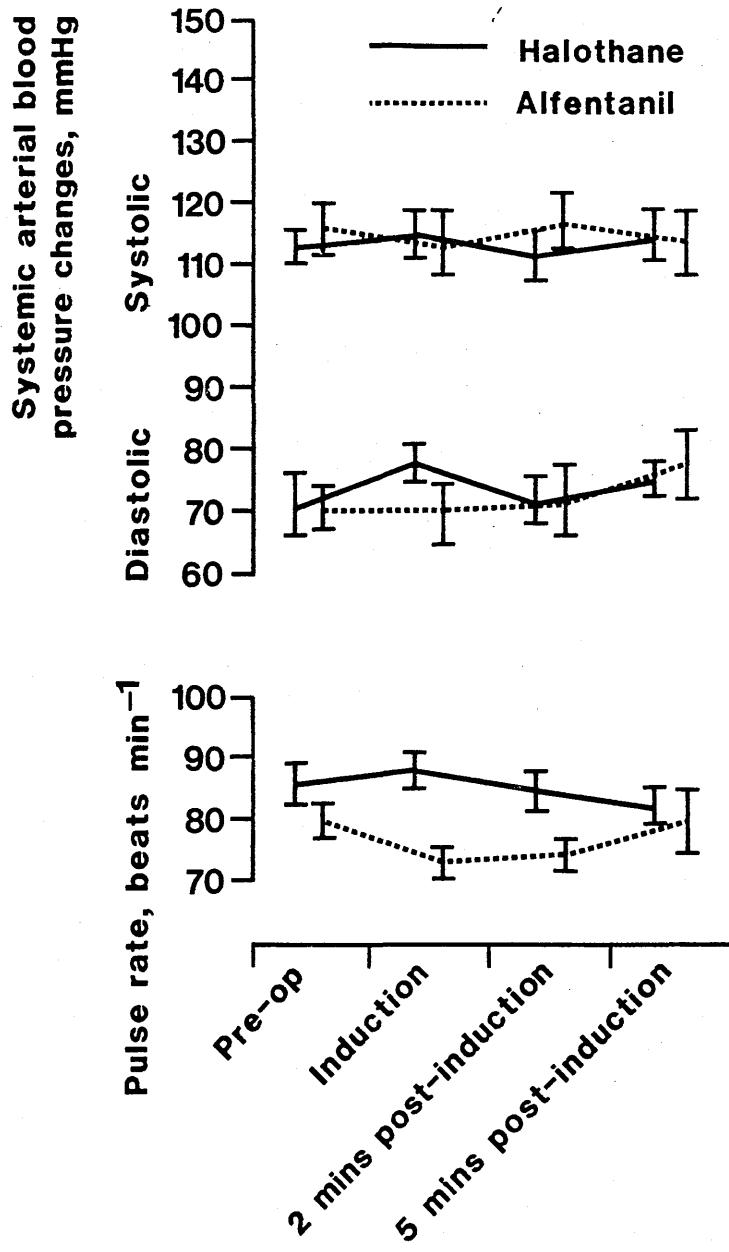
Early recovery was faster in the group receiving alfentanil with a mean time to recovery of 4 ± 0.5 minutes compared with the control mean time of 8 ± 0.7 minutes. This difference was statistically significant ($p < 0.01$). Two patients in the control group were nauseated, compared with four in the alfentanil group, one of whom was physically sick. This difference was not statistically significant.

Conclusions

The conclusions of this study were that the use of alfentanil greatly reduced the incidence of pain and myoclonic movement without reduction of cardiovascular stability or the speed of recovery.

Fig. 7

CARDIOVASCULAR CHANGES DURING THE FIFTH
ETOMIDATE INDUCTION STUDY



Although carried out on a very limited scale and with the addition of nitrous oxide, it appeared that the combination of etomidate and alfentanil was potentially suitable for further evaluation as a total intravenous anaesthetic technique.

CHAPTER SIX

STUDY SIX

PROPOFOL FOR THE INDUCTION OF ANAESTHESIA

Introduction

The aim of this study was to evaluate the effects of the injection of propofol into a small vein (dorsum of the hand), a large vein with a high blood flow (antecubital fossa) and pretreatment with intravenous lignocaine when injected into a small vein, on the quality of induction and maintenance of anaesthesia with an intravenous injection of propofol and to compare these effects with those of thiopentone.

Patients and Methods

One hundred and sixty eligible patients between the ages of 18 and 65 years, undergoing a variety of minor elective surgical and gynaecological procedures were randomly allocated to one of four groups. Details of the operations undergone in each group are shown in Table Ten.

Premedication and preparation of patients for anaesthesia were carried out as described in Chapter Two. In this study continuous monitoring of the E.C.G. was carried out before and during the induction and maintenance of anaesthesia. After the measurement of pulse rate and arterial systolic and diastolic blood pressures with a Dinamap 845 (Criticon Inc), a 23 S.W.G. cannula (Abbott "Butterfly". No. 4871) was inserted into a vein in the dorsum of the non-dominant hand in all groups, except in Group B where it was inserted into a vein in the antecubital fossa of the non-dominant arm. Patients in Group A received an induction dose of propofol alone via the dorsum of the hand. Patients in Group B received

TABLE TEN

OPERATIONS CARRIED OUT ON
EACH GROUP IN THE PROPOFOL
INDUCTION STUDY

| OPERATION | GROUP A | GROUP B | GROUP C | GROUP D |
|-------------------------------|---------|---------|---------|---------|
| DILATATION AND CURETTAGE | 18 | 17 | 18 | 19 |
| BREAST BIOPSY | 7 | 5 | 8 | 7 |
| REPAIR OF INGUINAL HERNIA | 3 | 3 | 2 | 3 |
| LIGATION OF VARICOSE VEINS | 2 | 3 | 4 | 3 |
| LAPAROSCOPY | 8 | 11 | 5 | 4 |
| HAEMORRHOIDECTOMY | 2 | 1 | 3 | 4 |
| | 40 | 40 | 40 | 40 |

propofol via the antecubital fossa. Patients in Group C received 10 mg. of lignocaine I.V. through the cannula followed sixty seconds later by the induction dose of propofol. The induction dose of propofol 2.5 mg.kg.^{-1} was administered over twenty seconds in all patients. Patients in Group D (the control group) received thiopentone 4.5 mg.kg.^{-1} also administered over twenty seconds.

After the induction of anaesthesia all patients breathed 33% oxygen in nitrous oxide for a period of two minutes without further inhalational or intravenous supplementation. Thereafter anaesthesia was supplemented with 0.5 - 2% halothane. The inspired concentration of halothane was altered according to clinical requirements as described in Chapter Two. Measurements of pulse rate and arterial systolic and diastolic blood pressures were made immediately before, and at one and two minutes after induction. Another measurement was made after surgery had commenced, five minutes after induction. Other observations of the quality of induction and maintenance of anaesthesia were made as described in Chapter Two. Of particular interest was the incidence of pain on injection, muscle movement and apnoea.

Immediately after surgery had been completed, patients were transferred to a trolley and moved to the recovery area where they were supervised as described in Chapter Two. There they breathed 40% oxygen via a Hudson mask until recovery was complete. Due to the differences in the types of operations and their duration, the time to recovery was not looked at in detail. All patients were visited in the ward some hours after operation and again

within the next 24 hours when this was possible.

Results

Composition of the Groups

The composition of the groups is shown in Table Eleven. There were no statistically significant differences between the groups.

Quality of Induction and Maintenance

Anaesthesia was successfully induced with propofol or thiopentone in all patients. There was no coughing or laryngospasm. The incidence of pain on injection is shown in Table Twelve. Propofol when injected via a vein in the dorsum of the hand led to a 37.5% incidence of pain. The reduction of pain to 17.5% by pre-treatment with lignocaine was not statistically significant. Use of a larger vein in the antecubital fossa (Group B) reduced the incidence to 2.5%. Compared to the incidence of pain when propofol was injected alone into a vein in the dorsum of the hand, this difference was statistically significant ($p < 0.001$). The incidence of pain during thiopentone injection (7.5%) was similar to that found when injecting propofol into a large vein. The incidence of pain during the injection of thiopentone was less than that found when propofol was administered alone via a vein in the dorsum of the hand. This difference was statistically significant ($p < 0.01$). Other sensations such as heat, cold and tingling at the site of injection

TABLE ELEVEN

DETAILS OF PATIENTS IN THE PROPOFOL INDUCTION STUDY.

| | SUBJECT NOS. | MEAN AGE (YRS.) \pm S.E.M. | MEAN WT. (Kg.) \pm S.E.M. |
|---------|-----------------|------------------------------------|-----------------------------------|
| GROUP A | 34F 40 6M | 35 ± 3 | 59 ± 2 |
| GROUP B | 35F 40 5M | 37 ± 4 | 60 ± 3 |
| GROUP C | 31F 40 9M | 35 ± 3 | 60 ± 2 |
| GROUP D | 39F 40 1M | 32 ± 3 | 62 ± 3 |

TABLE TWELVE

INCIDENCE OF PAIN ON INJECTION, MUSCLE MOVEMENT
AND APNOEA IN THE PROPOFOL INDUCTION STUDY.

| | NO. OF PATIENTS | PAIN ON INJECTION | OTHER SENSATION | MUSCLE MOVEMENT | INCIDENCE OF APNOEA | |
|---------|-----------------|-------------------|-----------------|-----------------|---------------------|-----------------------|
| | | | | | LESS THAN 60 SECS. | GREATER THAN 60 SECS. |
| GROUP A | 40 | 15 | 9 | 4 | 26 | 6 |
| GROUP B | 40 | 1 | 7 | 1 | 31 | 6 |
| GROUP C | 40 | 7 | 9 | 2 | 21 | 8 |
| GROUP D | 40 | 3 | 8 | 2 | 18 | 5 |

were similar in all groups as shown in Table Twelve. Six patients induced with propofol complained of tingling in the neck or face.

Six of the patients induced with propofol had spontaneous muscle movement of short duration compared with two in the thiopentone group. No other side-effects were noted.

Maintenance of anaesthesia was satisfactory in all patients.

Cardiovascular Changes

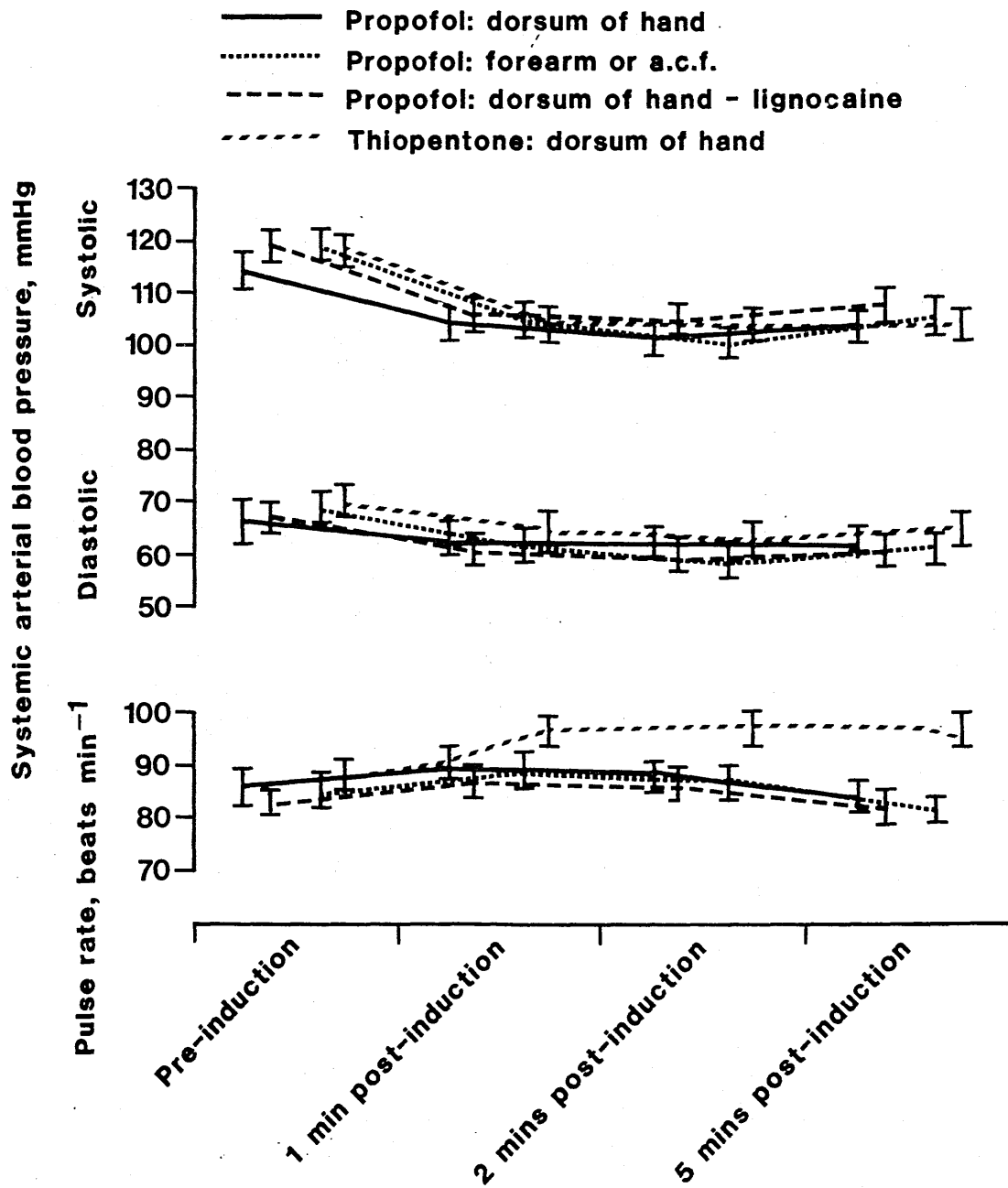
The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates in each group with their associated standard errors of the mean are shown in Figure Eight. The mean systolic and diastolic blood pressures and pulse rates before induction were similar in all four groups. After induction, all groups showed a small drop in their mean arterial systolic pressures. This drop was statistically significant in all the groups ($p < 0.01$). The thiopentone group showed a rise in the mean pulse rate at 1, 2 and 5 minutes compared with the propofol groups. This difference was statistically significant ($p < 0.01$). There were no statistically significant changes in the mean arterial diastolic blood pressures in any group.

Respiratory Changes

The incidence of apnoea is shown in Table Twelve. The

Fig. 8

CARDIOVASCULAR CHANGES DURING THE PROPOFOL INDUCTION STUDY



group induced with thiopentone showed a lower overall incidence of apnoea compared with the combined propofol groups. This difference was statistically significant ($p < 0.01$). At 60 seconds after induction, the incidence of apnoea in all groups was similar, ranging from 12 - 20%. All patients who remained apnoeic were ventilated manually until spontaneous respiration returned.

Recovery

Recovery was rapid in all patients, but this was not investigated in detail due to the variety of operations undergone by the patients. One patient felt nauseated for some hours, and another had a persistent cough. No patient in any group showed any evidence of histamine release. One patient who had received propofol via the antecubital fossa had evidence of thrombophlebitis at the injection site which disappeared within 48 hours. All patients were willing to receive propofol again.

Conclusions

Di-isopropyl phenol in the new emulsified formulation (propofol) was found to be an effective short acting hypnotic. A high incidence of pain on injection, particularly when injected via small veins in the dorsum of the hand, and apnoea on induction also occurred. There was a modest drop in arterial systolic and diastolic pressures in all groups.

CHAPTER SEVEN

STUDIES SEVEN, EIGHT AND NINE

THE INFUSION OF ETOMIDATE FOR THE MAINTENANCE OF
TOTAL INTRAVENOUS ANAESTHESIA

Introduction

Because of the cardiovascular and respiratory stability found during the induction studies, the potential of etomidate to maintain anaesthesia by continuous infusion was investigated. As etomidate possesses no analgesic properties, fentanyl was used to provide supplementary analgesia.

Preliminary Study

To find out whether the technique was feasible, and acceptable to both patients and staff, a preliminary dose finding study was carried out. Fifty patients undergoing a variety of minor surgical and gynaecological procedures gave informed consent for the administration of etomidate and fentanyl for the induction and maintenance of anaesthesia. Fentanyl 100 mcg. and etomidate 30 mg. in propylene glycol, were mixed in a 20 ml. syringe. A 23 S.W.G. cannula (Abbott, "Butterfly", No.4871) was inserted into a vein in the dorsum of the non-dominant hand, through which all injections were given. Patients were induced with etomidate 0.3 mg.kg.^{-1} in the propylene glycol formulation. Bolus increments of the etomidate and fentanyl mixture were injected as required to maintain anaesthesia. The results of this study suggested that an average amount of $20 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of etomidate and $0.056 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of fentanyl was adequate to maintain anaesthesia. However to provide adequate initial anaesthesia, it was found that an increased induction dose of 0.46 mg.kg.^{-1} of etomidate was necessary.

Aims of the Infusion Studies

The aims of the total intravenous anaesthesia studies were to improve the intermittent bolus technique and to investigate the safety, ease of use, quality of anaesthesia, side-effects and possible limitations of the technique and its use in anaesthetic practice.

Study Seven

The First Etomidate Infusion Study

The aim of this study was to assess the feasibility of replacing the intermittent bolus technique by a continuous infusion of a mixture of etomidate and fentanyl. In particular the effects of this technique on cardiovascular and respiratory stability and speed of recovery were investigated.

Patients and Methods

One hundred and six eligible patients took part in this study. Fifty one patients were to be ventilated and fifty five were to breathe spontaneously. The types of surgery carried out are shown in Table Thirteen. There were no control patients.

The anaesthetic machine and a combined infusion of etomidate and fentanyl were prepared and patients premedicated as described in Chapter Two. All patients were attached to an E.C.G. monitor and had an oscillotonometer cuff attached on arrival in the anaesthetic room. A 500 cc. bag of normal saline (Steriflex, Travenol) was connected via a standard fluid administration set (C2071 Travenol) and a three-way tap to an 18 S.W.G. cannula (Quik - Cath, Travenol) inserted into a vein in the dorsum of the non-dominant hand and allowed to flow at 20 - 30 drops per minute. If required, an arterial blood sample was taken under local anaesthesia as described in Chapter Two. The induction of anaesthesia

TABLE THIRTEEN

OPERATIONS CARRIED OUT ON EACH GROUP IN
THE FIRST ETOMIDATE INFUSION STUDY.

| VENTILATED CASES | NO. | SPONTANEOUSLY BREATHING CASES | NO. |
|---------------------|-----|----------------------------------|-----|
| UPPER ABDOMINAL | 9 | MASTECTOMY; BREAST BIOPSY | 15 |
| LOWER ABDOMINAL | 16 | INGUINAL HERNIA | 6 |
| MAJOR GYN. | 20 | HAEMORRHOIDECTOMY | 7 |
| PERIPHERAL VASCULAR | 6 | VARICOSE VEINS | 6 |
| | | MINOR GYN. | 10 |
| | | ENT | 6 |
| | | ORTHOPAEDIC | 5 |
| TOTAL | 51 | | 55 |

was carried out by the intravenous injection of fentanyl 1.3 mcg.kg.^{-1} followed 1 - 2 minutes later by etomidate 0.46 mg.kg.^{-1} . Both drugs were administered via the free port of the three-way tap. If endotracheal intubation was required, succinylcholine 100 mg. was given intravenously. Immediately after induction, anaesthesia was maintained with an infusion of etomidate and fentanyl attached to the free port of the three-way tap. The tap was set so that both infusions could run concurrently. All patients breathed 100% oxygen during the induction period.

Maintenance of anaesthesia was carried out as described in Chapter Two. Measurements of pulse rate and arterial systolic and diastolic blood pressures were made immediately before induction, after induction, at incision and at five minute intervals during surgery unless more frequent measurements were clinically indicated. Other observations of the quality of induction and maintenance of anaesthesia, including arterial blood gas measurements, were carried out as described in Chapter Two. Injections of other drugs such as tubocurarine, atropine and neostigmine were administered as required through the injection port of the fluid administration set.

Recovery from anaesthesia, during which a third arterial blood sample was taken, if required, under local analgesia and the post-operative visits were carried out as described in Chapter Two.

Results

Composition of the Groups

The composition and physical characteristics of the patients

are shown in Table Fourteen. Also shown is the mean duration of anaesthesia in the two groups.

Quality of Induction and Maintenance

Anaesthesia was successfully induced in most patients. Ten patients (9.4%) complained of pain on injection and two had to have thiopentone substituted to complete induction. Five patients complained of tingling in their hand and arm. The overall incidence of venous sensation was 14%. In the spontaneously breathing group, severe muscle movement was seen in six patients (11%) delaying the start of surgery and mild to moderate muscle movement in another eight. The overall incidence of muscle movement was 25%. Anaesthesia remained unsatisfactory in three patients due to continued muscle movement and supplementation with halothane was required to produce satisfactory anaesthesia. There was no evidence of histamine release in any of the patients anaesthetised in this study.

Infusion Rates

No significant differences were found in the infusion rates between male and female patients in either group. These rates were then combined. The mean amounts of etomidate infused in the ventilated and spontaneously breathing groups are shown in Figure Nine. For clarity, standard error of the mean (S.E.M.) values have been shown at 5 minute intervals. The infusion rates were statistically significantly different during three periods of time. The initial infusion rate from 0 - 10 minutes was significantly higher in the spontaneously breathing group ($p < 0.05$).

TABLE FOURTEEN

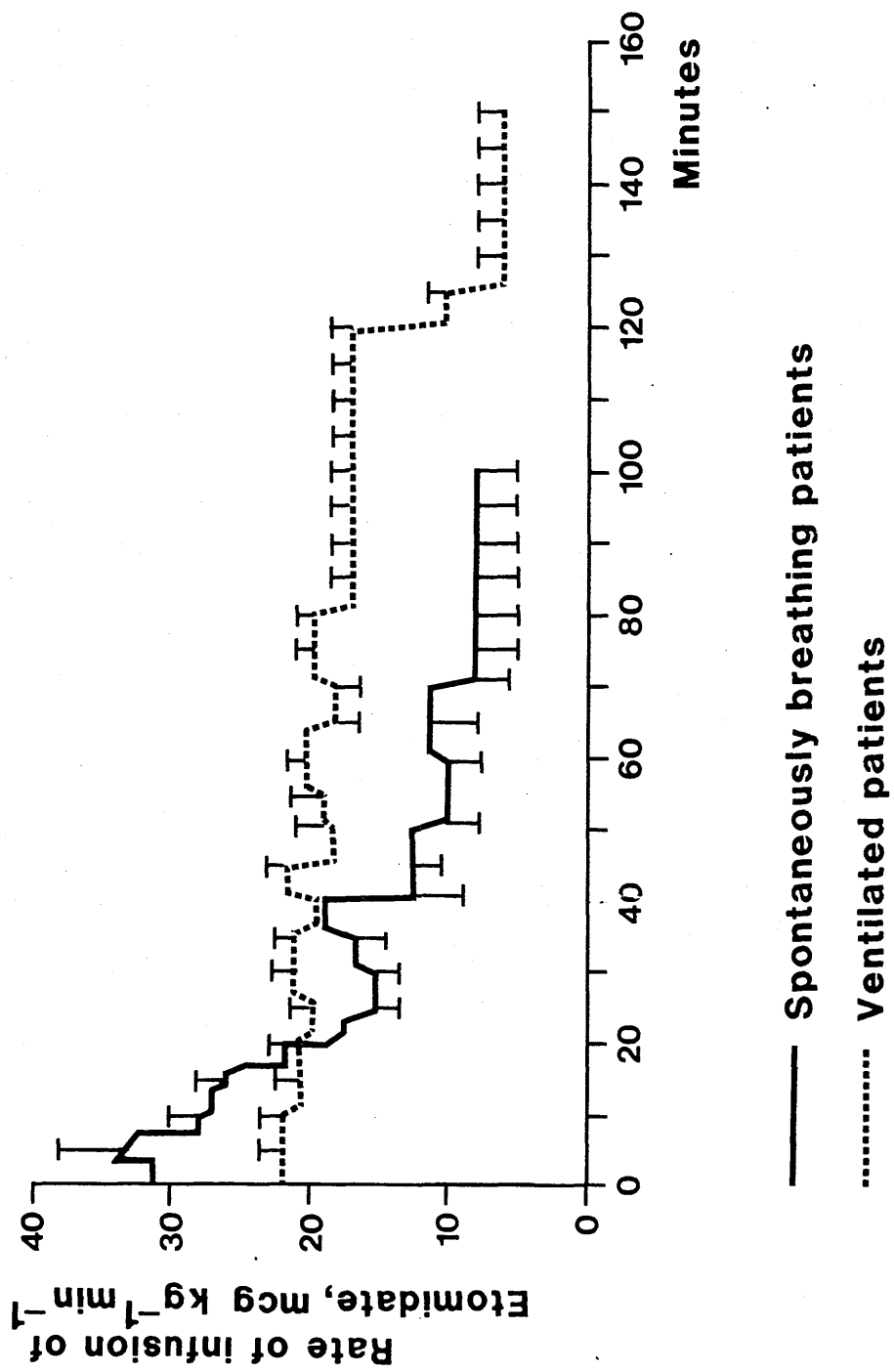
DETAILS OF PATIENTS AND DURATION OF ANAESTHESIA IN THE

FIRST ETOMIDATE INFUSION STUDY.

| RESP. MODE | NO. OF PATIENTS | MEAN AGE (YRS.) + S.E.M. | MEAN WT. (Kg.) + S.E.M. | DURATION (MINS.) + S.E.M. |
|------------|--------------------|--------------------------------|-------------------------------|---------------------------------|
| I.P.P.V. | 51 12M 39F | 62 ± 3 | 67 ± 4 | 80 ± 15 |
| SPT. V. | 55 22M 33F | 46 ± 4 | 60 ± 4 | 36 ± 5 |

Fig. 9

INFUSION RATES OF ETOMIDATE DURING THE FIRST ETOMIDATE INFUSION STUDY



In the other two periods from 25 - 31 minutes and from 41 minutes onwards, the mean infusion rate for the I.P.P.V. group was statistically significantly higher, the significance values ranging from $p < 0.05$ to $p < 0.01$. The overall mean infusion rate was $20.5 \pm 1.8 \text{ mcg.kg.}^{-1}\text{min.}^{-1}$ of etomidate and $0.057 \pm 0.0055 \text{ mcg.kg.}^{-1}\text{min.}^{-1}$ of fentanyl. The mean coefficient of variation of the infusion rate was $33 \pm 1.2\%$ for the ventilated group and $66 \pm 1.1\%$ for the spontaneously breathing group.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and pulse rates in each group with their associated standard errors of the mean are shown in Figure Ten. Both groups showed a statistically non-significant fall in the mean systolic and diastolic arterial pressures during the induction period. No statistically significant changes were seen in the mean pulse rates. Table Fifteen shows the variation in cardiovascular parameters during maintenance anaesthesia, expressed as the mean coefficient of variation.

Respiratory Changes

During surgery the levels of arterial carbon dioxide tension rose from a pre-induction mean value of $5.2 \pm 0.1 \text{ kPa.}$ to a mean value of $6.4 \pm 0.2 \text{ kPa.}$ during anaesthesia. This rise was statistically highly significant ($p < 0.001$). The mean level fell during the post-operative period to a mean value of $6.1 \pm 0.2 \text{ kPa.}$, although still significantly raised from pre-operative levels.

Fig. 10

CARDIOVASCULAR CHANGES DURING THE FIRST ETOMIDATE INFUSION STUDY

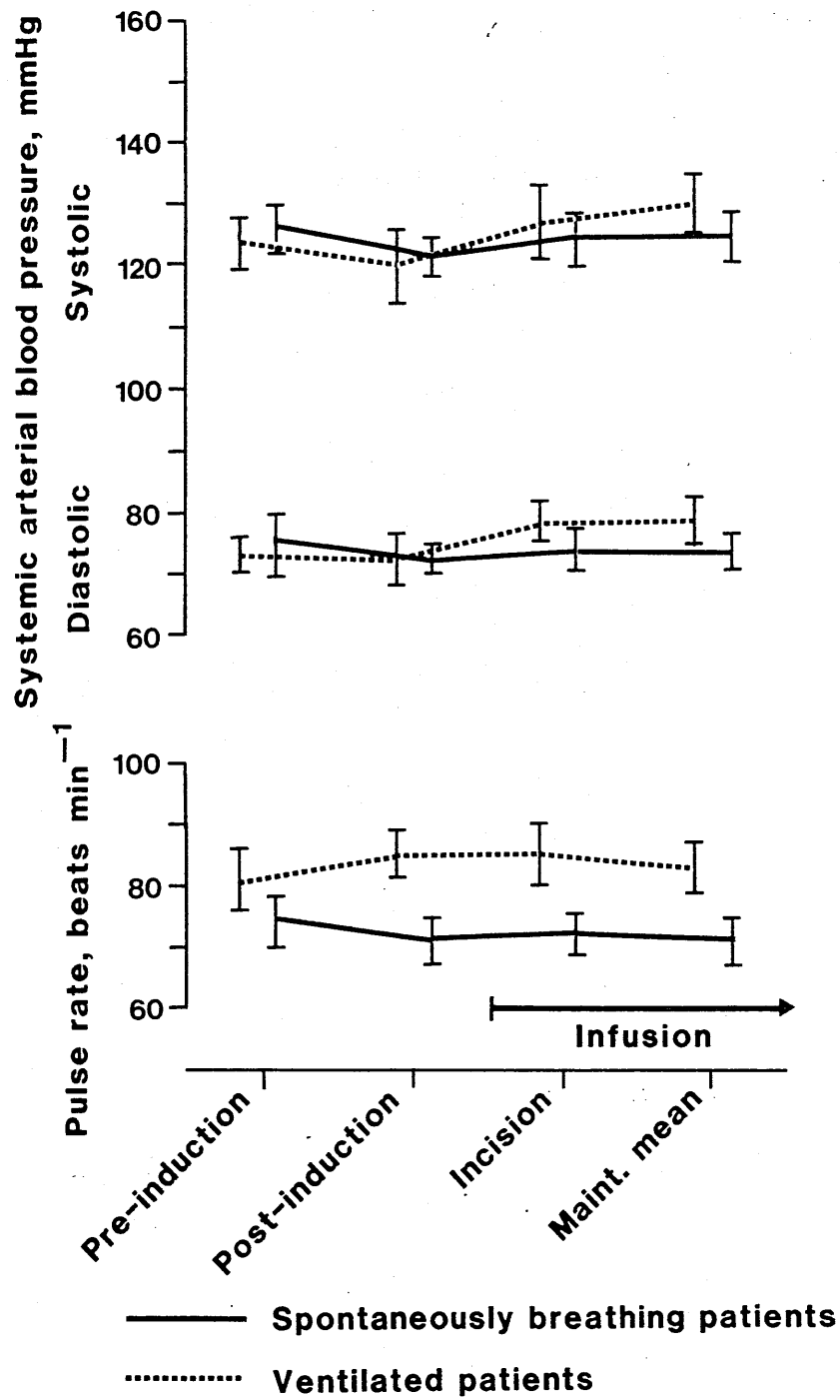


TABLE FIFTEEN

COEFFICIENTS OF VARIATION OF THE
CARDIOVASCULAR PARAMETERS IN THE
FIRST ETOMIDATE INFUSION STUDY.

| RESPIRATORY MODE | SYSTOLIC ARTERIAL PRESSURE \pm S.E.M. | DIASTOLIC ARTERIAL PRESSURE \pm S.E.M. | PULSE RATE \pm S.E.M. |
|---------------------|--|---|----------------------------|
| I.P.P.V. | 9.4 \pm 1.4 | 9.9 \pm 1.5 | 10.6 \pm 1.5 |
| SPT. V. | 5.5 \pm 0.6 | 7.9 \pm 0.8 | 7.8 \pm 0.8 |

Ventilation was assisted in eight patients whose respiration became depressed to a rate of six breaths per minute or less. The infusion rate was slowed until spontaneous respiration was restored. The levels of arterial carbon dioxide tension were not measured in these patients.

Recovery

The median time to recovery was 5 minutes in the ventilated group with an interquartile range of 4 - 10 minutes. This was lower than the median of 15 minutes with an interquartile range of 7 - 25 minutes for the spontaneously breathing group. This difference was statistically significant ($p < 0.01$). Only one patient in the ventilated group had not regained consciousness within 30 minutes compared with 7 in the spontaneously breathing group. Nausea and vomiting was seen in 5 patients. Marked venous thrombophlebitis was seen around the infusion site in two patients 24 - 48 hours after operation. No patient gave any evidence of having been aware during the period of anaesthesia.

Conclusions

The conclusions of this study were that total intravenous anaesthesia was possible using a mixture of etomidate and fentanyl, but several problems were found. These were mainly a high incidence of pain on injection and muscle movement. Inadequate anaesthesia, prolonged recovery and severe thrombophlebitis also occurred.

Study Eight

The Second Etomidate Infusion Study

In an attempt to reduce the incidence of some of the complications found in the first study, particularly during induction, thiopentone was used to induce anaesthesia instead of etomidate. A more detailed study of the extent that the degree of venous damage could be attributed to the infusion of etomidate was also carried out. The infusion anaesthetic techniques were also compared with more conventional anaesthetic techniques. Control and infusion patients were matched as described in Chapter Two.

Patients and Methods

Two hundred eligible patients were allocated to either the infusion or control groups. Fifty patients in each group were to be ventilated and fifty to breathe spontaneously. The operations carried out are shown in Table Sixteen.

The anaesthetic machine and a combined infusion of etomidate and fentanyl were prepared and patients premedicated as described in Chapter Two. All patients were attached to an E.C.G. monitor and had an oscillotonometer cuff attached on arrival in the anaesthetic room. A 23 S.W.G. cannula (Abbott "Butterfly" No. 4871) was inserted into a vein in the dorsum of the non-dominant hand. If required, an arterial blood sample was taken under local anaesthesia as described in Chapter Two. The induction of anaesthesia was carried out by an intravenous injection of fentanyl 1.3 mcg.kg.^{-1}

TABLE SIXTEEN

OPERATIONS CARRIED OUT ON EACH GROUP IN
THE SECOND ETOMIDATE INFUSION STUDY.

| VENTILATED CASES | NO. | SPONTANEOUSLY BREATHNG CASES | NO. |
|---------------------|-----|---------------------------------|-----|
| UPPER ABDOMINAL | 14 | BREAST BIOPSY; MASTECTOMY | 15 |
| LOWER ABDOMINAL | 16 | INGUINAL HERNIA | 10 |
| MAJOR GYN. | 15 | HAEMORRHOIDECTOMY | 7 |
| PERIPHERAL VASCULAR | 5 | VARICOSE VEINS | 5 |
| | | MINOR GYN. | 11 |
| | | E.N.T. | 2 |
| TOTAL | 50 | | 50 |

followed after 1 - 2 minutes by thiopentone 5 mg.kg.^{-1} , injected through the membrane of the injection port of the cannula. If endotracheal intubation was required, succinylcholine 100 mg. was injected intravenously. Immediately after induction, anaesthesia was maintained with an infusion of etomidate and fentanyl via a 21 S.W.G. needle inserted through the membrane of the injection port of the 23 S.W.G. cannula. All patients breathed 100% oxygen during the induction period.

Maintenance of anaesthesia was carried out as described in Chapter Two. An 18 S.W.G. cannula (Quik - Cath, Travenol) was inserted into a vein in the dorsum of the opposite hand through which blood, saline or dextrose 5% was infused as required during anaesthesia. Injections of other drugs required during the operations such as tubocurarine, atropine and neostigmine, were administered as required through the injection port of the fluid administration set.

Patients in the control groups who were to be ventilated or to breathe spontaneously were anaesthetised as described in Chapter Two. In an attempt to separate the effect of the infusion of etomidate from the effects of the infusion of saline alone, the control patients had normal saline infused during the operation via a 23 S.W.G. cannula inserted into a vein in the dorsum of the non-dominant hand at a rate similar to the infusion rate of etomidate received by the infusion groups.

Measurements of pulse rate and arterial systolic and diastolic

blood pressures were made immediately before induction, after induction, at incision and at five minute intervals during surgery unless more frequent measurements were clinically indicated. Other observations of the quality of induction and maintenance of anaesthesia, including arterial blood gas measurements, were carried out as described in Chapter Two. Recovery from anaesthesia and the post-operative visits were carried out as described in Chapter Two. The time to the first administration of intramuscular post-operative analgesia was noted.

Results

Composition of the Groups

Details of the physical characteristics of the patients and the duration of anaesthesia are shown in Table Seventeen. There were no statistically significant differences between the demographical data of each infusion group and its control group.

Quality of Induction and Maintenance

Anaesthesia was successfully induced and maintained in all patients. There were no induction complications such as pain on injection and muscle movement. There was no evidence of histamine release in any of the patients anaesthetised in this study.

Infusion Rates

There were no statistically significant differences between

TABLE SEVENTEEN

DETAILS OF PATIENTS AND DURATION OF ANAESTHESIA
IN THE SECOND ETOMIDATE INFUSION STUDY.

| | RESPIRATORY MODE | NO. OF PATIENTS | MEAN AGE (YRS.) + S.E.M. | MEAN WT. (Kg.) + S.E.M. | DURATION (MEAN) + S.E.M. |
|-----------|---------------------|--------------------|--------------------------------|-------------------------------|--------------------------------|
| ETOMIDATE | I.P.P.V. | 19M 50 31F | 55 + 3 | 60 + 3 | 92 + 8 |
| | SPT. V. | 21M 50 29F | 47 + 3 | 64 + 3 | 35 + 3 |
| CONTROL | I.P.P.V. | 19M 50 31F | 55 + 3 | 60 + 3 | 87 + 5 |
| | SPT.V. | 21M 50 29F | 47 + 3 | 64 + 1 | 43 + 5 |

the infusion rates for male and female patients in either group, so these infusion rates were combined. The mean amounts of etomidate administered in $\text{mcg.kg.}^{-1} \text{ min.}^{-1}$ in the ventilated and spontaneously breathing group are shown in Figure Eleven. For clarity, the standard error of the mean (S.E.M.) values have been shown at 5 minute intervals. The initial rapid infusion rates were not statistically significantly different, but the ventilated group received a statistically significantly ($p < 0.01$) lower rate of infusion for the period 11 - 20 minutes. Thereafter there were no statistically significant differences between the two groups. The overall mean infusion rate was $20 \pm 1.6 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of etomidate and $0.056 \pm 0.0045 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of fentanyl. The coefficient of variation of the infusion rate was $62 \pm 3.3\%$ for the ventilated group and $74 \pm 3.1\%$ for the spontaneously breathing group.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and pulse rates in each group with their associated standard errors of the mean are shown in Figure Twelve. Both control groups showed statistically significant falls in arterial systolic pressure during the induction period ($p < 0.05$) for the spontaneously breathing group and ($p < 0.02$) for the ventilated group. These changes were not clinically significant, neither were measures taken to counteract them. The changes in the etomidate groups were not significant clinically or statistically. The changes which occurred during maintenance anaesthesia are shown in Table Eighteen, expressed as the mean.

Fig. 11

INFUSION RATES OF ETOMIDATE DURING THE SECOND ETOMIDATE INFUSION STUDY

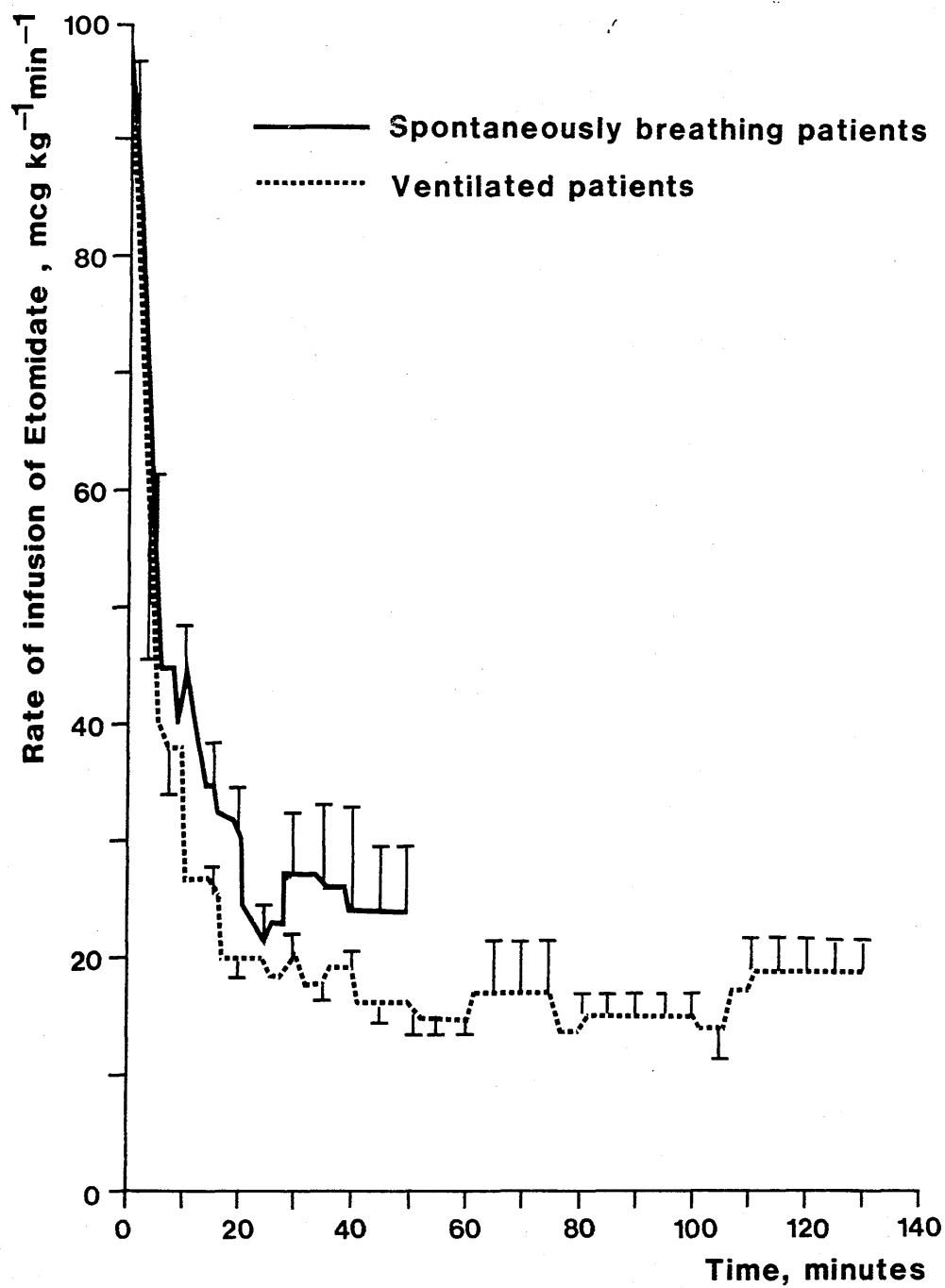


Fig. 12

CARDIOVASCULAR CHANGES DURING THE SECOND ETOMIDATE INFUSION STUDY

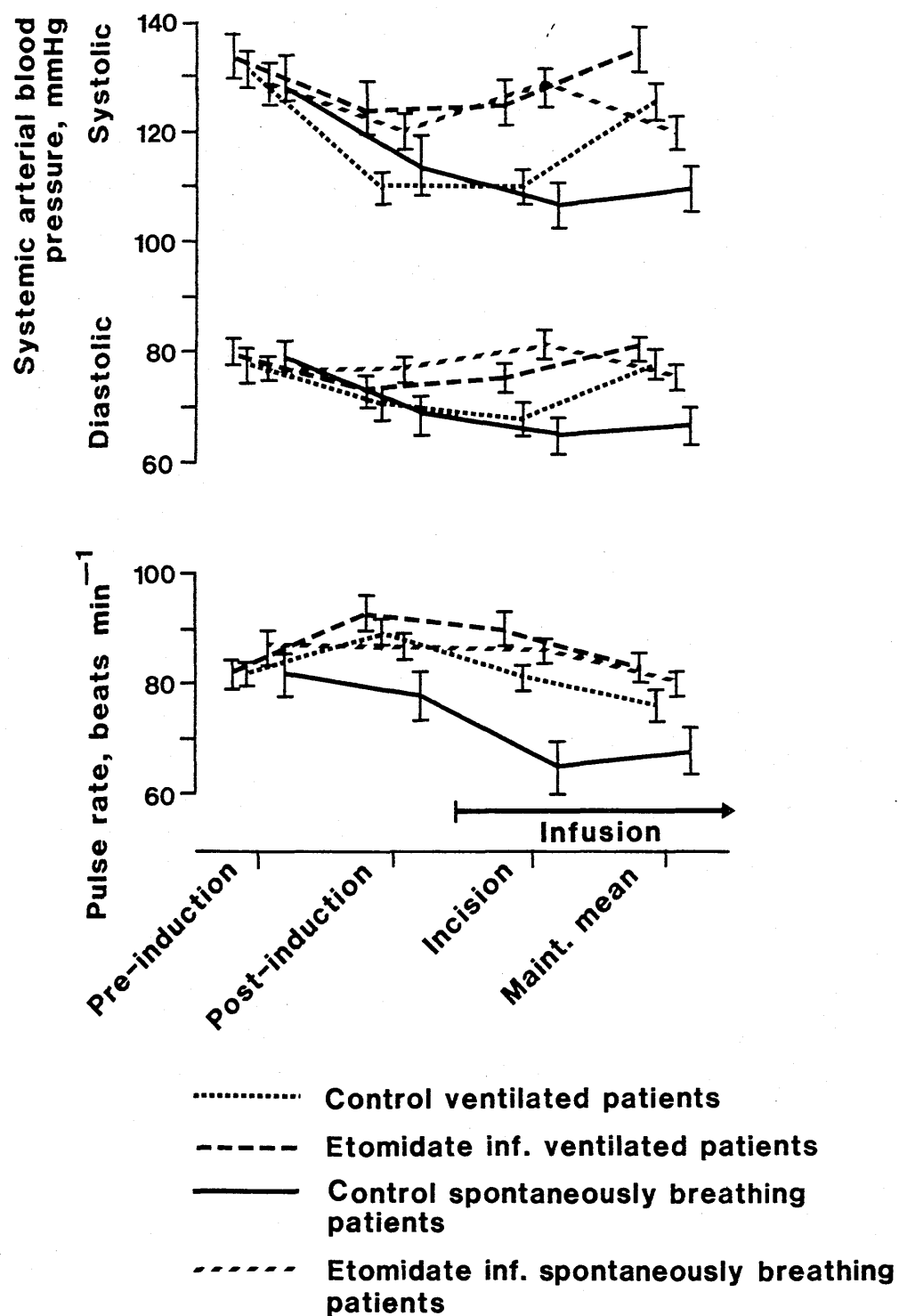


TABLE EIGHTEEN

COEFFICIENTS OF VARIATION OF THE
CARDIOVASCULAR PARAMETERS IN THE
SECOND ETOMIDATE INFUSION STUDY.

| | RESPIRATORY MODE | SYSTOLIC ARTERIAL PRESSURE \pm S.E.M. | DIASTOLIC ARTERIAL PRESSURE \pm S.E.M. | PULSE RATE \pm S.E.M. |
|-----------|---------------------|--|---|----------------------------|
| ETOMIDATE | I.P.P.V. | 9.2 \pm 0.8 | 8.5 \pm 0.9 | 10.2 \pm 1.0 |
| | SPT. V. | 8.5 \pm 0.6 | 8.5 \pm 0.9 | 7.3 \pm 0.5 |
| CONTROL | I.P.P.V. | 10.2 \pm 1.7 | 8.0 \pm 1.1 | 7.4 \pm 1.2 |
| | SPT. V. | 6.4 \pm 1.1 | 9.0 \pm 1.4 | 7.6 \pm 1.7 |

coefficients of variation.

Respiratory Changes

Both spontaneously breathing groups showed a statistically significant rise ($p < 0.001$) in the mean values of the arterial carbon dioxide tension during the course of anaesthesia. The group receiving etomidate rose from a mean pre-induction level of 5.2 ± 0.1 kPa. to a mean level of 6.5 ± 0.2 kPa. during anaesthesia. The control group showed a rise from a mean pre-induction value of 5.2 ± 0.2 kPa. to a mean value of 7.1 ± 0.3 kPa. during anaesthesia. Post-operatively the level in the etomidate group fell to a mean value of 6.1 ± 0.3 kPa. whereas the level in the control group fell to a mean value of 6.2 ± 0.3 kPa. Severe respiratory depression occurred during operation in 10, mainly elderly, patients who were being infused with etomidate and fentanyl. In these cases the infusion rates were reduced and the patients ventilated manually until spontaneous ventilation was resumed. Arterial carbon dioxide tension levels were not measured in these cases. No patients in the corresponding control group required assistance with ventilation.

Recovery

There was no statistically significant difference in the recovery times of the ventilated groups. The median value was 6 minutes in the control group with an interquartile range of 3 - 10 minutes, compared with a median value of 7 minutes with an interquartile range of 3 - 17 minutes for the etomidate group.

Five patients in the infusion group compared with one in the control ventilated group had not recovered after 30 minutes.

Recovery of the spontaneously breathing patients was faster in the control group with a median time of 18 minutes and an interquartile range of 15 - 23 minutes, compared with a median time of 25 minutes and an interquartile range of 14 - 35 minutes for the infused group. This difference was statistically significant ($p < 0.05$). However 14 patients in the spontaneous breathing group compared with 3 in the control group had not recovered within 30 minutes. Six patients in the etomidate infusion groups required 0.1 - 0.2 mg. of naloxone I.V. after which recovery was complete within a few minutes.

The mean time to the first administration of intramuscular postoperative analgesia was 6.9 ± 0.8 hours in the groups receiving etomidate compared with a mean time of 6.4 ± 0.9 hours in the control groups. This difference was not statistically significant. The incidence of nausea and vomiting during the recovery period was 4% in the etomidate group and 6% in the control group. No patient gave any evidence of having been aware during the period of anaesthesia.

Venous Damage

Inspection of the infusion site 24 - 48 hours after the infusion of etomidate or normal saline showed a 22% incidence of thrombosis 1 - 2 cm. long after the infusion of etomidate compared with the 10% after the infusion of normal saline in the

control group. This difference was statistically significant ($p < 0.02$).

Conclusions

The conclusions of this study were that the use of thiopentone as the induction agent followed by an infusion of etomidate and fentanyl provided an induction of anaesthesia which was free from pain and muscle movement whilst maintaining cardiovascular and respiratory stability. However problems arose due to delayed recovery. The infusion of etomidate appeared to be associated with an increased incidence of venous thrombosis. There was no evidence of any patient being aware during anaesthesia.

Study Nine

The Third Etomidate Infusion Study

A two stage infusion of etomidate for the induction and maintenance of anaesthesia based on the known pharmacokinetic properties of etomidate has been described (Schüttler et al, 1980, b). It was suggested that this infusion scheme could maintain satisfactory anaesthesia, but with the infusion of smaller amounts of etomidate than that used by earlier techniques (Schwilden et al, 1981). A third study was carried out to investigate this infusion technique and to compare it with standard anaesthetic techniques for ventilated and spontaneously breathing patients.

Patients and Methods

Two hundred eligible patients were allocated to either the infusion or control groups. Fifty patients in each group were to be ventilated and fifty to breath spontaneously. The operations carried out are shown in Table Nineteen.

The anaesthetic machine and separate infusions of etomidate and fentanyl were prepared and the patients premedicated as described in Chapter Two. All patients were attached to an E.C.G. monitor and had an oscillotonometer cuff attached on arrival in the anaesthetic room. If required, an arterial blood sample was taken under local anaesthesia.

A 500 cc. bag of normal saline 0.9% or dextrose 5% was

TABLE NINETEEN

OPERATIONS CARRIED OUT ON EACH GROUP
IN THE THIRD ETOMIDATE INFUSION STUDY.

| VENTILATED CASES | NO. | SPONTANEOUSLY | NO. |
|---------------------|-----|------------------------------|-----|
| UPPER ABDOMINAL | 13 | BREAST BIOPSY; MASTECTOMY | 18 |
| LOWER ABDOMINAL | 17 | INGUINAL HERNIA | 16 |
| MAJOR GYN. | 18 | HAEMORRHOIDECTOMY | 8 |
| PERIPHERAL VASCULAR | 2 | VARICOSE VEINS | 8 |
| TOTAL | 50 | | 50 |

connected via two three-way taps to an 18 S.W.G. cannula (Quik - Cath, Travenol) inserted into a vein in the dorsum of the non-dominant hand and allowed to flow at 20 - 40 drops per minute. The etomidate and fentanyl infusion sets were connected to the free limbs of the three way taps when required. The induction of anaesthesia was carried out by an intravenous injection of fentanyl 1.3 mcg.kg.^{-1} followed after 1 - 2 minutes by a rapid infusion of etomidate $100 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for ten minutes. If endotracheal intubation was required, succinylcholine 100 mg. was administered intravenously via the second three-way tap, once the eyelash reflex had disappeared. During the induction of anaesthesia, all patients breathed 100% oxygen.

Maintenance of anaesthesia was carried out as described in Chapter Two. After the elapse of 10 minutes the infusion of etomidate was reduced to a maintenance infusion rate of $10 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ until the end of the operation. Once in the operating theatre, a separate infusion of fentanyl was commenced. The rate of the fentanyl infusion was altered when necessary as described in Chapter Two.

An 18 S.W.G. cannula (Quik - Cath) was inserted into a vein in the dorsum of the opposite hand through which blood, saline or dextrose 5% was infused as required during anaesthesia. Injections of other drugs required during the operation such as tubocurarine, atropine and neostigmine, were given through the injection port of the fluid administration set.

Measurements of pulse rate and arterial systolic and diastolic

blood pressures were made immediately before induction, after induction, at incision and at five minute intervals during surgery unless more frequent measurements were clinically indicated. Other observations of the quality of induction and maintenance of anaesthesia, including arterial blood gas measurements, were carried out as described in Chapter Two. Recovery from anaesthesia and the post-operative visits were carried out as described in Chapter Two. The time to the first administration of intramuscular postoperative analgesia was noted.

Patients in the control groups were anaesthetised and their post-operative progress observed as described in Chapter Two.

Results

Composition of the Groups

The composition, physical characteristics and duration of anaesthesia in the groups are shown in Table Twenty. There were no statistically significant differences between the groups, except that the duration of anaesthesia in the ventilated control group was statistically significantly longer ($p < 0.02$) than the corresponding control group.

Quality of Induction and Maintenance

Anaesthesia was successfully induced and maintained in all patients. The mean time to loss of the eye-lash reflex in the infusion groups was 103 ± 3 seconds. Four patients complained of pain on injection, and fourteen complained of tingling when the

TABLE TWENTY

DETAILS OF PATIENTS AND DURATION OF ANAESTHESIA

IN THE THIRD ETOMIDATE INFUSION STUDY.

| | RESPIRATORY MODE | NO. OF PATIENTS | MEAN AGE (YRS.) + S.E.M. | MEAN WT. (KG.) + S.E.M. | DURATION (MINS.) + S.E.M. |
|-----------|---------------------|--------------------|--------------------------------|-------------------------------|---------------------------------|
| ETOMIDATE | I.P.P.V. | 50 13M 37F | 53 + 3 | 65 + 2 | 57 + 3 |
| | SPT. V. | 50 24M 26F | 48 + 3 | 68 + 2 | 47 + 4 |
| CONTROL | I.P.P.V. | 50 13M 37F | 49 + 3 | 63 + 2 | 67 + 6 |
| | SPT. V. | 50 24M 26F | 51 + 3 | 69 + 1 | 41 + 3 |

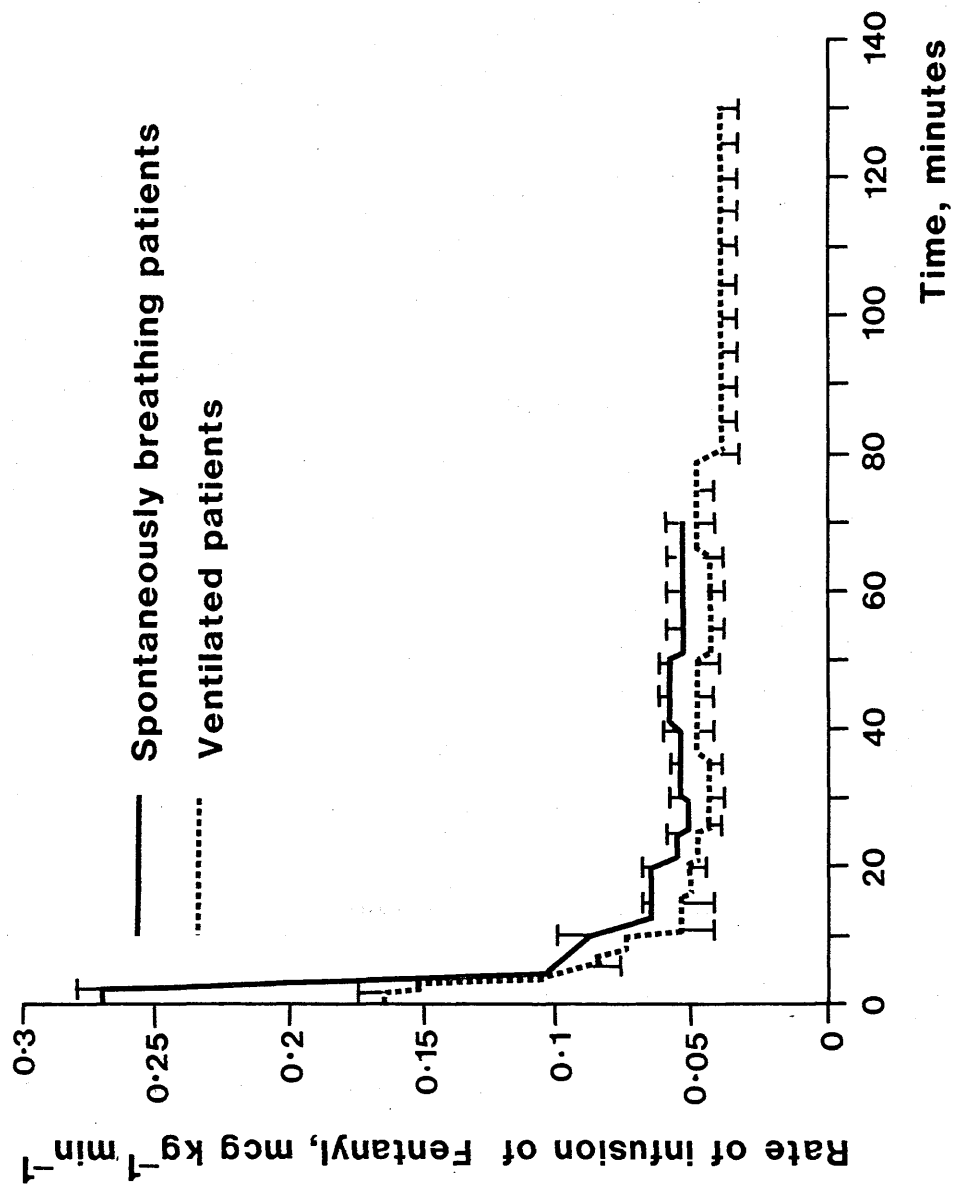
etomidate was infused. In the spontaneously breathing group which received etomidate, severe muscle movement was not seen, although mild muscle movement was seen in six patients. All patients were satisfactorily anaesthetised using this technique. A rapid loss of the eye-lash reflex was found in the patients induced with thiopentone. No muscle movement or pain on injection occurred in these patients. There was no evidence of histamine release in any of the patients anaesthetised in this study.

Infusion Rates

The rate of infusion of etomidate was fixed for both groups. There were no significant differences between the infusion rates of fentanyl for male or female patients in any group, which were then combined. The amounts of fentanyl infused in the ventilated and spontaneously breathing groups are shown in Figure Thirteen. For clarity, the standard error of the mean (S.E.M.) values have been shown at 5 minute intervals. The spontaneously breathing group received a significantly higher infusion rate of fentanyl in the first three minutes ($p < 0.01$ at 1 and 2 minutes and 0.05 at three minutes). Thereafter there were no significant differences between the two infusion groups. The infusion rates for the fentanyl varied considerably between patients, but the mean infusion rate was found to be $0.23 \pm 0.015 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 3 - 4 minutes followed by $0.1 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 8 - 9 minutes and $0.05 \pm 0.003 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The mean coefficient of variation of the infusion rates was $54 \pm 1.3\%$ for the ventilated group and $51 \pm 3.1\%$ for the spontaneously breathing group.

Fig. 13

INFUSION RATES OF FENTANYL DURING THE THIRD ETOMIDATE
INFUSION STUDY



Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and the pulse rates and their associated standard errors of the mean for each group are shown in Figure Fourteen. There were no statistically significant changes in the mean arterial systolic, or diastolic blood pressures, or pulse rates in the etomidate groups. In both control groups there were statistically significant falls in the mean systolic arterial blood pressure, ($p < 0.05$) in the ventilated group and ($p < 0.01$) in the spontaneously breathing group during the period of the induction of anaesthesia. These changes were not clinically significant and no measures were taken to correct them. During maintenance anaesthesia these values tended to return to their pre-operative levels. There were no statistically significant changes in the mean diastolic blood pressures or pulse rates in the control groups. The changes occurring during maintenance anaesthesia are shown in Table Twenty One, expressed as the mean coefficients of variation.

Respiratory Changes

The mean pre-operative values of arterial carbon dioxide tension in spontaneously breathing patients were identical in both groups with a mean of 5.1 ± 0.2 kPa. These values rose significantly during anaesthesia ($p < 0.001$) in both groups. Values in the control group rose to a mean value of 6.5 ± 0.2 kPa. during anaesthesia falling to a mean value of 6.1 ± 0.2 kPa during recovery. In the etomidate group the arterial carbon dioxide tension rose to a mean value of 6.6 ± 0.2 kPa. during anaesthesia falling to a mean value

Fig. 14

CARDIOVASCULAR CHANGES DURING THE THIRD ETOMIDATE INFUSION STUDY

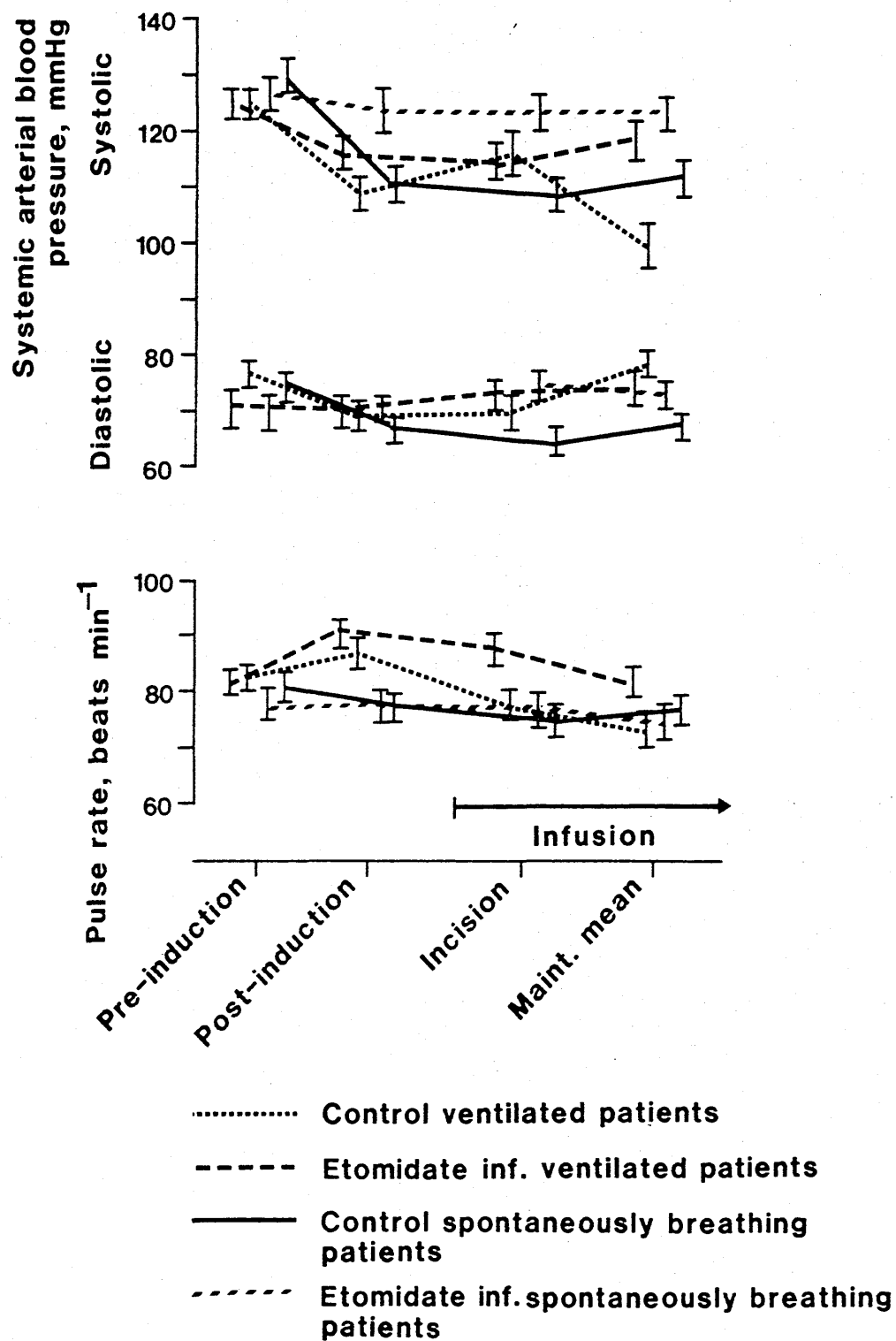


TABLE TWENTY ONE

COEFFICIENTS OF VARIATION OF THE

CARDIOVASCULAR PARAMETERS IN THE

THIRD ETOMIDATE INFUSION STUDY.

| | RESPIRATORY MODE | SYSTOLIC ARTERIAL PRESSURE + S.E.M. | DIASTOLIC ARTERIAL PRESSURE + S.E.M. | PULSE RATE + S.E.M. |
|-----------|---------------------|--|---|------------------------|
| ETOMIDATE | I.P.P.V. | 5.2 + 0.6 | 4.8 + 0.8 | 5.2 + 1.1 |
| | SPT. V. | 2.7 + 0.6 | 2.8 + 0.6 | 3.4 + 0.8 |
| CONTROL | I.P.P.V. | 7.2 + 0.9 | 6.8 + 0.9 | 9.5 + 1.1 |
| | SPT. V. | 6.5 + 0.6 | 6.5 + 0.9 | 7.3 + 1.3 |

of 6.1 ± 0.2 kPa. in the post-operative period. Episodes of severe respiratory depression occurred in four elderly patients receiving etomidate and fentanyl. In these patients, ventilation was manually assisted and the infusion rate of fentanyl was slowed. No such assistance was required in any patient in the corresponding control group.

Recovery

The median time to recovery in both ventilated groups was 8 minutes. The interquartile range was 5 - 12 minutes for the etomidate group and 2 - 10 minutes for the control group. This difference was not statistically significant. All ventilated patients were awake within 30 minutes.

The infused group who were breathing spontaneously were awake in a median time of 15 minutes with an interquartile range of 10 - 20 minutes. The control group awoke in a median time of 23 minutes with an interquartile range of 15 - 32 minutes. This difference was statistically significant ($p < 0.01$). Four of the patients in the infused group had not recovered within 30 minutes compared with six in the control group.

Four female patients, who had been infused with etomidate for over an hour showed myoclonic movements in all four limbs for a period of 15 - 45 minutes after the end of infusion. These movements gradually settled without any treatment.

The mean time to the first administration of post-operative intramuscular analgesia in the etomidate groups was

5.8 \pm 0.6 hours compared with a mean time of 6.2 \pm 0.7 hours in the control groups. This difference was not statistically significant. The incidence of nausea and vomiting was 5% in the etomidate groups compared with 7% in the control groups. No patient gave any evidence of having been aware during the period of anaesthesia.

Venous Damage

One patient who had been infused with a 0.5% solution instead of the standard 0.25% solution of etomidate had a very severe venous thrombosis which lasted for several months. Two other patients had severe venous thrombosis.

Conclusions

The conclusions of this study were that the use of a fixed infusion rate of etomidate provided a good induction and maintenance of anaesthesia with rapid recovery, particularly in spontaneously breathing patients. The delay in the onset of hypnosis was not found to be unpleasant and several patients preferred it to the sudden loss of consciousness experienced during previous anaesthetic inductions. The incidence of pain on injection and muscle movement was reduced. There was no evidence of any patient having been aware during the period of anaesthesia. The use of a 0.5% solution of etomidate is not recommended.

CHAPTER EIGHT

STUDY TEN

THE EFFECTS OF THE MAINTENANCE OF ANAESTHESIA
BY THE INTRAVENOUS INFUSION
OF ETOMIDATE AND FENTANYL
ON HEPATIC AND RENAL FUNCTION

Study Ten

The Fourth Etomidate Infusion Study

Introduction

The aim of this study, the Fourth Etomidate Infusion Study, was to investigate the effects of the infusion techniques used in the second and third etomidate infusion studies on hepatic and renal function. The results found were compared with those obtained using a standard anaesthetic technique including the administration of nitrous oxide and morphine.

Patients and Methods

Sixty eligible patients aged from 18 - 65 years who were to undergo simple abdominal hysterectomy were randomly allocated to one of three groups. The control group (A) received a standard anaesthetic sequence of nitrous oxide/oxygen and morphine as described in Chapter Two. Patients in Group B received a combined infusion of etomidate and fentanyl for the maintenance of anaesthesia and patients in Group C were anaesthetised using the Two Stage Infusion Technique described in Chapter Nine. Any patient who showed evidence of pre-operative anaemia, electrolyte or liver function abnormality, who was found at operation to have an abdominal malignancy, who required rapid infusion of fluid to raise blood pressure, or who required blood transfusion at any time during or after the operation, was eliminated from the trial and replaced by the next suitable patient. All operations were carried out

by the same consultant gynaecologist.

Blood samples for the control measurements of haemoglobin, urea and electrolytes and liver function tests were taken two days before operation and repeated twenty four hours after operation. All patients were to be ventilated. The details of the anaesthetic techniques used in this study have been previously described in Chapter Two and Studies Eight and Nine. The only difference in technique between these studies and the techniques used in this study was that a fast flowing (30 - 40 drops per minute) infusion of Ringer Lactate solution was set up via an 18 S.W.G. cannula (Quik - Cath, Travenol) inserted into a vein in the dorsum of the non-dominant hand. Three-way taps were added in series as required for the number of hypnotic and analgesic infusions to be used.

Cardiovascular measurements, continuous E.C.G. monitoring, induction and maintenance of anaesthesia and recovery were carried out in all patients as described in Chapter Two and Studies Eight and Nine.

All patients had post-operative fluid regimes of 2000 ml. of dextrose 5% and 1000 ml. of 0.9% normal saline I.V. for 24 hours post-operatively, followed by a normal ward diet.

Biochemical Analysis

Biochemical analyses were carried out by the Biochemistry Department, Victoria Infirmary, Glasgow. Serum concentrations of sodium, potassium, chloride, urea and creatinine were measured

using a Sequential Multiple Analyser 6 - 60. Serum aspartate amino-transferase (A.S.T.) and serum alanine amino-transferase (A.L.T.) were measured using an L.K.B. Reaction Rate Analyser 2086. Serum alkaline phosphatase (A.L.P.), gamma-glutamyl transferase (G.G.T.) total bilirubin (T.B.), total protein (T.P.) and serum albumin (S.A.) were measured using a Centrifugal Analyser Union Carbide Centrifichem 400.

Results

Composition of the Groups

Patient details are shown in Table Twenty Two. There were no statistically significant differences between the groups.

Liver Function Test Changes

The results for the changes in the liver function tests are shown in Table Twenty Three. There were no statistically significant differences between the three groups pre-operatively. Both Groups A and B showed a statistically significant increase ($p < 0.02$) in G.G.T. post-operatively. The other liver function tests also tended to be elevated. Total protein showed a statistically significant fall ($p < 0.05$) in the control group only and serum albumin ($p < 0.01$) showed a statistically significant fall in Group A and B. A.S.T. values showed a statistically significant rise in Group C Only ($p < 0.02$).

TABLE TWENTY TWO

DETAILS OF PATIENTS AND DURATION OF ANAESTHESIA
IN THE FOURTH ETOMIDATE INFUSION STUDY

| | NO. OF PATIENTS | AGE (YRS.) + S.E.M. | WT. (Kg.) + S.E.M. | DURATION OF ANAESTHESIA (MINS.) + S.E.M. |
|------------------------------------|--------------------|------------------------|-----------------------|---|
| CONTROL (GROUP A) | 20 | 51 ± 3 | 62 ± 4 | 58 ± 3 |
| THIO + ET/FENT. (GROUP B) | 20 | 50 ± 3 | 62 ± 4 | 59 ± 3 |
| TWO STAGE INFUSION (GROUP C) | 20 | 52 ± 4 | 64 ± 4 | 60 ± 3 |

TABLE TWENTY THREE

CHANGES IN LIVER FUNCTION TESTS IN THE FOURTH ETOMIDATE INFUSION STUDY

| | A.S.T. (I.U.Litre ⁻¹) | A.L.T. (I.U.Litre ⁻¹) | G.G.T. (I.U.Litre ⁻¹) | ALK. PHOS. (I.U.Litre ⁻¹) | TOT. BIL. (μ mole/litre ⁻¹) | TOT. PROT. (g.litre ⁻¹) | ALBUMIN (g.litre ⁻¹) |
|--------------------|--------------------------------------|--------------------------------------|--------------------------------------|--|---|--|-------------------------------------|
| PRE-OP | 22 (18-28) | 25 (18-300) | 13 (10-18) | 48 (41-62) | 8 (6-10) | 71 (65-74) | 38 (36-41) |
| GROUP A POST-OP | 18 (18-27) | 26 (18-39) | 16 (11-26)** | 53 (44-62) | 8 (6-11) | 67 (65-72)* | 33 (33-37) *** |
| PRE-OP | 23 (19-29) | 17 (15-22) | 11 (5-15) | 35 (30-55) | 8 (7-9) | 69 (66-73) | 38 (35-41) |
| GROUP B POST-OP | 20 (17-25) | 18 (15-24) | 14 (11-33)** | 46 (35-57) | 8 (6-10) | 67 (67-74) | 35 (34-40) *** |
| PRE-OP | 23 (20-28) | 14 (13-19) | 12 (11-19) | 45 (40-62) | 10 (7-12) | 67 (65-73) | 37 (36-42) |
| GROUP C POST-OP | 28 (21-36)** | 14 (13-19) | 14 (9-26) | 46 (39-58) | 10 (9-11) | 56 (60-70) | 37 (36-40) |
| REFERENCE RANGE | < 37 | < 40 | < 30 | 60-260 | < 17 | 62-82 | 38-52 |

* SIGNIFICANT FALL P < 0.05

** SIGNIFICANT RISE P < 0.02

*** SIGNIFICANT FALL P < 0.01

Serum Electrolyte Changes

The changes in serum electrolyte results are shown in Table Twenty Four. There were no statistically significant differences between the pre-operative concentrations of sodium, potassium, creatinine or urea in any group. In all groups there were statistically significant falls in potassium and urea. In Groups A and B there were also statistically significant falls in creatinine concentrations post-operatively. The significance values are shown in Table 24.

Conclusions

These results suggest that the infusion of moderate amounts of etomidate and fentanyl do not cause greater upsets in hepatic or renal function than a standard anaesthetic technique including morphine and nitrous oxide.

TABLE TWENTY FOUR
CHANGES IN SERUM ELECTROLYTES, UREA AND CREATININE IN THE
FOURTH ETOMIDATE INFUSION STUDY.

| | POTASSIUM m.moles/litre | CREATININE m.moles/litre ⁻¹ | UREA m.moles/litre ⁻¹ | SODIUM m.moles/litre ⁻¹ | CHLORIDE m.moles/litre ⁻¹ |
|---------------------------|----------------------------|---|-------------------------------------|---------------------------------------|---|
| CONTROL PRE-OP | 3.8 (3.6-4) | 87 (70-100) | 4.0 (3.5-4.7) | 142 (136-143) | 102 (98-106) |
| (GROUP A) POST-OP. | 3.4 (3.3-3.9)** | 70 (66-84)* | 3.1 (2.3-4.0)*** | 141 (137-144) | 102 (97-107) |
| THIO + Et. PRE-OP | 3.9 (3.7-3.9) | 83 (65-100) | 4.7 (4.2-5.7) | 139 (135-141) | 99 (96-104) |
| (GROUP B) POST-OP | 3.4 (3.1-3.7)*** | 73 (67-80)* | 4.0 (2.9-5.1)** | 142 (137-144) | 100 (95-105) |
| TWO STAGE PRE-OP ETOM. | 4.1 (3.9-4.1) | 85 (75-97) | 4.7 (4.2-5.4) | 141 (136-143) | 103 (99-106) |
| (GROUP C) POST-OP | 3.8 (3.6-4.0)* | 79 (70-84) | 4.0 (2.5-5.2)** | 140 (135-142) | 100 (96-104) |
| REFERENCE RANGE | 3.5 - 5.0 | 55 - 105 | 2.5 - 6.5 | 137 - 147 | 96 - 105 |

* SIGNIFICANT FALL P < 0.05
 ** SIGNIFICANT FALL P < 0.02
 *** SIGNIFICANT FALL P < 0.01

CHAPTER NINE

STUDIES ELEVEN AND TWELVE

THE INFUSION OF PROPOFOL FOR THE
MAINTENANCE OF TOTAL INTRAVENOUS ANAESTHESIA

Introduction

The results of the induction study described in Chapter Six suggested that propofol might be suitable as the hypnotic component of a total intravenous anaesthetic technique. As with etomidate, analgesic supplementation was required for which fentanyl was used.

Study Eleven

The First Propofol Infusion Study

The aim of the first infusion study was to evaluate a pre-determined infusion regime based on pharmacokinetic data and designed to establish rapidly a constant blood concentration for operations lasting one to two hours (Cockshott 1985).

Patients and Methods

Fifteen patients, seven male and eight female, of mean age 59 ± 2 years and mean weight 56 ± 3 Kg. took part in an open uncontrolled study. The operations carried out were three each of peripheral vascular, upper abdominal, lower abdominal, orthopaedic (hand) or ligation and stripping of varicose veins. All patients were to be ventilated except the six patients who were to undergo hand operations or ligation and stripping of varicose veins.

The anaesthetic machine and separate infusions of propofol and fentanyl were prepared and the patients premedicated, as

described in Chapter Two. All patients were attached to an E.C.G. monitor and had a Dinamap cuff attached on arrival in the anaesthetic room. A 23 S.W.G. cannula ("Butterfly", Abbott, No. 4871) was inserted into a vein in the dorsum of the non-dominant hand, through which all injections and infusions of propofol, fentanyl and succinylcholine were given.

Induction was carried out by an intravenous injection of fentanyl 1.3 mcg.kg.^{-1} followed after 1 - 2 minutes by the injection of 2.5 mg.kg.^{-1} of propofol in all patients. If intubation was required, this was facilitated by the injection of succinylcholine 1 mg.kg.^{-1} . Propofol was then infused at a rate of $0.15 \text{ mg.kg.}^{-1} \text{ min.}^{-1}$ via a 21 S.W.G. cannula. All patients breathed 100% oxygen during the induction of anaesthesia.

Once a patient was positioned on the operating table and connected to the anaesthetic equipment and monitors, an infusion of fentanyl was connected to the patient by a second 21 S.W.G. needle inserted through the injection port of the 23 S.W.G. cannula. The infusion rate of fentanyl was altered according to the individual patient's requirements as described in Chapter Two. A fast flowing (30 - 40 drops per minute) infusion of dextrose 5% or normal saline 0.9% was set up and administered to the patient via an 18 S.W.G. cannula (Quik - Cath, Travenol) inserted into a vein in the dorsum of the opposite hand. Injections of other drugs required during the operations such as atracurium, atropine and neostigmine, were given through the injection port of the fluid administration set. When required, neuromuscular blockade was maintained with an initial

bolus injection of atracurium 400 mcg.kg.^{-1} followed by further bolus increments of 200 mcg.kg.^{-1} administered as described in Chapter Two.

After 30 minutes had elapsed, the infusion rate of propofol was reduced to $0.075 \text{ mg.kg.}^{-1} \text{ min.}^{-1}$ and was continued at that rate until the end of the operation.

Measurements of pulse rate and arterial systolic and diastolic blood pressures were made immediately before induction, at one, two and five minutes after induction and at five minute intervals thereafter, unless more frequent measurements were clinically indicated. Other observations of the quality of induction and maintenance of anaesthesia were carried out as described in Chapter Two. It had been intended to measure arterial carbon dioxide tension levels in the spontaneously breathing patients during and after anaesthesia. This was not carried out due to the difficulty in achieving adequate unaided spontaneous respiration in these patients.

The infusion of fentanyl was switched off at the beginning of wound closure. The infusion of propofol was switched off at the end of wound closure. This latter point was taken to be the beginning of the recovery period. Reversal of neuromuscular blockade, extubation after the onset of adequate spontaneous respiration and then transfer to the recovery area was carried out as described in Chapter Two. Further recovery of the patients was supervised as described in Chapter Two. In particular, the times the patients took to respond to command and to repeat their name and address were recorded. All patients were seen before their return to the

ward, and again 24 - 48 hours later, when the infusion site was inspected and the patients' comments about their anaesthetic experience elicited.

Results

Quality of Induction and Maintenance

Anaesthesia was successfully induced and maintained in all patients. Induction was smooth, there was no evidence of muscle movement or anaphylaxis and only one patient complained of pain on injection. Maintenance of anaesthesia was achieved without difficulty.

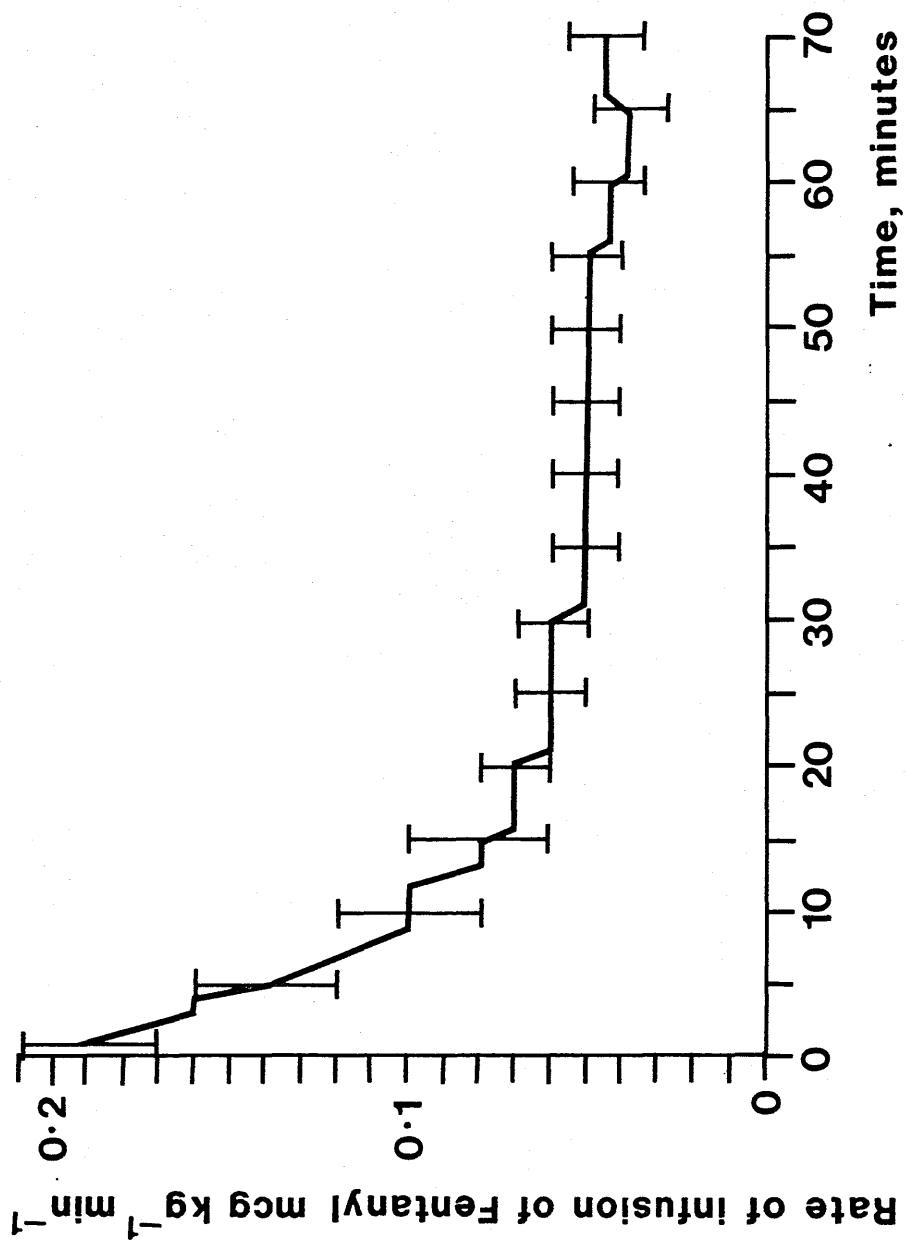
There was no evidence of histamine release during any of the anaesthetics.

Infusion Rates

Propofol was infused as described and switched off at the end of operation once wound suture was complete. The mean duration of infusion was 80 ± 15 minutes. Fentanyl was infused as required to maintain analgesia as shown in Figure Fifteen and switched off at a mean time of 15 ± 2.6 minutes before the end of the operation. The S.E.M. values are shown at five minute intervals. The infusion rate required by the individual patients varied considerably but the mean infusion rate was found to be $0.15 \pm 0.02 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 5 - 6 minutes followed by $0.1 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 8 - 10 minutes and $0.05 \pm 0.003 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The

Fig. 15

**RATE OF INFUSION OF FENTANYL DURING THE FIRST PROPOFOL
INFUSION STUDY**



mean coefficient of variation of the infusion rate was $56 \pm 1.3\%$. The cumulative amount of fentanyl infused in the spontaneously breathing patients compared with the corresponding two-stage etomidate infusion study is shown in Figure Sixteen. The S.E.M. values are shown at five minute intervals.

Cardiovascular Changes

The mean values of the measurements of the arterial systolic and diastolic blood pressures and pulse rates with their associated standard errors of the mean are shown in Figure Seventeen. The mean arterial systolic blood pressure fell during the induction period. This fall was maximal 5 minutes after induction and was statistically significant ($p < 0.05$). This fall did not cause clinical concern and no measures were taken to counteract it. During maintenance anaesthesia the mean systolic pressure returned to pre-induction levels. The mean coefficient of variation for systolic pressure was $9 \pm 2\%$. There were no significant changes in the mean diastolic pressure throughout the duration of anaesthesia. The mean coefficient of variation for the diastolic pressure was $8 \pm 2\%$. The mean pulse rate tended to rise during the induction period and fall again during maintenance anaesthesia, but the changes were not significant, either clinically or statistically. The mean coefficient of variation was $6 \pm 1\%$.

Respiratory Changes

All six spontaneously breathing patients became apnoeic and required manual assistance with ventilation.

Fig. 16

CUMULATIVE AMOUNTS OF FENTANYL INFUSED IN SPONTANEOUSLY BREATHING PATIENTS DURING THE FIRST PROPOFOL INFUSION STUDY, COMPARED WITH THE AMOUNTS INFUSED DURING THE THIRD ETOMIDATE INFUSION STUDY

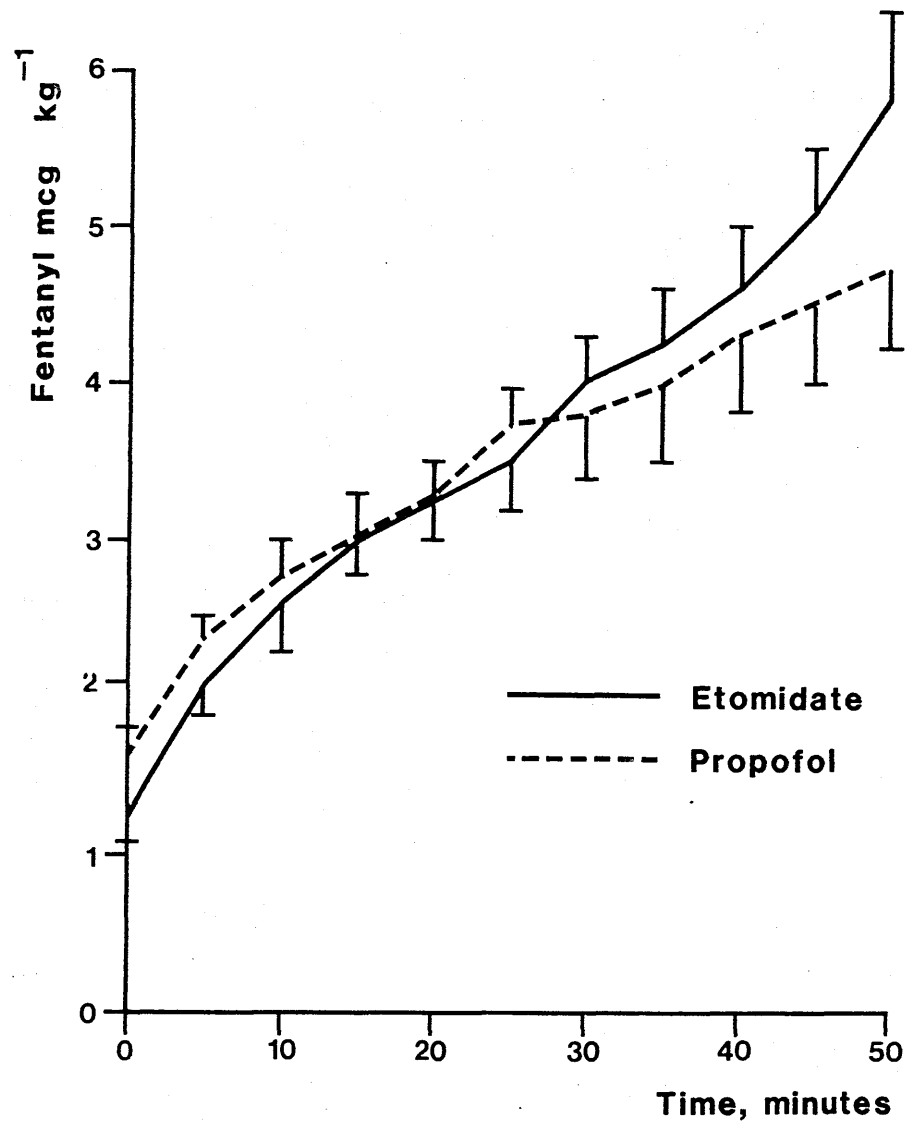
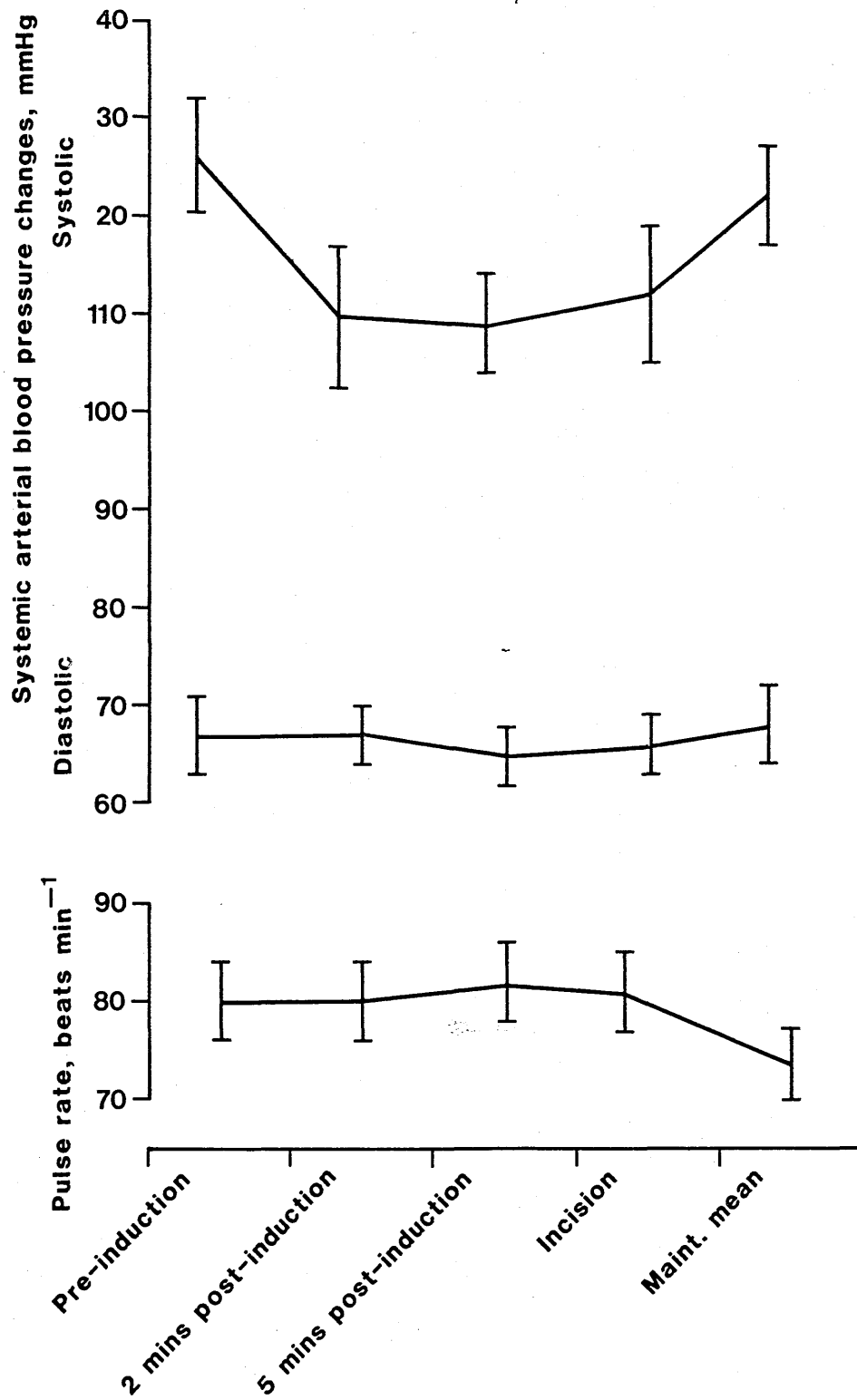


Fig. 17

CARDIOVASCULAR CHANGES DURING THE FIRST PROPOFOL INFUSION STUDY



Recovery

Recovery was rapid. The median time to the patients opening their eyes on command after switching off the propofol infusion was 8 minutes with an interquartile range of 5 - 10 minutes. Patients could repeat their date of birth at a median time of 10 minutes with an interquartile range of 9 - 16 minutes.

Inspection of the infusion site 24 - 48 hours after anaesthesia showed no evidence of venous thrombosis or other complications. No patient gave any evidence of having been aware during the period of anaesthesia.

Conclusions

This propofol infusion study showed that propofol could be used as the hypnotic component of a total intravenous anaesthetic technique. There was little impairment of cardiovascular stability and no muscle movement during the induction or maintenance of anaesthesia. Pain on injection was seen in only one patient. Maintenance of anaesthesia was smooth and recovery was rapid and complete. There was no evidence of any patient being aware during anaesthesia. However the technique was not suitable for spontaneously breathing patients due to the high incidence of apnoea.

Study Twelve

The Second Propofol Infusion Study

The second propofol infusion study was carried out to investigate the effects of an infusion of propofol over a longer period of time. Of particular interest were the effects of a prolonged infusion of propofol on the quality of anaesthesia, the duration of action of atracurium and vecuronium, the possible effects on cardiovascular stability, and the speed of recovery.

Patients and Methods

Thirty eligible patients who were to undergo prolonged peripheral vascular surgery (24), or orthopaedic surgery for the correction of Dupuytren's contracture of the hand (6) were randomly allocated to one of two groups. The premedication, induction, maintenance and monitoring of anaesthesia and the post-operative recovery of the patients were carried out as described in Chapter Two and for the ventilated patients described in Study Eleven. In particular, the same induction dose and infusion rates of propofol were used. As in Studies Nine and Eleven, the infusion rate of fentanyl was varied to meet the individual patient's requirements. The infusions of fentanyl and propofol were switched off at the same end points as described in Study Eleven.

The two major differences between Study Eleven and Study Twelve were the duration of the operations and the administration of

neuromuscular blocking agents. One group of patients was to receive bolus increments of atracurium 190 mcg.kg.^{-1} . The other group was to receive bolus increments of vecuronium 45 mcg.kg.^{-1} . These amounts were chosen as being the E.D. 90 of the drugs (Robertson et al, 1983, a). In the atracurium group 11 patients were to undergo peripheral vascular surgery and 4 were to undergo hand surgery compared with 13 and 2 patients respectively in the vecuronium group.

Neuromuscular blockade was monitored by supramaximal stimulation of the ulnar nerve in the forearm, using a Myotest Mark Two Peripheral Nerve Stimulator to produce a 'train of four' stimuli. The patient's response to the 'train of four' stimuli was assessed both visually and by the anaesthetist feeling the patient's response with his own fingers.

The initial 'train of four' stimuli was administered after the induction of anaesthesia with propofol 2.5 mg.kg.^{-1} . All patients were then intubated which was facilitated by the injection of succinylcholine 1 mg.kg.^{-1} . Once the patient's response to a 'train of four' stimuli had returned to the level observed and felt before the injection of succinylcholine, the first bolus injection of the allocated muscle relaxant was administered. When a response to the second stimulus of a 'train of four' was observed and felt, a further increment of the allocated muscle relaxant was administered.

Results

Composition of the Groups

The mean age and weight of the patients and the duration of

infusion in both groups is shown in Table Twenty Five. There were no statistically significant differences between the groups. The mean duration of infusion was 165 ± 19 minutes with a range of 90 - 300 minutes.

Quality of Induction and Maintenance

Anaesthesia was successfully induced and maintained in all patients. There was no muscle movement, but two patients complained of pain on injection. The quality of anaesthesia was good and easily maintained.

There was no evidence of histamine release in any of the patients anaesthetised during this study.

Infusion Rates

Anaesthesia was successfully maintained in all patients with propofol and fentanyl infused separately. As no statistically significant differences were found when the infusion rates for the two groups were compared, the amounts were combined and are shown in Figure Eighteen. The S.E.M. values are shown at five minute intervals. The rate of infusion of fentanyl varied considerably between patients. The combined mean infusion rate was found to be $0.17 \pm 0.006 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 4 - 10 minutes followed by $0.12 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 12 - 20 minutes and $0.06 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The mean coefficient of variation was $50 \pm 1\%$.

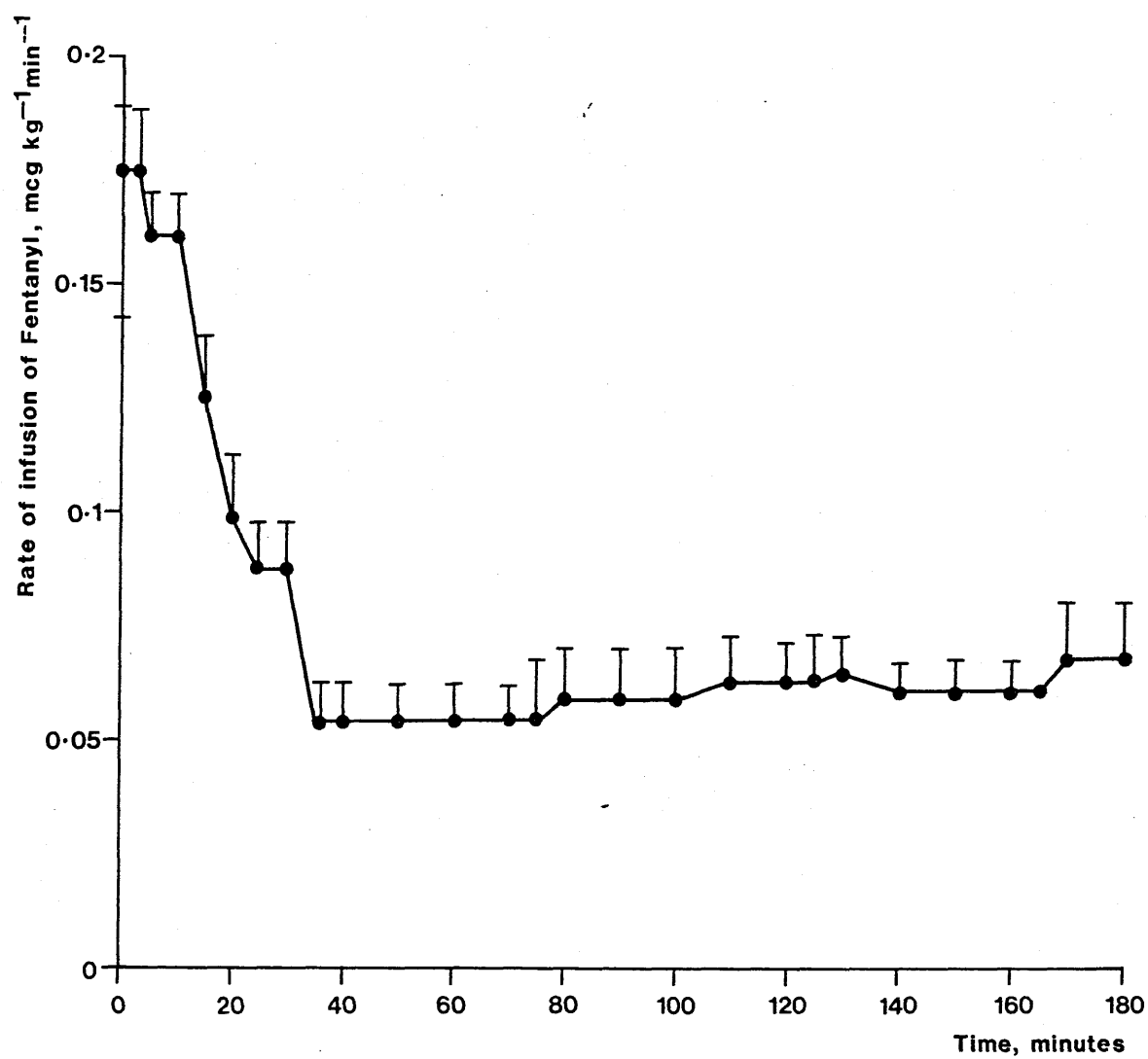
TABLE TWENTY FIVE

DETAILS OF PATIENTS AND DURATION OF INFUSION
IN THE SECOND PROPOFOL INFUSION STUDY.

| | AGE (YRS.) ± S.E.M. | WT. (Kg.) ± S.E.M. | DURATION OF INFUSION (MINS.) ± S.E.M. |
|------------|------------------------|-----------------------|---|
| ATRACURIUM | 62 ± 3 | 65 ± 3 | 156 ± 20 |
| VECURONIUM | 62 ± 2 | 62 ± 4 | 170 ± 20 |

Fig. 18

RATE OF INFUSION OF FENTANYL DURING THE SECOND PROPOFOL INFUSION STUDY



Cardiovascular Changes

The cardiovascular changes were similar in each group. The combined mean values of the measurements of the arterial systolic and diastolic blood pressures and pulse rates with their associated standard errors of the mean are shown in Figure Nineteen. The value of the mean arterial systolic pressure fell during the induction period. This fall was statistically significant ($p < 0.01$) after five minutes and also at incision but did not give rise to clinical concern. During maintenance anaesthesia there was a gradual return to the pre-induction values. The mean coefficient of variation during anaesthesia was $12 \pm 1\%$. The value of the mean arterial diastolic pressures showed little change during induction, but the mean value of the maintenance diastolic pressure was significantly higher ($p < 0.05$) when compared with the pre-induction value. The mean coefficient of variation of the diastolic pressure was $11 \pm 1\%$. The mean pulse rate changed little but tended to fall during maintenance anaesthesia. These changes were not statistically significant. The mean coefficient of variation was $8 \pm 2\%$.

Requirements for Muscle Relaxant

The duration of action of each increment of muscle relaxant is shown in Figure Twenty. The duration of action of atracurium was relatively constant, whereas the duration of action of vecuronium tended to increase. This increase was only statistically significant for the fourth ($p < 0.02$) and fifth ($p < 0.01$) increments.

Fig. 19

CARDIOVASCULAR CHANGES DURING THE SECOND PROPOFOL INFUSION STUDY

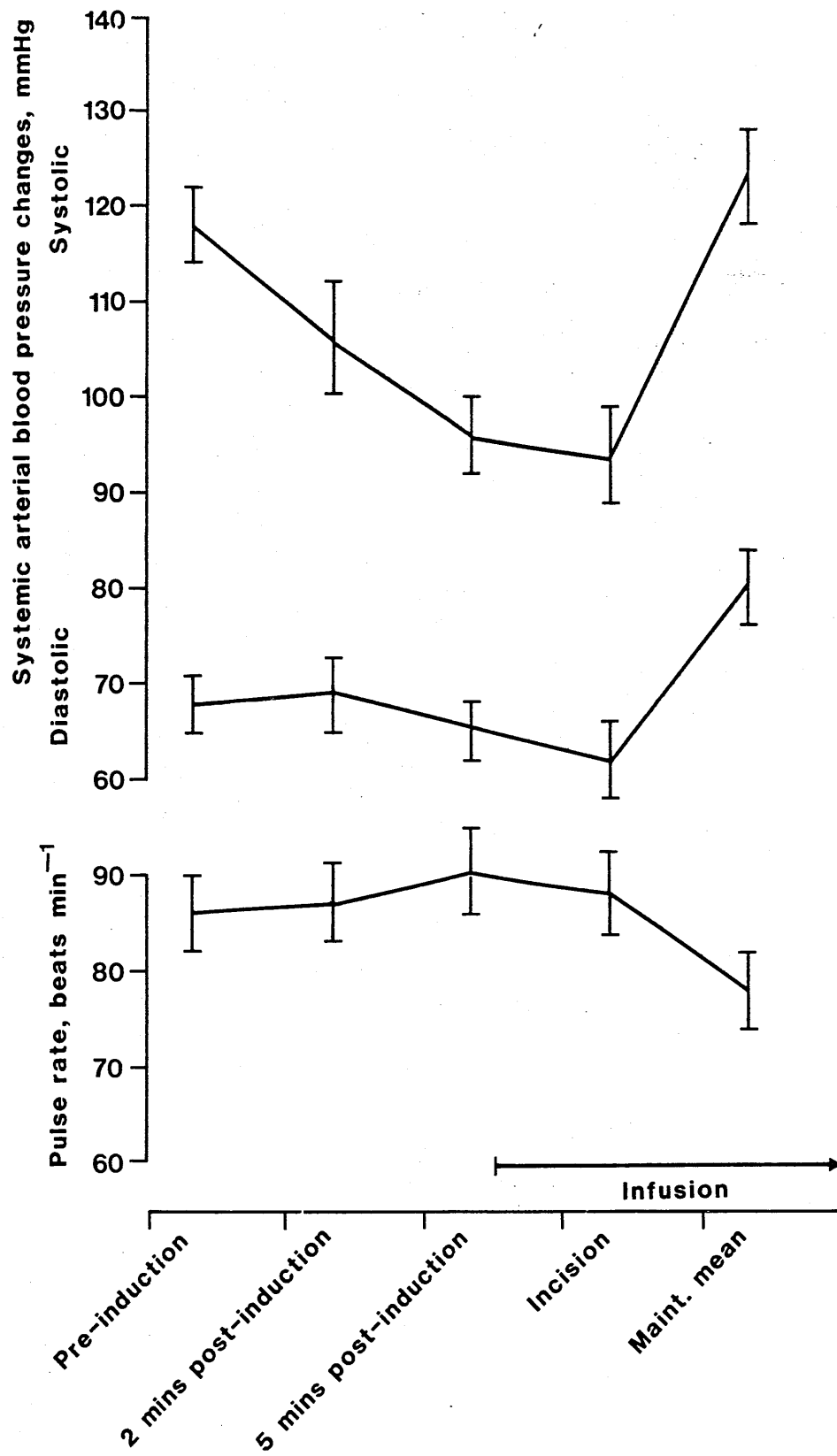
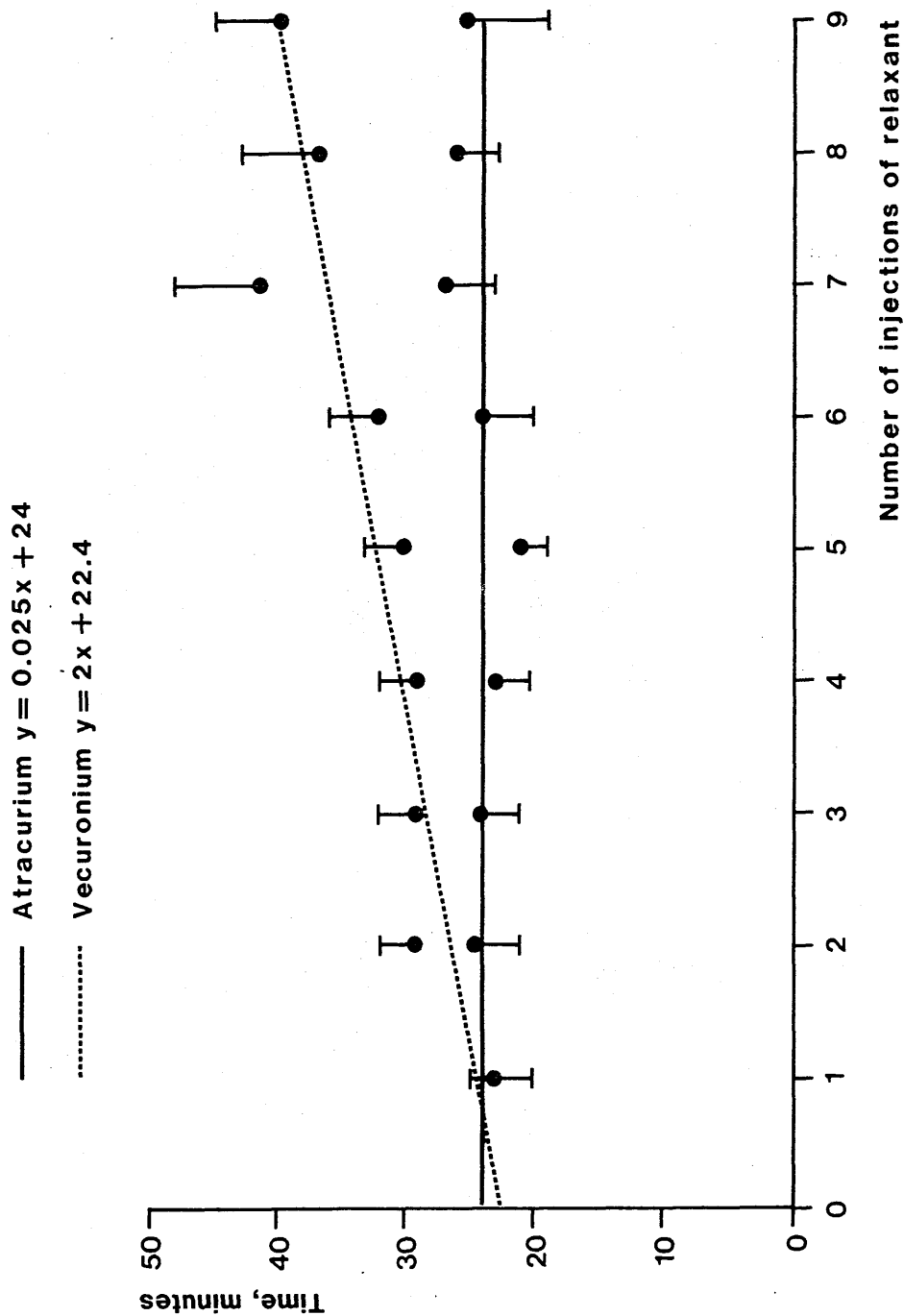


Fig. 20

DURATION OF ACTION OF REPEATED BOLUS INJECTIONS OF ATRACURIUM AND VECURONIUM IN THE SECOND PROPOFOL INFUSION STUDY



Recovery

The time to recovery was very similar in both groups and the difference was not statistically significant. The results for both groups were combined. The fentanyl infusion was switched off at a mean time of 21 ± 3 minutes before wound closure. The infusion of propofol was switched off after wound suture had been completed. The median time to opening of eyes on command after stopping the infusion of propofol was 10 minutes with an interquartile range of 6 - 17 minutes. The median time to recall of date of birth was 17 minutes with an interquartile range of 12 - 24 minutes.

Inspection of the infusion site 24 - 48 hours after anaesthesia showed no evidence of venous thrombosis or other complications in any patient. No patient gave any evidence of having been aware during the period of anaesthesia.

Conclusions

The infusion scheme of propofol used was effective and easy to use, particularly in ventilated patients. Two patients complained of pain on injection. Falls in systolic arterial blood pressure did not give rise to clinical concern, and readily reversed spontaneously. There was some evidence that there was progressive prolongation of the action of vecuronium compared with that of atracurium. Recovery was rapid and uncomplicated. There was no evidence that any patient was aware during the period of anaesthesia.

CHAPTER TEN

SUMMARY OF RESULTS

Study One

Induction with Etomidate in Phosphate and Water

1. The groups were very similar in weight and sex distribution. One group was younger than the other two groups. This difference was statistically significant ($p < 0.02$). The mean age of the groups was 56.5 years.
2. Anaesthesia was successfully induced in all patients.
3. No clinically or statistically significant changes in mean arterial systolic or diastolic blood pressures or pulse rates were observed during the induction of anaesthesia.
4. No evidence of severe respiratory depression, in particular, no significant apnoea was observed in any group.
5. There was no evidence of histamine release in any patient in this study.

Study Two

Comparison of Induction with Etomidate in Phosphate and Water with Propanidid

1. There were no statistically significant differences in age, weight or sex distribution in any group. The mean age of the groups was 56 years.

2. Anaesthesia was successfully induced in all patients.
3. No clinically or statistically significant changes in the mean arterial systolic or diastolic blood pressures or pulse rates were observed during the induction period in the etomidate groups who had been premedicated with atropine. There was a statistically significant ($p < 0.01$) fall in the mean arterial systolic blood pressure in the propanidid group during induction. No significant changes were observed in the mean arterial diastolic pressures or pulse rates in any group during induction. The mean pulse rates in the group which had not been premedicated with atropine were statistically significantly slower than the mean pulse rates in the other groups throughout the induction and maintenance of anaesthesia ($p < 0.01$).
4. There was no evidence of severe respiratory depression, in particular, no apnoea was seen in any group.
5. Recovery from anaesthesia was rapid in all groups, with mean times ranging from 6 to 8 minutes. There was no difference clinically between the groups. The group who had received etomidate over 15 seconds and had been premedicated with atropine recovered faster than the group who had received etomidate over 30 seconds. This difference was statistically significant ($p < 0.05$).
6. There was no evidence of histamine release in any patient in this study.

7. The incidence of complications observed during induction during both etomidate studies were combined. The overall incidence of pain on injection was 24% (37/152) and muscle movement was 29% (44/152). Both these results were statistically significantly ($p < 0.0001$) higher than their incidence in the propanidid group which was zero.

Patients who had etomidate injected over 15 seconds had an incidence of pain on injection of 13% (8/62) and an incidence of muscle movement of 14.5% (9/62). Patients who had etomidate injected over 30 seconds had an incidence of pain on injection of 33% (19/58) and of muscle movement of 43% (25/58). Patients who had etomidate injected over 60 seconds had an incidence of pain on injection of 31% (10/32) and muscle movement of 31% (10/32). The incidence of both pain on injection and muscle movement were statistically significantly lower ($p < 0.025$) in the group which received etomidate over 15 seconds compared with the other two groups which had also received etomidate.

8. The overall incidence of nausea and vomiting was 7.5%. Two patients who had received etomidate had hallucinations and one had an epileptiform fit.

Study Three

Induction with Etomidate in Polyethylene Glycol

1. There were no statistically significant differences in age,

weight or sex distribution between the groups. The mean age of the groups was 58 years.

2. Anaesthesia was successfully induced in all patients.
3. The incidence of pain on injection was 4% (1/25) in both groups. The incidence of muscle movement in the group receiving etomidate over 15 seconds was 16% (4/25) compared with 20% (5/25) in the group receiving etomidate over 30 seconds. This difference was not statistically significant.
4. Cardiovascular changes during the induction period were found to be minimal in both groups.
5. No evidence of respiratory depression, in particular apnoea, was seen in either group.
6. Recovery was rapid in both groups. The mean time to recovery in the group receiving etomidate over 15 seconds was 4.5 minutes compared with a mean time of 5.0 minutes in the group receiving etomidate over 30 seconds. This difference was not statistically significant.
7. The overall incidence of nausea and vomiting was 8%.
8. There was no evidence of histamine release in any patient in this study.

Study Four

Induction with Etomidate in Propylene Glycol compared with Methohexitone

1. There were no statistically significant differences in age, weight, or sex distribution between the groups. The mean age of the groups was 56.5 years.
2. Anaesthesia was successfully induced in all patients.
3. The incidence of pain on injection was 4% (2/50) in the etomidate group and 6% (3/50) in the methohexitone group. The incidence of muscle movement was statistically significantly higher ($p < 0.01$) in the etomidate group at 22% (11/50) compared with 0% (0/50) in the methohexitone group.
4. Cardiovascular changes during the induction period were found to be minimal in both groups.
5. No serious respiratory depression, in particular apnoea, was seen in either group.
6. Recovery was rapid in both groups, the mean time to recovery in the etomidate group was 4.5 minutes compared with a mean time of 4.0 minutes in the methohexitone group. This difference was not statistically significant.
7. The incidence of nausea and vomiting was 6% in the etomidate

group and 4% in the methohexitone group. This difference was not statistically significant.

8. There was no evidence of histamine release in any patient in this study.

Study Five

Induction with Etomidate and Alfentanil

1. There were no statistically significant differences in age or weight distribution between the groups. The mean age of the groups was 33 years.
2. Anaesthesia was successfully induced in all patients.
3. There was no spontaneous complaint of pain on injection in the alfentanil group but the incidence was 48% (12/25) in the control group. The incidence of muscle movement was 4% (1/25) in the alfentanil group and 80% (20/25) in the control group. Both these differences were statistically significant ($p < 0.001$)
4. Cardiovascular changes during the induction period were minimal in both groups.
5. Recovery was rapid in both groups, the mean time to recovery in the control group was 8.0 minutes compared with 4.0 minutes in the alfentanil group. This difference was

statistically significant ($p < 0.01$).

6. Eight per cent of patients were nauseated or vomited in the control group compared with 16% in the patients who received alfentanil. This difference was not statistically significant.
7. There was no evidence of histamine release in any patient in this study.

Study Six

Induction with Propofol and Comparison with Thiopentone

1. There were no statistically significant differences in age, weight, or sex distribution between the groups. The mean age of the groups was 35 years.
2. Anaesthesia was successfully induced in all patients.
3. The incidence of pain on injection when propofol was administered via the dorsum of the hand was 37.5% (15/40) and 22.5% of patients in this group (9/40) had other sensations. The overall incidence of venous sensation was 60% (24/40) in this group.

When administered via a vein in the antecubital fossa, the incidence of pain was statistically significantly reduced ($p < 0.001$) to 2.5% (1/40) and the incidence of other

sensations was reduced to 17.5% (7/40). The overall incidence of sensation in this group was 20% (8/40).

When lignocaine was pre-administered into a vein in the dorsum of the hand, the incidence of pain was 17.5% (7/40). This reduction in the incidence of pain of injection was not statistically significant when compared with the group receiving propofol in the dorsum of the hand. The incidence of other sensations in this group was 22.5% (9/40). The overall incidence of sensation was 40% (16/40).

In the thiopentone group, the incidence of pain on injection was 7.5% (3/40). This was statistically significantly less ($p < 0.01$) than the incidence of pain on injection of propofol in the dorsum of the hand. The incidence of other sensations was 20% (8/40). The overall incidence of venous sensation in this group was 27.5% (11/40).

The incidence of muscle movement was 10% (4/40) when propofol was administered via the dorsum of the hand and ranged from 2.5% (1/40) to 5% (2/40) in the other groups. These differences were not statistically significant.

4. All groups showed a statistically significant fall in the mean arterial systolic blood pressure during the induction period ($p < 0.01$). The rise in the mean pulse rate during the induction period was not statistically significant in the propofol groups, but there was a statistically significant rise in the mean pulse rate in the thiopentone group ($p < 0.01$).

There were no statistically significant changes in the mean arterial diastolic pressure in any group after induction.

5. A high incidence of apnoea of short duration was seen in the propofol groups, ranging from 52.2% (21/40) to 77.5% (31/40) compared with 45% (18/40) in the thiopentone group. The overall incidence of apnoea in the thiopentone group was statistically significantly ($p < 0.01$) lower compared with the overall incidence of apnoea in the groups receiving propofol. The incidence of apnoea lasting longer than 60 seconds was similar in all groups.
6. There was no evidence of histamine release in any patient in this study.

Study Seven

Etomidate Infusion with Bolus Etomidate Induction

1. The mean age of the ventilated group was 62 years and the mean age of the spontaneously breathing group was 46 years.
2. Anaesthesia was successfully induced and maintained in 100 of the 105 patients in this study.
3. The incidence of pain on injection was 9.4% (10/106) and 4.7% of patients (5/106) had other venous sensations. The overall incidence of venous sensation was 14% (15/106). The

incidence of severe muscle movement was 11% (6/55) and the incidence of mild to moderate muscle movement was 14.5% (8/55). The overall incidence of muscle movement was 25% (14/55).

4. Unsatisfactory anaesthesia occurred in 5.5% (3/55) of patients in the spontaneously breathing group due to prolonged muscle movement which caused the proposed infusion anaesthetic to be abandoned.
5. The mean infusion rate was $20.5 \pm 1.8 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of etomidate and $0.057 \pm 0.0055 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ of fentanyl. The mean coefficient of variation of the infusion rate was $33 \pm 1.2\%$ for the infusion group and $66 \pm 1.1\%$ for the spontaneously breathing group.
6. Cardiovascular changes in both groups were small during the induction and maintenance of anaesthesia. Only the mean coefficient of variation for the pulse rate in the ventilated group was greater than 10% (10.6%).
7. Manual assistance with ventilation was required by 14.5% of patients (8/55) in the spontaneously breathing group. The mean arterial carbon dioxide tension rose from a pre-induction mean level of 5.2 kPa to a mean intra-operative level of 6.4 kPa. This rise was statistically highly significant ($p < 0.001$). Fifteen minutes after the end of operation this value had fallen slightly to a mean level of 6.1 kPa.

8. The median time to recovery was 5 minutes in the ventilated group compared with a median time of 15 minutes in the spontaneously breathing group. This difference was statistically significant ($p < 0.01$). One (1/51) patient in the ventilated group had not recovered within 30 minutes compared with seven (7/55) patients in the spontaneously breathing group.
9. There was no evidence of histamine release in any patient.
10. Nausea or vomiting occurred in 4.6% (5/105) of patients.
11. Two patients had marked venous thrombophlebitis around the infusion site 24 - 48 hours after anaesthesia.
12. No patient appeared to be aware during anaesthesia.

Study Eight

Etomidate Infusion with Bolus Thiopentone Induction

1. The mean age of both groups of the ventilated patients was 55 years. The mean age of both groups of the spontaneously breathing patients was 47 years.
2. Anaesthesia was successfully induced and maintained in all patients in this study.
3. Pain on injection and muscle movement was not found in any group.

4. The mean infusion rate was 20.0 ± 1.6 mcg.kg.⁻¹ min.⁻¹ of etomidate and 0.056 ± 0.0045 mcg.kg.⁻¹ min.⁻¹ of fentanyl. The mean coefficient of variation of the infusion rate was $62 \pm 3.3\%$ for the ventilated group and $74 \pm 3.1\%$ for the spontaneously breathing group.
5. Cardiovascular changes during the induction and maintenance of anaesthesia in both etomidate groups were slight. Statistically significant falls in the mean arterial systolic blood pressure during the induction period were seen in the I.P.P.V. control group ($p < 0.02$) and in the spontaneously breathing control group ($p < 0.05$). There were no statistically significant changes in the mean arterial diastolic blood pressures or pulse rates during the induction and maintenance of anaesthesia in the control groups. All mean coefficients of variance were less than 11%.
6. Manual assistance was required by 20% of patients (10/50) in the spontaneously breathing group receiving etomidate infusion. Such assistance was not required by any patient in the corresponding control group. The mean arterial carbon dioxide tension rose from a pre-induction mean level of 5.2 kPa to a mean intra-operative level of 6.5 kPa in the etomidate group and from a mean pre-induction level of 5.2 kPa to a mean intra-operative level of 7.1 kPa in the control group. These rises were statistically highly significant ($p < 0.001$). Fifteen minutes after the end of operation these values had fallen slightly to a mean level of 6.1 kPa. in the etomidate group; and to a mean level of 6.2 kPa in the control group.

7. The median time to recovery was 7 minutes in the ventilated etomidate group. In the ventilated control group the median time to recovery was 6 minutes. This difference was not statistically significant. Five (5/50) patients in the ventilated etomidate group had not recovered within 30 minutes compared with one (1/50) patient in the control group. In the spontaneously breathing groups, the median time to recovery was 25 minutes in the etomidate group compared with a median time of 18 minutes in the control group. This difference was statistically significant] different ($p < 0.05$). Fourteen (14/50) patients in the spontaneously breathing etomidate group had not recovered within 30 minutes compared with 3 (3/50) in the spontaneously breathing control group.
8. The incidence of nausea and vomiting was 4% in the etomidate groups compared with 6% in the control groups.
9. There was no evidence of histamine release in any patient in this study.
10. The mean time to the first administration of post-operative intramuscular analgesia was 6.9 hours in the etomidate groups compared with a mean time of 6.4 hours in the control groups. This difference was not statistically significant.
11. Twenty two percent of patients (22/100) had evidence of venous damage 24 - 48 hours after the infusion of etomidate, compared with 10% (10/100) in the control group. This difference was statistically significant ($p < 0.02$).

12. No patient appeared to be aware during anaesthesia.

Study Nine

Etomidate Infusion for Induction and Maintenance

1. The mean age of the patients in the ventilated groups was 52 years. The mean age of the patients in the spontaneously breathing groups was 48.5 years.
2. Anaesthesia was successfully induced and maintained in all patients in this study.
3. The incidence of pain on injection was 4% (4/100) and tingling occurred in a further 14. Mild muscle movement was seen in 12% (6/50) of patients. No pain on injection or muscle movement occurred in any patients in the control groups.
4. The infusion rate of etomidate was $100 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for the first 10 minutes followed by $10 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The mean time for the onset of hypnosis was $103 \pm$ seconds. The mean infusion rate of fentanyl was found to be $0.23 \pm 0.015 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 3 - 4 minutes followed by $0.1 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 8 - 9 minutes and $0.05 \pm 0.003 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The mean coefficient of variation of the infusion rate was $54 \pm 1.3\%$ for the ventilated group and $51 \pm 3.1\%$ for the spontaneously breathing group.
5. The cardiovascular changes in both etomidate groups were minimal during the induction and maintenance of anaesthesia.

Statistically significant falls in the mean arterial systolic blood pressure in the ventilated control group ($p < 0.05$) and in the control spontaneously breathing group ($p < 0.01$) were seen during the induction period. There were no significant changes in the mean diastolic blood pressures or pulse rates in the control groups during the induction period. No significant changes in the mean arterial systolic or diastolic blood pressures or pulse rates occurred during maintenance anaesthesia in any group. All mean coefficients of variance were less than 10%.

6. Four (4/50) patients required manual assistance in the spontaneously breathing group which had received etomidate infusion. Such assistance was not required by any patient in the corresponding control group. The mean rise in the level of the arterial carbon dioxide tension was from a pre-induction mean of 5.1 kPa to an intra-operative mean level of 6.6 kPa. in the etomidate group and from a mean pre-induction level of 5.1 kPa to a mean intra-operative level of 6.5 kPa. in the control group. These rises were statistically highly significant ($p < 0.001$). Fifteen minutes after the end of operation these values had fallen slightly to a mean of 6.1 kPa. in both groups.
7. The median time to recovery was 8 minutes in both ventilated groups. All patients were awake within 30 minutes. In the spontaneously breathing groups, the median time to recovery was 15 minutes in the etomidate group compared with a median of 23 minutes in the control group. This difference was statistically significant ($p < 0.01$). Four (4/50) patients

in the etomidate group and 6 (6/50) patients in the control group had not recovered within 30 minutes.

8. Four patients who had received an infusion of etomidate showed the presence of myoclonic movements for up to 45 minutes after the end of infusion.
9. The incidence of nausea and vomiting in the etomidate groups was 5% compared with 7% in the control groups.
10. There was no evidence of histamine release in any patient in this study.
11. The mean time to the first administration of analgesia was 6.2 hours in the control groups compared with a mean time of 5.8 hours in the etomidate infusion groups. This difference was not statistically significant.
12. Three (3/100) patients in the etomidate groups showed evidence of venous damage, one of which lasted for several months. This patient had received a 0.5% solution of etomidate
13. No patient appeared to be aware during anaesthesia.

Study Ten

Etomidate Infusion and Hepatic and Renal Function

1. Neither infusion scheme was found to cause adverse effects

on renal or hepatic function when compared with a standard anaesthetic technique.

Study Eleven

The First Propofol Infusion Study

1. The mean age of the group was 59 years.
2. Anaesthesia was successfully induced and maintained in all patients in this study.
3. The incidence of pain on injection was 6.7% (1/15).
4. The infusion rate of propofol was initially $150 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 30 minutes followed by $75 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. Fentanyl was infused separately. The mean infusion rate of fentanyl was found to be $0.15 \pm 0.02 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 5 - 6 minutes followed by $0.1 \pm 0.005 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 8 - 10 minutes and $0.05 \pm 0.003 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter. The mean coefficient of variation of the infusion rate was $56 \pm 1.3\%$.
5. The mean arterial systolic blood pressure fell during the induction period. This fall was statistically significant ($p < 0.05$). The mean arterial diastolic blood pressure and pulse rate did not change significantly during the induction and maintenance of anaesthesia. All the mean coefficients of variance were less than 10%.

6. All six spontaneously breathing patients required manual assistance with ventilation.
7. There was no evidence of histamine release in any patient in this study.
8. The median time to early recovery was 8 minutes and the median time to recall of the date of birth was 10 minutes.
9. No evidence of venous damage was evident 24 - 48 hours after infusion.
10. No patient appeared to be aware during anaesthesia.

Study Twelve

The Second Propofol Infusion Study

1. There were no statistically significant differences in age, weight, sex distribution or duration of infusion between the groups. The mean age of the groups was 62 years.
2. Anaesthesia was successfully induced and maintained in all patients in this study.
3. The incidence of pain on injection was 6.7% (2/30).
4. The infusion of propofol was initially $150 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 30 minutes followed by $75 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ thereafter.

There were no statistically significant differences between the infusion rates of fentanyl in the two groups. The combined mean rate of infusion of fentanyl was found to be 0.17 ± 0.006 mcg.kg.⁻¹ min.⁻¹ for 4 - 10 minutes followed by 0.12 ± 0.005 mcg.kg.⁻¹ min.⁻¹ for 12 - 20 minutes and 0.06 ± 0.005 mcg.kg.⁻¹ min.⁻¹ thereafter. The mean coefficient of variation of the infusion rate was $50 \pm 1.0\%$.

5. The mean arterial systolic pressure fell after induction. This fall was statistically significant ($p < 0.01$). There were no significant changes in the mean diastolic blood pressure during the induction period of anaesthesia, but the maintenance mean of the diastolic pressure was statistically significantly higher than the induction levels ($p < 0.05$). There were no statistically significant changes in the mean pulse rate during the induction and maintenance of anaesthesia. The highest mean coefficient of variation was 12%.
6. There appeared to be an increase in the duration of action of consecutive bolus increments of vecuronium compared with those of atracurium. These differences were statistically significant when the fourth ($p < 0.02$) and fifth ($p < 0.01$) increments of the two drugs were compared.
7. The times to recovery after the infusions of propofol were switched off were very similar in the two groups. The median time to early recovery was 10 minutes and to recall of date of birth was 17 minutes.

8. No evidence of venous damage was evident 24 - 48 hours after infusion.
9. No patient appeared to be aware during anaesthesia.

CHAPTER ELEVEN

DISCUSSION OF ETOMIDATE AND PROPOFOL
FOR THE INDUCTION OF ANAESTHESIA

Introduction

During the induction studies described in Chapters Three, Four, Five and Six, many of the advantages and disadvantages of etomidate and propofol for the induction of anaesthesia became apparent.

Etomidate

Induction Dosage

The early German studies (Doenecke et al, 1973; 1974) suggested that etomidate was a short acting agent with an optimum induction dose of 0.3 mg.kg.^{-1} . Early British and American induction studies (Studies One to Four; Morgan, Lumley and Whitwam, 1975; Kay, 1976; Holdcroft et al, 1976; Gooding and Corssen, 1976; Fragen, Caldwell and Brunner, 1976; Ghoniem and Yamada, 1977) confirmed that this dose was suitable for induction and this has remained so despite changes in formulation.

Cardiovascular Changes

The induction studies of etomidate showed it to be cardiovascularly stable using the standard induction dose of 0.3 mg.kg.^{-1} . None of the patients in any study described in this thesis who were anaesthetised with etomidate, regardless of formulation or rate of injection, showed a marked drop in arterial pressure. Similar findings of cardiovascular stability using the same dose have been described by other workers (Brückner et al, 1974; Morgan, Lumley and Whitwam, 1975;

Kay, 1976; Holdcroft et al, 1976; Gooding and Corssen, 1976; Fragen, Caldwell and Brunner, 1976; Ghoneim and Yamada, 1977). Invasive studies in fit volunteers (Gooding and Corssen, 1977; Patsche et al, 1977) and in patients with known cardiac disease (Hemplemann et al, 1974, a; Gooding et al, 1979; Tarnow, Hess and Klein, 1980) have also reported minimal cardiovascular depression with etomidate. In Study Seven, the use of a higher dose, 0.46 mg.kg.^{-1} of etomidate showed no adverse effects on cardiovascular stability.

However, some clinical studies have described small negative inotropic effects (Rifat, Gamulin and Gemperle, 1975; Colvin et al, 1979; Criado et al, 1980) and two cases of severe cardiac complications, attributed either to etomidate or to propylene glycol, have been reported (Van Den Hurk and Teijen, 1983). A negative inotropic effect on papillary muscle both in rabbits (Komai, Dewitt and Rusy, 1985) and dogs (Kissen et al, 1983) has been demonstrated as well as a direct chronotropic depressant effect in cats when the baroreceptors are denervated (Skovsted and Saphavichakul, 1977). The cardiovascular stability of etomidate may be due to the lack of inhibition of baroreceptor function (Hughes and McKenzie, 1978; Bernards, Marrone and Priano, 1985). Unlike methohexitone, ketamine and althesin, etomidate has not been shown to inhibit efferent cardiac vagal drive in cats (Inoue and Arndt, 1982) possibly accounting for the lack of tachycardia associated with its use.

Respiratory Changes

Respiratory stability, particularly the short duration of

any apnoea, was described in Chapters Three and Four. Similar findings of respiratory stability have been described by other investigators (Morgan, Lumley and Whitwam, 1975; Zacharias et al, 1978; Kay, 1979). Small changes in blood carbon dioxide gas tensions have been reported ranging from 5% (Gooding et al, 1979), 8% Carlos and Innerarity, 1979) to 14% (Colvin et al, 1979). This lack of respiratory depression may be due, in part, to carbon dioxide independent stimulation of ventilation (Choi et al, 1985).

Anaphylactic Reactions

No patient in any etomidate induction or infusion study showed any evidence of histamine release. The reported incidence of anaphylactic reactions to etomidate has been very low (Watkins, 1983; 1985). Some histaminoid reactions have occurred in the peri-operative period with widespread urticaria. Two cases with generalised erythema have been reported (Krumholz et al, 1984; Sold and Rothhammer, 1985). In the second case, skin testing was positive for etomidate only. Asthmatic patients have been shown to release significantly higher amounts of histamine than normal patients after provocation with althesin, but not with etomidate (Guldager et al, 1985).

Complications

During the clinical investigations of etomidate, certain disadvantages became apparent. The complications which gave concern were pain on injection, muscle movement, emergent psychosis and venous sequelae.

Pain on Injection

Pain on injection was a particular problem with the initial formulation of etomidate (Studies One and Two). The overall incidence of pain on injection was 24%. Other authors found an incidence ranging from 15% (Morgan, Lumley, and Whitwam, 1975; O'Carroll et al, 1977, a) 40% - 50% (Zacharias et al, 1978), 50% (Gooding and Corssen, 1976; Fragen, Caldwell and Brunner, 1976) to 81% when injected via the dorsum of the hand (Holdcroft et al, 1976

Reformulation in polyethylene glycol reduced the incidence of pain compared with the original formulation. The incidence varied from 4% (Study Three), to 6% (Van Dijk, 1978) to 24 - 30% (Zacharias et al, 1978).

The final formulation in propylene glycol was also found to have a 4% incidence of pain on injection compared with 6% for methohexitone (Study Four). Fragen and Caldwell (1979) also found a marked reduction in the incidence of pain to around 10%. Higher figures have been reported, 17% (Helmers, Adam and Giezen, 1981); 25% (Van Eeden, 1980); 25 - 35% (Zacharias et al, 1978); and 68% (Yelavich and Holmes, 1980).

The incidence of pain in the control group of Study Five (etomidate and alfentanil) was much greater (48%) than that found in the earlier studies, although all the studies were unpremedicated. The patients in this study were younger with a mean age of 33 years compared with a mean age of 60 years in the earlier studies and were female compared with the predominately male older groups.

Mixing lignocaine with etomidate had little effect in children (Kay, 1976), but showed some benefit in adults (Brown and Moss, 1981). Some authors found that the pain was reduced by administration via the antecubital fossa (Holdcroft et al, 1976; Kay 1976). Increasing or slowing the rate of injection reduced both pain and muscle movement (Studies One, Two, Three and Nine). Intralipid has been used as a solvent for etomidate with a marked reduction in the incidence of pain on injection and venous thrombosis to 2% (Gran et al, 1983).

Muscle Movement

The overall incidence of muscle movement using the original formulation was 29%. Other estimations of muscle movement have ranged from 25% (Morgan, Lumley and Whitwam, 1975; Gooding and Corssen, 1976) to 65% (Holdcroft et al, 1976); 70% (Fragen, Caldwell and Brunner, 1976) and 70 -75% (Zacharias et al, 1978).

Changing the solvent to polyethylene glycol did not significantly lower the incidence of muscle movement (16%) compared with the original formulation (Study Three). A similar lack of reduction (80%) has been reported by other investigators (Zacharias et al, 1978; Van Dijk, 197

Reformulation in propylene glycol had no effect on the incidence of muscle movement (22%), (Study Four). A variable, but high incidence of muscle movement has been reported from many authors using this formulation. These range from 10% (Fragen and Caldwell, 1979), 38% (Helmers, Adam and Giezen, 1981), 50% (Yelavich and Holmes, 1980), 70% (Copeland, Howell and Ryan, 1981) to 85% - 95%

(Zacharias et al, 1978). Thus the changes in formulation do not appear to significantly reduce the incidence of involuntary muscle movement after bolus injection. Altering the rate of injection had little effect on the incidence of muscle movement (Studies One, Two, Three and Nine). In Study Nine where the induction dose was infused, the incidence of muscle movement was reduced to 12%, with a lack of severe muscle movement. A similar lack of change with different formulations has been reported by Zacharias et al (1978), as has the injection of different dosages over a constant period of time (Holdcroft et al, 1976).

As with the pain on injection, a very high - 80% incidence of muscle movement was seen in the control group of Study Five. Although the incidence of muscle movement was high, it was not found to be dangerous and was easily controlled by the administration of halothane.

Movements in the post-operative period after induction with etomidate have been reported (McIntosh et al, 1979; Tasch, 1985) possibly due to earlier recovery of the extrapyramidal system compared with the cerebral cortex (Laughlin and Newberg, 1985).

Recovery

Recovery in the patients receiving etomidate (Studies One to Four) was rapid and this has been confirmed by other investigators, both in adults (Morgan, Lumley and Whitwam, 1975; Gooding and Corssen, 1976; Fragen, Caldwell and Brunner, 1976) and in children (Kay, 1976).

The incidence of nausea and vomiting in these studies was low at 5%. Higher incidences have been reported varying from 28% (Holdcroft et al, 1976); 40% (Yelanovitch and Holmes, 1980) and 40 - 55% regardless of formulation (Zacharias et al, 1978). Several reports have commented on the occurrence of emergent dysphoria or delirium - 12% (Chiu and Van, 1978), 25% (Yelavitch and Holmes, 1980).

Long Term Venous Damage

The incidence of venous thrombosis fourteen days after etomidate administration has been found to vary from 24% (4% for thiopentone) (Schou Olsen, Huttel and Hole, 1984) to 43% (20% for thiopentone) (Kortilla and Aromaa, 1980). Although there are no figures available in this thesis concerning long term venous damage several patients complained of severe prolonged venous thrombosis either after receiving a bolus dose for induction or after prolonged infusion, regardless of formulation.

Effect of Premedication

Pain on Injection

After intramuscular opiate premedication and intravenous fentanyl given immediately before induction, the incidence of pain in the first etomidate infusion study (Study Seven), using a bolus injection of etomidate (0.46 mg.kg.^{-1}) for induction, increased to 9%, and a further 5% of patients complained of tingling, compared with the 4% incidence of pain described in the fourth induction study. Other studies of the influence of premedication have given

conflicting results. Reduction of the incidence of pain with opiates has been described in some studies (Holdcroft et al, 1976; Kay, 1976; Gooding and Corssen, 1976; Zacharias et al, 1979). Other studies (Carlos and Innerarity, 1979; Kortilla, Tammisto, and Aromaa, 1979; Helmers, Adam and Giezen, 1981) have not. Using the same premedication as in Study Seven, a rapid infusion of etomidate in alcohol and saline (Study Nine) reduced the incidence of pain to 4% but there was a higher incidence of tingling of 14%, suggesting that infusion of etomidate reduced the intensity of the pain rather than the incidence. Intravenous alfentanil significantly reduced the spontaneous complaint of pain (Study Five) but no such difference was found by Collin, Drummond and Spence (1986).

Muscle Movement

Intravenous fentanyl or diazepam reduced the incidence of muscle movement (Gooding and Corssen, 1976; Carlos and Innerarity, 1979; Kortilla, Tammisto and Aromaa, 1979; Helmers, Adam and Giezen, 1981) as did intramuscular pethidine (Zacharias et al, 1979). In Study Seven, intramuscular opiate premedication and a bolus dose of 1.3 mcg.kg.^{-1} of fentanyl immediately before a bolus injection of etomidate (0.46 mg.kg.^{-1}) did not alter the incidence of muscle movement. This was 25% compared with the 22% described in Study Four. Using a similar premedication, and intravenous fentanyl, but inducing anaesthesia with an infusion of etomidate in alcohol (Study Nine), the incidence of muscle movement was reduced to 12%, none of which was severe. The use of intravenous alfentanil (Study Five) reduced the incidence of muscle movement to 4%, none of which was severe (Collin, Drummond and Spence, 1986).

Propofol

Induction Dosage

The induction dose of 2.5 mg.kg.^{-1} (Cummings et al, 1984) was found to be satisfactory in all cases in the induction study (Study Six). Other studies using the new formulation (Nightingale et al, 1985; Briggs and White, 1985; Noble and Ogg, 1985) also found this induction dose to be satisfactory. However, lower dose requirements have been found in the elderly (Dundee et al, 1986).

Cardiovascular Changes

A moderate reduction of systemic arterial blood pressure with little change in heart rate following propofol induction was described in Study Six and also by other investigators (Cummings et al, 1984; Nightingale et al, 1985; Henriksson et al, 1985). Speed of injection did not appear to affect cardiovascular stability when administered in a dose of 2 mg.kg.^{-1} (Rolly et al, 1985).

Respiratory Changes

Sixty five per cent of propofol induced patients in the induction study became apnoeic, 17% lasting over a minute. Using the same formulation, an incidence of apnoea of 44% has been described (Briggs and White, 1985) of which 21% lasted over a minute. Apnoea was not found when an induction dose of 2 mg.kg.^{-1} was administered compared with 2.5 mg.kg.^{-1} (Cummings et al, 1984).

Anaphylactic Reactions

In neither the propofol induction nor the infusion studies was there any evidence of histamine release. That propofol releases little histamine has been shown experimentally (Doenecke et al, 1985).

Pain on Injection

There was a high incidence of pain on injection of 37.5% and 60% of patients in this group had some form of venous sensation when small veins were used (Study Six). Similar findings were reported by other investigators - 25% (Mirakhur and Shepherd, 1985), and 30% (Briggs and White, 1985). The use of veins in the ante-cubital fossa significantly reduced the incidence of pain (Study Six; Briggs and White, 1985; Cummings et al, 1984). Pretreatment with I.V. lignocaine appeared to have little effect (Study Six) although mixing lignocaine with propofol immediately before injection reduced the incidence of pain to 4% (Redfern, Stafford and Hull, 1985).

Pain on injection was reduced to 6.7% using intramuscular opiate premedication (Studies Eleven and Twelve), compared with the 37.5% found in the unpremedicated induction study, although the patients tended to be older (the average age was 60 years compared with an average age of 35 years in Study Six). A higher incidence of 20% (De Grood et al, 1985, b) and 45% (Uppingham, Kay and Sear, 1985) despite morphine premedication has been described.

Muscle Movement

A low incidence of muscle movement has been reported (Chapter Nine; Kay and Healy, 1985; Rolly et al, 1985) although an incidence of 23%, attributed to lightening of anaesthesia, has been reported (Cummings et al, 1984).

Comparison of Etomidate and Propofol with other Agents

Cardiovascular Changes

Various studies comparing etomidate 0.3 mg.kg.^{-1} with propanidid 7.0 mg.kg.^{-1} (Study Two; Brückner et al, 1974) suggested that the cardiovascular stability of etomidate was superior to propanidid. Compared with thiopentone 4 mg.kg.^{-1} , etomidate 0.3 mg.kg.^{-1} produced a similar degree of cardiovascular depression (Gooding and Corssen, 1976; Fragen, Caldwell and Brunner, 1976; McCollum and Dundee, 1986). The cardiovascular depression found with etomidate 0.4 mg.kg.^{-1} and thiopentone 4 mg.kg.^{-1} was also very similar (Chiu and Van, 1978; Giese et al, 1985). Methohexitone 1.5 mg.kg.^{-1} produced either a very similar (Study Four; Dubois-Primo et al, 1976) or slightly greater degree of depression (Vercuysse, Hanegreefs and Delooz, 1976; Van Eeden, 1980; McCollum and Dundee, 1986).

In the induction study with propofol (Study Six) the changes were similar to those found with thiopentone 4.5 mg.kg.^{-1} except that there was an increase in pulse rate in the thiopentone group only. Similar changes comparing propofol 2 mg.kg.^{-1} (Rolly

and Versichelen, 1985) and 2.5 mg.kg.^{-1} (Mouton et al, 1985) with thiopentone 4 mg.kg.^{-1} have been described. In contrast a greater fall was described with propofol 2.5 mg.kg.^{-1} compared with thiopentone 4 mg.kg.^{-1} (Grounds et al, 1985) or 5 mg.kg.^{-1} (Fahy, Van Mourik and Utting, 1985; Mackenzie and Grant, 1985, a; McCollum and Dundee, 1986). Greater cardiovascular changes with propofol 2.5 mg.kg.^{-1} compared with methohexitone 1.5 mg.kg.^{-1} were found (Mackenzie and Grant, 1985, a; Kay and Healy, 1985).

Respiratory Changes

The respiratory effects of etomidate may be less depressant than those found with althesin or thiopentone (Morgan, Lumley and Whitwam, 1975) or methohexitone (Kay, 1979). A higher incidence of apnoea was found with thiopentone 4 mg.kg.^{-1} compared with etomidate 0.3 mg.kg.^{-1} (Ghoneim and Yamada, 1977; Chiu and Van, 1978; McCollum and Dundee, 1986).

Propofol 1.5 and 2 mg.kg.^{-1} produced a similar degree of respiratory depression as thiopentone 4 mg.kg.^{-1} (Rolly and Versichelen, 1985). Propofol has been shown to have a greater degree of respiratory depression compared with thopentone 4 mg.kg.^{-1} (Mouton et al, 1985; Taylor et al, 1986; McCollum and Dundee, 1986) 4.5 mg.kg.^{-1} (Study Six) and 5 mg.kg.^{-1} (Mackenzie and Grant, 1985, a; McCollum and Dundee, 1986) and methohexitone 1.5 mg.kg.^{-1} (Mackenzie and Grant, 1985, a; McCollum and Dundee, 1986).

Pain on Injection

Both agents cause pain on injection, but there was a wide variation in the incidence reported in different studies.

Muscle Movement

Muscle movement appeared to be less with propofol compared with methohexitone (Mackenzie and Grant, 1985, a) or althesin (Kay and Healy, 1985), and is a major advantage compared with etomidate.

Recovery

Recovery from both etomidate and propofol was rapid and complete. Emergence phenomena may be a problem with etomidate.

Venous Damage

Although no specific comparisons have been made in these studies, venous damage would appear to be much less than that found after the injection of etomidate.

Conclusions

The bolus injection of both etomidate and propofol appeared to cause only slight physiological changes, except for some cardiovascular and respiratory depression by propofol. However, their clinical acceptability was reduced by the incidence of pain on injection and etomidate also caused muscle movement. Under most circumstances when cardiovascular stability is not of paramount importance, propofol would appear to be closer to the ideal induction agent than etomidate. This is mainly due to the lower incidence of side effects, particularly muscle movement and venous sequelae.

Etomidate may be more suitable for the elderly and unfit patients because of its greater cardiovascular stability.

Compared with thiopentone, propofol may offer advantages in outpatient anaesthesia due to its shorter recovery time, provided the incidence of pain and apnoea are not found to be too great a disadvantage. For inpatient anaesthesia in fit patients, neither etomidate or propofol would appear to offer major advantages over thiopentone.

Thiopentone has enjoyed extensive use over more than fifty years. Its advantages and disadvantages have become well known and can usually be compensated for whenever necessary. In contrast, etomidate was freely available for nearly ten years before problems such as adrenal depression (Fellows et al, 1983) and possible generalised epileptiform activity (Krieger, Coppermann and Laxer, 1985) were reported. A similar period of time elapsed between the introduction and withdrawal of althesin. Di-isopropylphenol has already required reformulation and was released for general use only in June 1986. Caution has to be expressed concerning the relative merits of any new induction agent as long term use may reveal unsuspected disadvantages.

Areas for further Investigation

Possible Relationship between the Rate of Injection and the Incidence of Complications

There is some evidence that the rate of injection and therefore

the concentration of the bolus of the drug may influence the incidence of side-effects. This may occur before or after the drug reaches its main site of action. The minimum therapeutic level for etomidate is 0.3 mcg.ml.^{-1} , the safe maximum level is 1.0 mcg.ml.^{-1} and the optimum level is 0.5 mcg.ml.^{-1} (Schüttler, Schwilden and Stoekel, 1985). A bolus injection of etomidate 0.3 mg.kg.^{-1} over 10 seconds can result in a mean plasma concentration of $1.59 \text{ mcg.ml.}^{-1}$ within a minute and 1.3 mcg.ml.^{-1} when injected over sixty seconds (Doenecke et al, 1982).

In the studies reported in Studies One, Two, Three and Nine the maximal incidence of side effects, particularly muscle movement, occurred when the drug was injected over 30 - 60 seconds.

When the same amount of etomidate was infused over 3 minutes (Study Nine; Scorgie, 1983) there was a marked reduction in the incidence of pain and muscle movement. This could be due to the blood levels of etomidate failing to reach the levels found during rapid injection. In a similar study with disopropofol, fewer side-effects were found when disopropofol was injected over three minutes (Major et al, 1982).

Little difference in the complication rates have been described when the induction dose of etomidate was injected over 10 - 15 seconds or 20 - 30 seconds (Zacharias et al, 1978), or when differing amounts were injected over thirty seconds (Holdcroft et al, 1976), although a slight decrease in the incidence of pain and muscle movement was found in Study Two, when etomidate was

injected over 15 seconds. One explanation is that such differences which might exist, are greatly reduced because etomidate is very highly bound to plasma - 90% (Doenecke et al, 1982).

The cardiovascular and respiratory depression described in several studies of induction with propofol could also be due to its rapid injection, although little change in cardiovascular and respiratory depression has been described when propofol was injected over 5, 20, or 60 seconds (Rolly et al, 1985). A wide variation in the sensitivity to propofol and a marked variation in incidence of side effects with rapid injection has been described (Dundee et al, 1986).

Because such effects may be important particularly in the elderly, further investigations of the effects of the rate of injection on the incidence of complications are planned.

Possible Relationship between Age or Sex and the Incidence of Complications

The differences in the incidence of pain on injection in Studies Four and the control group in Study Five have been commented upon earlier in this chapter. Methodological changes could account for some of this as different observers took part in the two studies. Many patients in the Fourth Study had had previous experience of anaesthesia which could have influenced their assessment of pain.

The incidence of pain in the fifth study was similar to

that found by Zacharias et al (1978) also in unpremedicated patients undergoing minor gynaecological surgery. In contrast, a high incidence of pain (68%) was described in patients undergoing cystoscopy (Yelavitch and Holmes, 1980). Although no indication of age or sex distribution was given, it could be expected that this group would be demographically similar to that of Study Four. The reasons for these differences are not clear and will be the subject of further investigation.

CHAPTER TWELVE

DISCUSSION OF THE INFUSION OF
ETOMIDATE AND PROPOFOL
FOR THE MAINTENANCE OF ANAESTHESIA

Introduction

The induction studies discussed in the previous chapter showed that both etomidate and propofol were potent hypnotics which were rapid in onset and recovery. These findings have been confirmed by formal pharmacokinetic studies of etomidate (Van Hamme, Ghoneim and Ambre, 1978; Schüttler et al, a, 1980; De Ruiter et al, 1981; Doenecke et al, 1982) and propofol (Briggs et al, 1985; Kay et al, 1985, a). The infusion studies extended the induction studies by investigating the effects of administering large amounts of hypnotic over a relatively short period of time. The studies have allowed the assessment of such techniques for the provision of total intravenous anaesthesia and how such techniques might be improved. Since neither etomidate nor propofol have any analgesic activity, supplementation was provided with intravenous fentanyl.

Infusion of Etomidate

The infusion rates of etomidate in the earliest studies were derived empirically. Rates in adults ranged from 20 - 50 mcg.kg.⁻¹min.⁻¹ (Kay and Rolly, a, 1977; O'Carroll et al, 1977, b; Van Dijk, 1979; Gepts and Camu, 1981) and similar amounts were infused in children (Kay, 1977, a; b). These high rates of infusion were associated with high complication rates (O'Carroll et al, 1977, b; Kay 1977, a; Kay and Rolly, a, 1977).

Lower infusion rates of around 20 mcg.kg.⁻¹min.⁻¹ supplemented

with either fentanyl or nitrous oxide were used to maintain anaesthesia for both spontaneously breathing and ventilated patients (Studies Seven, Eight and Nine; Van Dijk, 1979; Booij, Rutten and Crul, 1978).

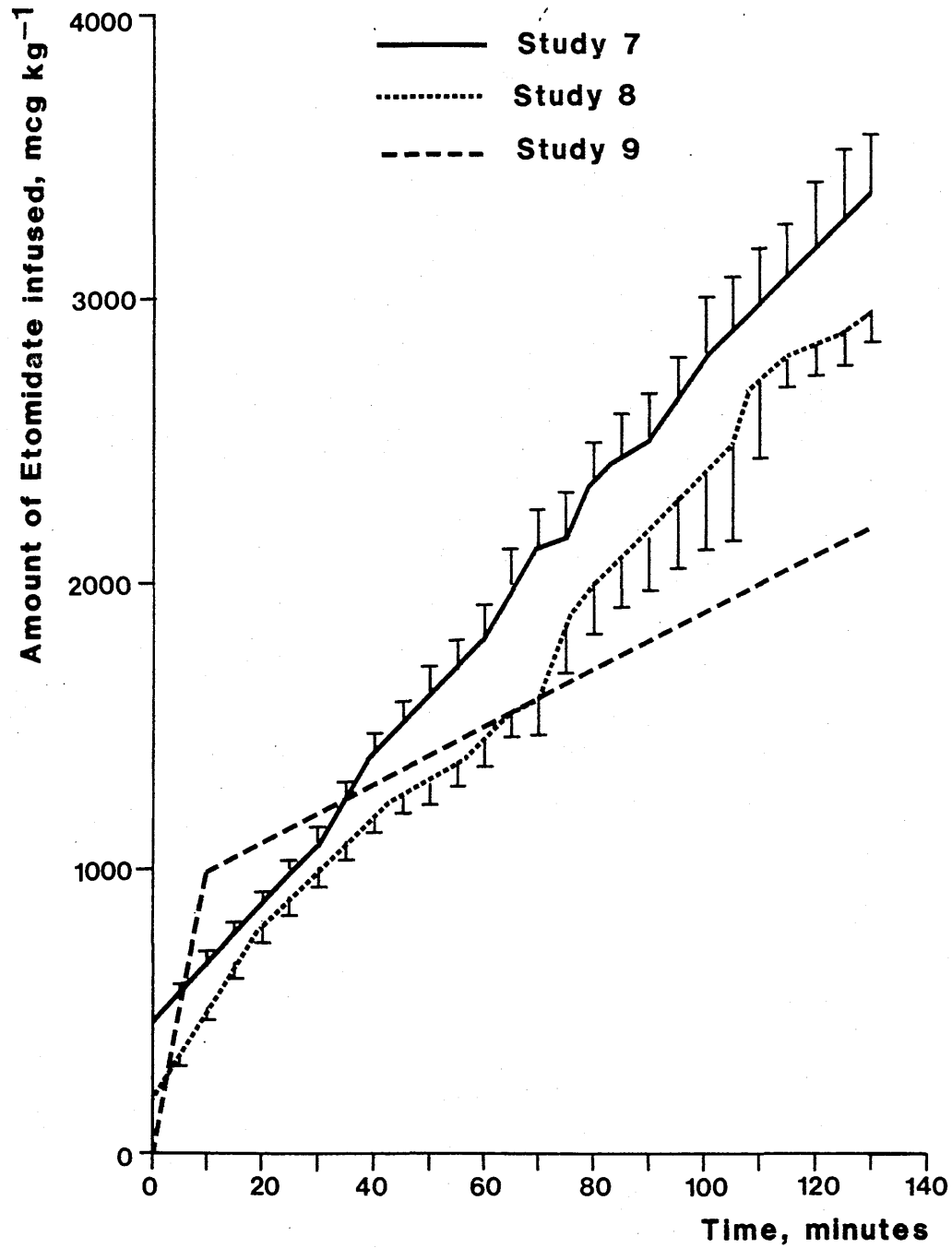
The relationship between blood levels of etomidate, and the degree of hypnosis was investigated (Schüttler et al, 1980, b; Doenecke et al, 1982) using power spectral analysis of the E.E.G. The former group described a simple two stage infusion regime which rapidly achieved an adequate, steady blood level of etomidate. Computer simulation using the available pharmacokinetic data suggested that this infusion scheme would provide better conditions with lower etomidate blood levels compared with the earlier empirical regimes (Schwilden et al, 1981). Study Nine was carried out to investigate this suggestion.

The differences in the amounts of etomidate administered using this two stage infusion regime are shown in Figure Twenty One. This shows the cumulative amounts of etomidate administered in the three ventilated groups in Studies Seven, Eight and Nine. The differences in the amounts administered to Studies Seven and Eight are not significant and are due mainly to the initial bolus of etomidate given for induction in Study Seven.

The contrast between the amounts of etomidate administered with the two stage infusion technique and the empirical infusion rates is best seen comparing the amounts administered during the Seventh and Ninth Studies as both studies were induced with etomidate.

Fig. 21

CUMULATIVE AMOUNTS OF ETOMIDATE INFUSED IN VENTILATED PATIENTS DURING THE THREE ETOMIDATE INFUSION STUDIES



After 50 minutes Study Nine had received significantly less etomidate than Study Seven. This difference was also statistically significant ($p < 0.01$). Compared with Study Eight where thiopentone was used for induction significantly less etomidate was administered to patients in Study Nine after 105 minutes.

Analgesic Supplementation

Etomidate has no analgesic action and an antanalgesic action has been described in rats (Kissen, Green and Reeves, 1984). Investigation of etomidate and fentanyl in dogs (Erhardt et al, 1978; Arndt and Mameghani, 1980; Renemans, 1981) and humans (Hempleman, Seitz and Piepenbrock, 1977) have shown that the combination of etomidate and fentanyl has little effect on cardiovascular parameters except for a slowing in pulse rate and some depression of respiration (Schockenhoff, Hoffman and Plantiko, 1980). Baroreceptor function, in particular, appears to remain unaltered.

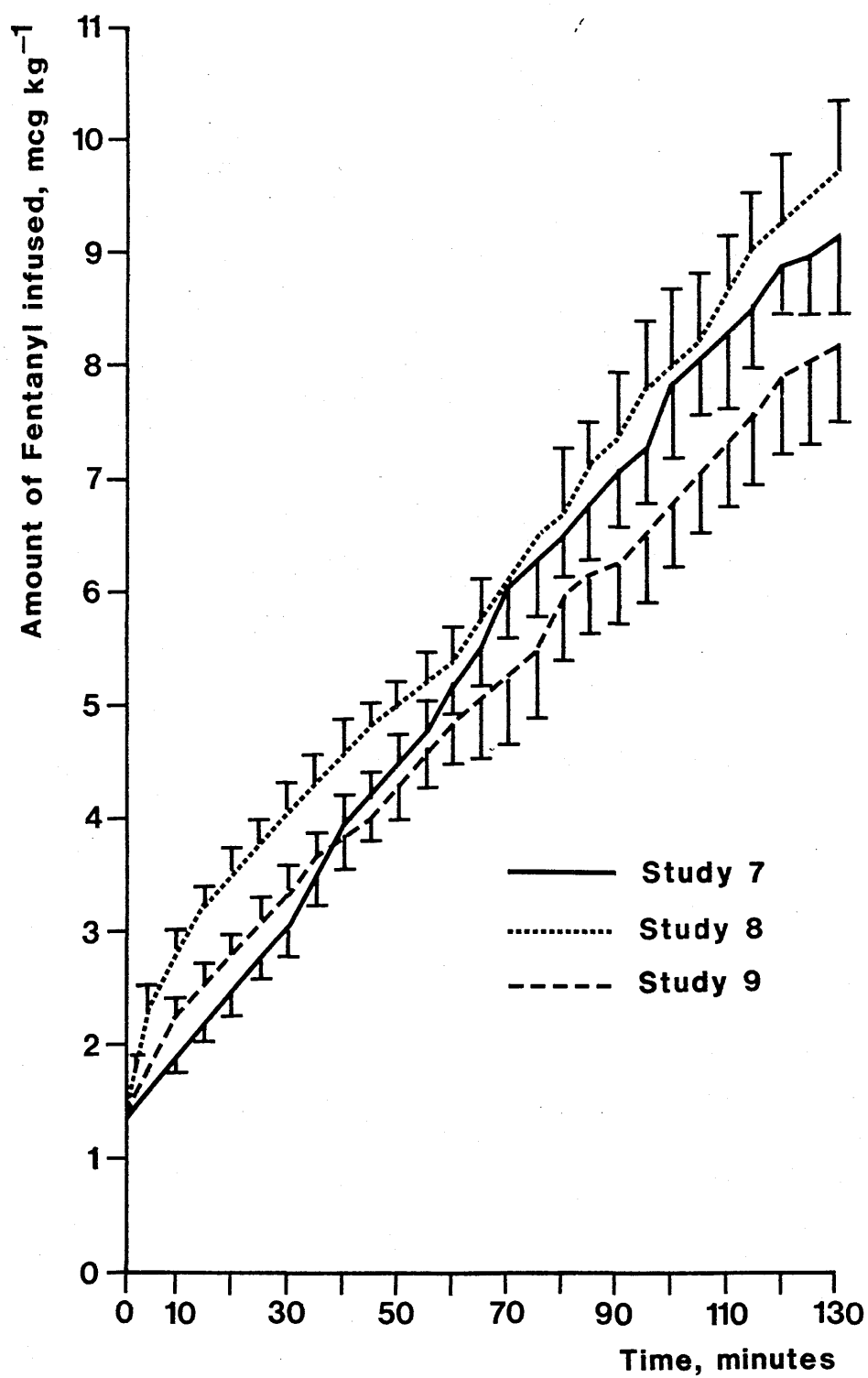
The amounts of fentanyl infused in the ventilated patients in the three studies are shown in Figure Twenty Two. Statistically significant differences are seen within the first 40 minutes between the groups. Thereafter there were no statistically significant differences between the three studies, although the mean amounts of fentanyl infused were lower in the third.

Cardiovascular Changes

In animal studies, doses of etomidate varying from 0.1 mg.kg.^{-1}

Fig. 22

CUMULATIVE AMOUNTS OF FENTANYL INFUSED IN VENTILATED PATIENTS DURING THE THREE ETOMIDATE INFUSION STUDIES



to 1.6 mg.kg.^{-1} have been shown to have little cardiovascular effect (Weymar et al, 1974). Larger doses of etomidate of 2 - 8 mg.kg.^{-1} have been shown to have a dose-related central and peripheral direct depressant effect on the rabbit myocardium (Hughes and McKenzie, 1978). As shown in Figure Twenty One, about 2 mg.kg.^{-1} is administered within 90 -120 minutes depending on the infusion rate. The cardiovascular stability found in the induction studies was also found in the infusion studies, reflected in the low coefficients of variation described in Studies Seven, Eight and Nine. This tends to confirm the animal work suggesting that either such amounts of etomidate do not cause myocardial depression or that the baroreceptor reflexes are maintained when etomidate and fentanyl are infused together over a period of time. Bradycardia has been described (O'Carroll et al, 1977, b; Chapter Seven) possibly due to centrally mediated bradycardia associated with fentanyl (Eisle et al, 1975; Reitan et al, 1978). All episodes responded to the intravenous administration of small amounts of atropine. Induction with thiopentone did not appear to affect the cardiovascular stability of the infusion of etomidate and fentanyl.

Respiratory Changes

All studies showed rises in arterial carbon dioxide tension, comparable to that seen in the control groups. Similar findings of respiratory stability have been described in spontaneously breathing patients in other studies (Van Dijk, 1979; Van Eeden and Leiman, 1980). However, in individual patients, there were problems of respiratory depression or apnoea which required manual ventilation until spontaneous respiration returned. Such episodes

frequently occurred after increases in the infusion rate of fentanyl or etomidate and fentanyl because of signs of inadequate anaesthesia (as defined in Chapter Two). Complications such as "stiff chest" and post-operative respiratory depression were not seen.

Recovery

Recovery in most patients in Studies Seven and Nine was rapid, usually within 12 - 20 minutes. Despite the use of differing techniques (Kay, 1977, a, b; O'Carroll et al, 1977, b; Van Dijk, 1979; Van Eeden and Leiman, 1981; Rocke et al, 1981) similar recovery times have been described in those studies. Recovery could be prolonged in individual patients (O'Carroll et al, 1977; Van de Walle et al, 1979). The use of thiopentone in the second series was associated with prolonged recovery, possibly due to the combination of the hypnotic effect of thiopentone and the infusion of etomidate. Detailed study of the immediate post-operative period (Hoffman and Schockenhoff, 1981) showed minimal changes in cardiovascular and respiratory systems after the infusion of etomidate. The infusion of fentanyl did not appear to influence the time interval to the first administration of post-operative analgesia in the second or third infusion studies. The occurrence of prolonged myoclonus has been reported after the infusion of etomidate (Laughlin and Newberg, 1985). Similar effects were seen in four patients in Study Nine.

Liver Function Tests

The problem of which liver function tests should be carried out and their significance remains unresolved (Sear et al, 1984). Changes in liver function tests occur after routine upper abdominal surgery (Clarke, Daggart and Lavery, 1976). In the liver function study (Chapter Eight) no clinically significant changes were found. Similar small, non-significant changes have been described in other studies (Hoffman and Schockenhoff, 1982; Sear et al, 1984). The only series where there was a consistent rise in liver enzymes was reported by Blunnie et al (1981) using a high infusion rate of $40 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$. These findings suggest that the use of moderate infusion rates of etomidate with fentanyl do not upset liver function significantly, but that this may not be true of higher infusion rates.

Fluid and Electrolyte Balance

The infusion of etomidate and fentanyl (Study Ten) appeared to cause little upset in renal function and the results found were similar to those found after a standard anaesthetic technique. Similar minor changes in serum electrolytes post-operatively after the infusion of etomidate have been described (Hoffman and Schockenhoff, 1982).

Infusion of Propofol

The rate of infusion of propofol in Studies Eleven and Twelve was initially $150 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ for 30 minutes which was then reduced to $75 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$. Other quoted rates vary from $72.6 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (Kay et al, 1985,b), $102.8 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (Jessop et al, 1985), and $130 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (Mackenzie and Grant, 1985,b) used to supplement spinal or epidural analgesia in spontaneously breathing patients to $160 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (Hunter, Spencer and McLaren, 1985), $197 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (Robinson, 1985) and $214 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$ (McLeod and Boheimer, 1985) infused as part of intravenous anaesthetic techniques.

Cardiovascular Changes

Cardiovascular changes in the various studies tended to be very similar with a drop in arterial pressure, particularly systolic, in both fit patients (Coates et al, 1985; Robinson, 1985; Chapter Nine) and patients undergoing cardiac operations (Patrick et al, 1985; Stephen et al, 1986) soon returning to pre-operative levels during maintenance anaesthesia. Pulse rates tended to remain constant (Robinson, 1985; Uppingham, Kay and Sear, 1985). Myocardial blood flow may be decreased resulting in possible myocardial ischaemia (Stephen et al, 1986).

Respiratory Changes

Apnoea during induction with propofol has been described in

many studies (Chapter Eleven). Other infusion studies, using similar rates of infusion to those described in Chapter Ten, did not describe any particular difficulties with apnoea during maintenance anaesthesia. This difference may be due to the infusion of fentanyl to provide analgesia, causing additional respiratory depression. The elevation of blood propofol levels associated with the administration of fentanyl (Briggs et al, 1985) could also contribute to this effect.

Prolongation of Duration of Action of Muscle Relaxant

In Study Twelve it was suggested that there might be a progressive prolongation of the effect of vecuronium compared with that of atracurium over a period of 2 - 3 hours. Bolus injections of propofol had no effect on the neuromuscular blockade produced by suxamethonium, atracurium (Nightingale et al, 1985) or vecuronium (De Grood et al, 1985, a). Disopropofol has been shown to potentiate suxamethonium, pancuronium and vecuronium in rats (Fragen et al, 1983, b), and atracurium and vecuronium in humans, but without prolonging the duration of action (Robertson et al, 1983, b). This finding in Study Twelve requires further investigation, but could be due to other factors such as alteration of hepatic metabolism, or hepatic blood flow, especially as the patients tended to be elderly and undergoing prolonged anaesthesia. No such effect was found to occur with atracurium, possibly due to its spontaneous degradation.

Recovery

Recovery in the infusion studies was rapid and complete (Studies Eleven and Twelve; Upppingham, Kay and Sear, 1985; Jessop et al 1985).

The rate of recovery remained rapid even after relatively high infusion rates (Mackenzie and Grant, 1985, b; McLeod and Boheimer, 1985), and was comparable with the times found with etomidate.

Venous Damage and other Safety Aspects

The safety aspects of propofol have been extensively investigated. The incidence of venous damage in the studies described in Chapters Six and Nine was very low - only one patient had transient thrombophlebitis in 120 induction administrations and 45 infusions of propofol. Prolonged observation of the administration site after the administration of propofol and methohexitone revealed no evidence of thrombophlebitis after 14 days (Mattila and Koski, 1985). No changes in liver function after doses of 140 to 330 mg. have been detected (Robinson and Patterson, 1985).

Quality of Anaesthesia

Although such infusions have been shown to be feasible, the question remains as to how effective they are when used clinically.

The results obtained for etomidate varied considerably, but its use in paralysed patients was found to be satisfactory in Studies Seven, Eight and Nine. Similar findings have been described (Booij, Rutter and Crul, 1978; Florence, 1981; Rocke et al, 1981; Thomson et al, 1982; Oduro et al, 1983; Carli, Stribley and Clark, 1983).

Not all studies involving paralysed patients found the

technique satisfactory. Failure to suppress reflex activity has been described (Van de Walle et al, 1979; Gepts and Camu, 1981), and much higher infusion rates were found to be necessary for resection of abdominal aneurysms and abdoperineal resections (Hutschenreuter et al, 1981). One case of awareness has been described (Braude, Lieman and Galloway, 1985) and several instances of inadequate anaesthesia (O'Carroll et al, 1977, b; Van Dijk, 1979).

The lower infusion rate of etomidate described in Study Nine appeared to be satisfactory, although one study found that 24% of patients required supplementation (Jones, Lawrence and Thornton, 1983). In a large multi-centre trial (Boyes et al, 1981) evaluating this infusion scheme, awareness occurred in one patient, and anaesthesia was inadequate in another three.

In spontaneously breathing patients the results were more variable. Difficulties found in Studies Seven, Eight and Nine related to pain on injection, muscle movement and difficulty in maintaining respiration when the infusion rates had to be increased. Pain on injection and muscle movement could be reduced by infusion of the induction dose of etomidate (Study Nine) or by the substitution of thiopentone for the bolus injection of etomidate (Study Eight), but the respiratory problems remained. Good results in spontaneously breathing patients have been reported (Booij, Rutten and Crul, 1978; Van Dijk, 1979; Helmers, Giezen and Adam, 1981).

The two stage infusion scheme has been found to provide satisfactory sedation for operations under local anaesthesia (Scorgie, 1983; Birks, Edbrooke and Munday, 1983). These results are in

marked contrast to those described in the earlier studies of Kay and Rolly (1977, a).

Although experience with propofol is much less, problems were found during Studies Eleven and Twelve. These were pain on injection during induction and the difficulties in maintaining spontaneous respiration in Study Eleven.

All the infusion studies showed a very high coefficient of variation in the infusion rates required. This high degree of variation of infusion rates could create difficulties in spontaneously breathing patients when an unprotected airway had to be maintained while adjusting the infusion rate.

Comparison between Etomidate and Propofol

Both etomidate and propofol have been found to provide satisfactory hypnosis for the induction and maintenance of anaesthesia. Etomidate caused less cardiovascular depression during the initial infusion period, but during the maintenance of anaesthesia, cardiovascular changes were very similar. Predetermined infusion rates were found to be successful for both hypnotics, except for the spontaneously breathing patients infused with propofol. All studies showed a very similar coefficient of variation for the infusion rates of fentanyl.

Clinically, the major differences between the two hypnotics were due to side-effects. The lack of muscle movement with propofol was a major advantage and the incidence of pain on injection in premedicated patients was less. The infusion of etomidate for

both induction and maintenance of hypnosis reduced the incidence of side-effects although they were not abolished. The major disadvantages of etomidate are the high incidence of pain, muscle movement and venous thrombosis.

Conclusions

The conclusions are that prolonged infusion of etomidate and propofol with fentanyl does not affect cardiovascular stability, and that recovery is rapid after stopping infusion. There would appear to be no adverse effect on hepatic or renal function. However several problems remain to be solved before total intravenous anaesthesia using these agents becomes practical for routine use. These are concerned with the adequacy of hypnosis, flexibility of analgesic administration without respiratory depression and side-effects, particularly pain on injection.

CHAPTER THIRTEEN

GENERAL DISCUSSION OF
TOTAL INTRAVENOUS ANAESTHESIA

Introduction

Althesin was the first of the new hypnotics used for continuous infusion, both for total intravenous anaesthesia (Savage et al, 1975; Jago and Restall, 1977), and for supplementation of local analgesia (Park and Wilson, 1978). Combined with the development of accurate infusion equipment, these advances suggested that total intravenous anaesthesia could become an alternative to conventional inhalation based anaesthesia. This optimism was illustrated by a survey (Wright and Dundee, 1982) where 92% of anaesthetists expressed an interest in using total intravenous anaesthetic techniques. Failure to use such techniques were attributed mainly to lack of information, equipment, and experience, which could be easily corrected. More serious difficulties such as assessing depth of anaesthesia, or lack of a suitable agent had caused some 10% of those who had used such techniques to subsequently abandon them.

The conclusions of the previous chapter suggest that several problems remain to be solved. This chapter looks at these problems, attempts to assess whether they may be soluble and their implications for the continued use of total intravenous techniques and the prolonged infusion of hypnotic agents.

Hypnosis

One major problem is how to assess the depth of anaesthesia when many of the signs of patient response have been obtunded by the administration of other drugs, particularly muscle relaxants

(Lancet, 1986, a,b). Awareness may be a horrific experience for the individual concerned (Anonymous, 1979) and has been described as the greatest single potential drawback to intravenous anaesthesia (Morgan, 1983). In the studies reported in this thesis, no patient gave any indication of awareness when questioned after anaesthesia, although this is an extremely crude means of assessment.

Administration of Hypnotics

Cerebral Function Monitors have been used to control the infusion of althesin and etomidate (Dubois et al, 1978) and thiopentone (Frank et al, 1982). As such machines are not yet widely available, other methods have been more commonly used. Early infusion schemes were empirical. Advances in pharmacokinetic and pharmacodynamic theory and the ability to measure blood levels of drugs, has allowed the development of theoretically more rational infusion schemes (Norman, 1983; Sear, 1983) such as those described in Chapter Twelve for etomidate and propofol. These are based on the premise that a constant pre-determined infusion of hypnotic agent results in a blood level guaranteed to produce the desired effect, the "therapeutic window" (Ausems, Stanski and Hug, 1985). Other effects are due to surgical stimulation and can be treated with varying amounts of analgesic as required.

Pharmacokinetic modelling cannot be used uncritically. The coefficient of variation of pharmacokinetic parameters in fit patients may be in the order of 25% (Norman, 1983) and the parameters are derived from plasma assays, which have their own inaccuracies (Faulding and Hall, 1984). It has been suggested that the

variability in certain pharmacokinetic parameters may be over-emphasized (Schwilden, Schüttler and Stoeckel, 1985), but fentanyl is an example of how variable such data can be (Reilly, Wood and Wood, 1982).

An empirical approach has been developed to allow comparison between different hypnotics and infusion rates using an intravenous equivalent to the M.A.C. values of the inhalational agents. This is the Minimum Infusion Rate (M.I.R.) or E.D.50 (Prys-Roberts, 1980; 1983; Prys-Roberts and Sear, 1984). The technique has been extended and E.D.95 values can now be obtained as well as the E.D.50 (Spelina et al, 1986).

Infusion rates suggested by this method have been found to be similar to empirical infusion rates for althesin (Morgan and Dawson, 1984). The E.D. 95 values for propofol (Spelina et al, 1986) are very similar to other reported infusion rates (Chapter Twelve) although recent studies have suggested a much higher E.D.95 for propofol when the pre-medication was changed from morphine to lorazepam (Turtle et al, 1987). The infusion rates tend to be lower in the M.I.R. studies due to the use of 67% nitrous oxide which reduces the required infusion rate by about 30% (Keeri-Szanto, 1980, b) to 40% - 50% (Prys-Roberts, 1983; Sear et al, 1983). The M.I.R. for etomidate was found to be much higher than the infusion rates for etomidate derived from a pharmacokinetic model (Prys-Roberts and Sear, 1984). This was possibly caused by the high infusion rate of etomidate in the M.I.R. studies causing excessive muscle movement. Thus for althesin and propofol, but not for etomidate, the agreement between M.I.R.

and other regimes are reasonably close. Alterations in M.I.R. have been found to be altered by age, premedication, drug therapy and pre-existing disease (Prys-Roberts, 1983; Prys-Roberts and Sear, 1984).

Pre-determined infusion rates have been used successfully in limited clinical circumstances although difficulties have been described in some series (Chapter Twelve). To be used in routine clinical practice, the underlying assumptions would have to hold for a wider patient population varying both in operations undergone and the incidence of co-existing disease.

Individual variation is important and may be considerable (Keeri-Szanto, 1980, a; b). A wide variation in cumulative dose requirements with a right skew has been described for methohexitone (Dundee and McMurray, 1985) and for propofol (Wright et al, 1984; Robinson, 1985). Other influences include nutrition, (Bowman and Rand, 1980), physical fitness, sex (Dundee et al, 1982) and the concomitant administration of other drugs, such as nicotine (smoking), alcohol and caffeine (Stanley and De Lange, 1984). Changes occur with age (Greenblatt, Sellers and Shaden, 1982) and such changes have been described for thiopentone (Christensen, Andreassen and Jansen, 1982; Atkinson and Henthorn, 1985), methohexitone (Ghoneim et al, 1985), midazolam (Dundee et al, 1985), etomidate (Carlos, Calvo and Erill, 1981; Arden, Holley and Stanski, 1984) and propofol (Dundee et al, 1986; Hilton, Dev and Major, 1986).

Many of the reported studies have been carried out on volunteers and patients where analgesia has been provided by spinal

or epidural blockade. In sheep, spinal analgesia has been shown to have little effect on cardiac output, hepatic and renal blood flow, and drug distribution and metabolism, whereas general anaesthesia with halothane may cause substantial variation (Runcieman et al, 1984; 1986; Mather et al, 1986). Thus the results of investigations of infusion schemes in one clinical situation may not be applicable to others. This could account for the differences found when comparing the pharmacokinetic and pharmacodynamic results of propofol in volunteers and anaesthetised patients (Schüttler, Stoekel and Schwilden, 1985).

Operative procedures may influence drug action and metabolism (Pessayre et al, 1978). Hypovolaemia can also reduce plasma clearance, with prolongation of elimination as has been shown for midazolam (Adams et al, 1985). Changes occurring during cardiopulmonary by-pass are even more complex (Morgan et al, 1986). Parenteral nutrition has a marked but variable effect on drug metabolism (Vesell and Biebuyck, 1984; Pantuck et al, 1984). There are, therefore, many factors which may influence drug handling in apparently healthy patients, accounting for instances of awareness which have been reported with apparently adequate infusion rates of etomidate (Boyes et al, 1981; Braude, Leiman and Galloway, 1985).

Co-existing disease may also cause complications. Hepatic disease has been shown to prolong etomidate elimination (Van Beem et al, 1983). Respiratory disease may reduce the amount of plasma binding of etomidate (Carlos, Calvo and Erill, 1981). Severe illness such as sepsis can alter volumes of distribution and hepatic clearance (Reitbrook, 1980).

Drug interaction is an important cause of unexpected variation. Nitrous oxide has been shown to reduce hepatic blood flow in rats (Seyde, Ellis and Longnecker, 1986) and has been found to raise the plasma levels of etomidate in humans, in association with a prolongation of recovery time (Sear et al, 1984). The infusion of fentanyl has been shown to cause a 2 - 3 fold reduction in the volume of distribution and a reduction in the plasma clearance of etomidate. This may be due to the displacement of etomidate from tissue binding sites by fentanyl or by a reduction of liver blood flow (Schüttler et al, 1983). A similar interaction between fentanyl and propofol has been described (Briggs et al, 1985).

The consequences appear to depend to some extent on the physiological properties of the drugs themselves. The interaction between etomidate and fentanyl appeared to cause much less respiratory depression (Studies Seven, Eight and Nine) compared with propofol and fentanyl (Study Eleven), possibly due to the marked respiratory stability of etomidate. With the administration of three drugs, the situation becomes even more complex and could explain the findings with thiopentone (Study Eight) and vecuronium (Study Twelve).

Although not found in the studies reported in this thesis, the duration of infusion may also cause important changes in kinetic properties. With prolonged administration, fentanyl may become more cumulative and its kinetics resemble those of morphine and pethidine (Stanski, 1983). It has been suggested that acute

tolerance may occur with etomidate (Doenecke et al, 1982; Schlüttler, Schwilden and Stoeckel, 1985; Schwilden, Schlüttler and Stoeckel, 1985). Infusion with etomidate caused dose dependent changes in cardiovascular dynamics and reduced renal and cerebral blood flow in pigs (Prakash et al, 1980), and liver blood flow in dogs (Thomson et al, 1986). A similar reduction in liver blood flow, associated with a progressive rise in etomidate levels has been described in dogs (Van Lambalgen et al, 1982). As the clearance of etomidate is sensitive to hepatic blood flow rather than hepatic enzymic activity (Hebron et al, 1983), these findings could be caused by etomidate impairing its own metabolism. Acute tolerance has also been reported to occur with thiopentone (Dundee, Price and Dripps, 1956) and morphine (Marshall et al, 1985).

Thus methods based on a 'predicted' basis may be inherently unsatisfactory, although the use of the E.D.95 concept may be useful in the quantification of such variation. Comments on the limitation of the average rate of infusion as means of providing anaesthesia in 100% of patients have also been made by Dundee and McMurray (1985). Increasing infusion rates to prevent awareness in all patients may produce toxic effects in patients sensitive to the effects of the drug (Mather, 1980).

Administration of Analgesia

The other major problem was the administration of analgesia. Requirements for analgesia vary throughout an operation, being greater during laryngoscopy, (Kay, Healy and Bolder, 1985)

skin incision and wound closure (Mattilla et al, 1979). A fixed infusion rate of fentanyl ($0.05 \text{ mcg.kg.}^{-1} \text{ min.}^{-1}$) in patients undergoing superficial body surgery showed that 29% of the patients required supplementation (Andrews and Prys-Roberts, 1984). A high coefficient of variation in the amounts of fentanyl infused was found in all the infusion studies described in this thesis, whether combined with etomidate or not. Requirements for analgesia may also vary for different operations (Ausems et al, 1986). These findings suggest that analgesics are best infused as required in response to perceived patient need.

In most cases in the infusion studies described in this thesis, fentanyl was found to be satisfactory, but it has a slow response time of 4 - 7 minutes (Scott, Ponganis and Stanski, 1985). This led in some cases to larger amounts than necessary of fentanyl being administered in an attempt to increase speed of response. This resulted in apnoea in several patients. Although not seen in these studies, overdosage may result in post-operative respiratory depression (Adams and Pybus, 1978) possibly caused by secondary plasma peaks (McQuay et al, 1979; Stoeckel et al, 1982) or changes in kinetics (Stanski, 1983).

Alfentanil may be a superior analgesic for infusion compared with fentanyl because of its faster response time of 1 minute (Scott, Ponganis and Stanski, 1985). Alfentanil infusions may therefore be easier to control, with rapid response to changes in infusion rate. Such findings have been reported clinically (Steegers, Booij and Pelgram, 1982; Helmers et al, 1983; Versichelen, Rolly and Beerens, 1983; Kay, 1984; 1986). However, post-operative

respiratory depression has been reported with its use (Sebel et al, 1984).

Hazards of Intravenous Anaesthesia

Injection and infusion of drugs may be associated with hazards such as extravasation, thrombophlebitis, sepsis, the presence of particulate material and possible toxicity of plastic materials and additive compounds (Woods and Newton, 1978). For infusion, the physical properties of the drugs have to be considered more carefully than for bolus injection. Water solubility is desirable, as large amounts of solvent such as alcohol and intralipid may be infused. These may cause problems such as the sub-clinical complement activation associated with the continuous infusion of cremophor (Benoit et al, 1983). Physical compatibility (Huddy and Durcan, 1984), stability on exposure to light and lack of absorption to plastics as occurs with insulin, are also important (Morgan and Dawson, 1984).

Mechanical problems may also occur. A case has been reported of a pump discharging etomidate too quickly although without resulting in clinical harm (Calhaem, 1983). Although pump malfunctions appear to be uncommon, they present an added hazard of the technique.

The techniques are based on the premise that the drugs used are safe. Although great care is taken in the evaluation of all drugs, unexpected toxicity may occur. Etomidate has been shown to cause adrenocortical suppression (Fellows et al, 1983;

Mehta et al, 1985; Duthie, Fraser and Nimmo; 1985). Caution in the use of etomidate, particularly for infusion has been advised by the Committee on Safety of Medicines (Goldberg, 1983, a; b). In contrast, propofol has not been shown to have any deleterious effect on adrenal or testicular steroidogenesis (Robertson et al, 1985; Keynon, McNeil and Fraser, 1985; Lambert, Mitchell and Robertson, 1985).

Comparison of Intravenous and Conventional Anaesthesia

Being volatile, the inhalational agents obey physical laws. Increasing the inspired concentration rapidly increases the depth of anaesthesia and vice versa. This rapid response to changes in alveolar concentration makes the inhalational agents very flexible and easily adjusted to individual requirements. Also, there are no secondary increases in blood levels once the supply of such agents is stopped (Norlander, 1980). This flexibility cannot be matched by the intravenous agents where reversal of effects depend on metabolism. The problems due to biotransformation are greatly reduced by the use of the newer, and much less biometabolised agents, ethrane (Chase et al, 1971) and isoflurane (Holaday et al, 1975).

To provide anaesthesia for procedures when patients are breathing spontaneously, inhalational agents remain superior. In the infusion studies the incidence of transient or prolonged apnoea was much higher than in the control groups. One hazard which is of great practical importance is the danger of diversion of attention. In intravenous anaesthesia, attention has to be divided between the

airway and the infusion pump. This division of attention is potentially very dangerous as unexpected complications such as venous extravasation, may occur at any time and require immediate attention while the airway may be left unprotected.

The two methods are more comparable when anaesthetised patients are being ventilated. Under these circumstances, the airway has been secured and often an infusion is required for the administration of other drugs and fluids. The lack of nitrous oxide make total intravenous techniques particularly valuable when the cumulation of nitrous oxide may cause difficulties, as in abdominal, thoracic, cardiothoracic, neurosurgical and E.N.T. operations. Total intravenous anaesthetic techniques have been used in thoracic operations (Carli, Stribley and Clark, 1983) and cardiothoracic operations (Oduro et al, 1983). In these situations intravenous anaesthesia may offer advantages, particularly when post-operative ventilation is required. Sedation and analgesia can be continued using the same drugs as used during the operation.

The use of intravenous techniques may also be useful in less common situations, such as hyperbaric conditions; where jaundice has occurred subsequent to previous anaesthesia; where high inspired levels of oxygen are required and possibly in cases of malignant hyperpyrexia.

Provision of sedation is an area where intravenous techniques may be advantageous. This is best seen when provision of hypnosis is the main objective and clinical assessment is available, as when providing sedation for operations under local analgesia or sedation

for ventilated patients in the intensive care (Cohn et al, 1983) or neurosurgical unit (Dearden and McDowell, 1985). In these circumstances the amount of hypnotic agent required can be judged by individual response. Several of the studies quoted in Chapter Twelve suggest that propofol would be useful for sedation with local analgesia (Mackenzie and Grant, 1987). Its use for sedation in the intensive care units is currently being evaluated (Grounds et al, 1987 ; Newman et al, 1987).

Conclusions

Although short acting hypnotics and analgesics and the means to administer them accurately are now available, total intravenous techniques based on their use do not appear to be superior to currently available inhalational based techniques at the present time. The difficulty of finding the optimum dosage for each individual, and the relative lack of flexibility of response, places such techniques at a disadvantage unless the avoidance of nitrous oxide or other inhalational agents is of prime importance.

Possible Future Developments

The current situation could be changed in two ways. Hypnotic infusions, currently propofol, could be substituted for nitrous oxide and the less biometabolised inhalational agents used to provide the required flexibility in closed circuit anaesthesia. This would eliminate the dangers of hypoxic gas mixtures; allow a

safer use of closed circuit anaesthesia both for ventilated and spontaneously breathing patients, as well as reducing the hazards of theatre pollution.

The use of total intravenous techniques for routine use in the longer term could become more popular if better methods of assessment of anaesthetic depth were available. The development of improved methods of automated analysis of the E.E.G. by the use of cerebral function monitors (Maynard and Jenkinson, 1984; Sebel, Heneghan, and Ingram, 1985; Scott, Ponganis and Stanski, 1985; Jones and Konieczko, 1986) may allow more accurate titration of intravenous hypnotics and analgesics to individual requirements. This would allow a greater use of such techniques in ventilated patients. Such developments could eventually lead to computer assisted or controlled schemes as have been described for halothane (Chilcoate, Lunn and Mapleson, 1983; Ross et al, 1983; Morris, Tatnall and Montgomery, 1983). Such a system using E.E.G. and E.M.G. to control infusions of etomidate (Kay, 1984) and propofol (Kay, 1986) has already been described.

CHAPTER FOURTEEN

CONCLUSIONS

The bolus administration of etomidate or propofol was not associated with adverse physiological effects. However the incidence of side-effects of these drugs was such that for the routine induction of anaesthesia in fit patients, neither etomidate nor propofol would appear to offer any advantages over thiopentone, unless rapid recovery is required. Both may have advantages where the barbiturates are contra-indicated, or where histamine release is not desirable.

The infusion studies showed that in combination with fentanyl, total intravenous anaesthesia with etomidate or propofol was feasible, providing satisfactory hypnosis, and cardiovascular stability. Apnoea in spontaneously breathing patients was a frequent problem, particularly when propofol and fentanyl was infused.

The techniques were generally found easy to use, but in spontaneously breathing patients the division of attention between maintenance of an unprotected airway and the infusion or infusions, was potentially very dangerous. They cannot be recommended for use in this situation. The techniques were found to be practical in ventilated patients, but not yet superior to inhalational based methods for routine use.

This thesis does not support the hypothesis that total intravenous techniques can provide equally satisfactory anaesthesia for patients either breathing spontaneously or requiring mechanical ventilation, compared with the use of inhalational agents.

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