RECENT ADVANCES IN 13 ANAESTHESIA AND ANALGESIA

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ANAESTHESIA AND ANALGESIA

EDITED BY
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and
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Preface

The last volume of *Recent Advances in Anaesthesia and Analgesia* was published in 1976, but already sufficient material is available to warrant production of a new one. The subjects chosen are different to those considered last time and to some extent the two volumes are complementary. Topics of current interest have been included and it has been our aim to provide, with the help of expert contributors, readable accounts informative to the clinical anaesthetist who does not have time to go to the original sources himself.

The newer anaesthetic agents, enflurane and etomidate, are considered in some depth as is the concept of total intravenous anaesthesia, though the last is not yet, in our opinion, a satisfactory replacement for conventional methods.

There is current interest in the use of rebreathing systems and co-axial circuits, while recent accidents with flexible pipelines for medical gases and their connection to anaesthetic apparatus have indicated the need for improved safety precautions. One Chapter of this volume is devoted to both these aspects of the delivery of medical gases to patients.

The scope of cardiac surgery has increased greatly in recent years. The low mortality rate that now exists is a compliment to both the surgical technique itself and the excellent peri-operative care that patients receive. It is therefore appropriate that those aspects of interest to the anaesthetist are considered.

Avoidable maternal deaths still occur in obstetric practice associated with general anaesthesia, while perfect pain relief is not available to all mothers in labour. There is therefore a Chapter devoted to obstetric anaesthesia and analgesia.

Concern continues with regard to anaesthesia for the ambulant dental patient. Controversy exists with regard to clinical techniques and there are organisational problems to be overcome in the future if this work is to continue in premises outside the main hospital building. This subject is reviewed.

Sodium nitroprusside is considered in a separate Chapter. Though not a new drug, the indications and methods of use have only recently been evaluated. Toxic effects can also occur and their avoidance depends on an understanding of the metabolism of the compound.

Controlled ventilation in the intensive care unit is never without potential problems and complications. Mechanical ventilators are expensive items of equipment and it is not easy to advise on a best buy. Nor are the pros and cons of positive and expiratory pressure and intermittent mandatory ventilation easy to evaluate in a particular clinical situation. Monitoring is another area where economic constraints are operative since without this there would be no limit to the possible development of electronic expertise. Both these topics are therefore considered.

Postoperative care is a field which often receives less attention than it deserves. The patient may be in a critical condition in the few hours following completion of surgery and in all but the simplest case pain relief is necessary and arterial hypoxaemia may occur.

The anaesthetist is often involved in the acute management of the trauma patient whether this be in the accident centre, the operating theatre or the intensive care unit. Aspects of care which are the proper concern of the anaesthetist are reviewed.

Patients suffering from deliberate self-poisoning or accidental overdose form a significant percentage of those admitted to intensive care units. The availability of an ever widening range of potentially toxic substances means that the pattern of attempted suicide has changed greatly in recent years. It is no longer sufficient just to maintain lung ventilation and cardiac output and wait for the effects of the drug to wear off. We have therefore considered it appropriate to include a review of this subject.

In the last volume we noted that so many contributors had used abbreviations that an index of these was added at the end of the book. Since that date, the proliferation of abbreviations has become so enormous that a *Dictionary of Abbreviations in Medicine and the Health Sciences* (price over £14) is now available containing no fewer than 12 000 items. It is therefore inevitable that identical capital letter sequences may have two or more meanings which may lead to bizarre or even dangerous conclusions. An example of the former can be quoted from a most respected medical journal which carried a leading article entitled 'VIP and watery diarrhoea'. A physician interested in the effects of emotion on gastro-intestinal motility found to his annoyance that the writer was not discussing a member of the 'top brass' but vasoactive intestinal peptide. We must therefore point out that the new appendix refers only to abbreviations used *in this book*.

We thank the contributors who all met a rather tight schedule to ensure that there were no delays in publication. We also thank the publishers for their help and forbearance.

C.L.H.
R.S.A.

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Since the first *Recent Advances in Anaesthesia and Analgesia* was published in 1932, the developments in this progressing field have been examined in depth in twelve further volumes in the series, published respectively in 1937, 1939, 1943, 1944 (reprinted 1946), 1948, 1953, 1957 (reprinted 1958), 1963, 1967, 1972 and 1976, culminating in the publication of the present volume, number thirteen, in 1979.

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Contents

1. New anaesthetic drugs and techniques—enflurane, etomidate and total intravenous anaesthesia

T. M. Savege

In this Chapter recent research on two new anaesthetic agents are reviewed, one a volatile anaesthetic, the other an intravenous agent.

Techniques of continuous intravenous anaesthesia have recently been modified and refurbished under the term 'Total Intravenous Anaesthesia'. The application of this technique, its advantages and disadvantages will be discussed.

ENFLURANE

Enflurane has been an established anaesthetic agent for a number of years. However, it is still the subject of intense investigation.

Although it is said that enflurane is not flammable this is not strictly correct. High percentages of either halothane or enflurane in oxygen can be ignited. The addition of nitrous oxide reduces the percentage of volatile agent required to make the mixture flammable. 30 per cent oxygen in nitrous oxide can be ignited in the presence of 5.75 per cent enflurane. A reduction to 20 per cent oxygen in nitrous oxide allows the critical enflurane concentration to be reduced to 4.25 per cent whilst the mixture's flammability is retained. Fortunately, these concentrations of enflurane are not commonly used, furthermore a static discharge would not have sufficient energy to ignite the mixture. However, electro cautery used in the upper airway in the presence of high concentrations of enflurane could be dangerous.[1]

Earlier studies on enflurane reported that the agent was capable of inducing electroencephalographic (EEG) seizure activity often associated with tonic and/or clonic movements.[2] In addition, work in animals demonstrated that seizure activity could be detected on the EEG in the postoperative period and might persist for up to 16 days.[3] Subsequently two case reports of unexplained motor seizures occurring, one at six days and the other at eight days after anaesthesia, have been published.[4] Neither patient had had previous motor seizures but one had a family history of epilepsy.[4] Recently the EEG changes following prolonged exposure to enflurane (9.6 MAC hours) have been studied.[5] Two-thirds of the subjects developed spontaneous seizure activity revealed by the EEG during anaesthesia. In five of these subjects increased tone and clonic movements of the extremities developed at the same time. After anaesthesia all the EEG records showed diffuse slowing of α activity at one and two days, the trace becoming normal at the sixth day. Eight subjects showed minor changes on the EEG lasting from 6 to 30 days but none showed evidence of post anaesthetic seizure activity. It has been postulated that enflurane might precipitate seizure activity in patients with a pre-existing epileptic focus or in those with a clinical condition that could in itself lead to convulsions.[5] Consequently, enflurane is probably best avoided in patients

of this type. Treatment of clonic movements by administration of thiopentone may exacerbate the EEG signs of seizure at light levels of anaesthesia and suppress them at deep levels.[6]

Enflurane increases cerebral blood flow[7] but to a lesser extent than halothane.[8] Studies of cerebral blood flow using a specially adapted goat model show that both enflurane and halothane at 1 MAC abolish autoregulation of cerebral blood flow under conditions of normocarbia.[9] For each change in mean arterial blood pressure there was a parallel variation in cerebral blood flow. Hypocarbia exerted some residual effect in that both the magnitude of cerebral blood flow and the rate of change of flow in response to variation in mean arterial pressure were less marked.

It has also been shown that the quantity of water that collects in the tissues round an artificially induced cerebral lesion in an animal model is greater following enflurane and other halogenated volatile agents than after either barbiturate or fentanyl-droperidol-nitrous oxide anaesthesia. The volume of water could be directly correlated to the percentage change in cerebral blood flow.[10]

Initial reports on the cardiovascular effects of enflurane suggested that it only induced small changes at 1 MAC.[11] Recently, work undertaken on intact dogs has shown that enflurane depresses the cardiovascular system by as much if not more than does halothane when administered in comparable doses.[12,13,14] The depressant effect is dose related,[12,14] at 2.3 per cent enflurane mean systemic arterial pressure fell by 23 per cent, cardiac output by 18 per cent and LV dp/dt by 19 per cent compared with awake values.[12] Systemic vascular resistance was little changed and heart rate increased by over 30 per cent.[12] At higher doses (3.6–3.8 per cent) mean systemic arterial pressure, cardiac output and LV dp/dt fell by some 50 per cent[12,13] and left atrial pressure rose.[12] Some of these changes may have been exacerbated by the failure of heart rate to rise with the increased concentration of enflurane. These cardiovascular effects were accompanied by comparable falls in myocardial blood flow[12] but there was no evidence to suggest that the heart became anoxic. Myocardial oxygen consumption also fell, by over 50 per cent,[12,13] and oxygen consumption to other tissues was reduced but by a lesser amount.[13] Animal studies seem to reflect fairly accurately the changes in man.[14] However, different species do show variations, for example heart rate does not progressively rise in dogs,[12,14] whereas it does in man.[15] In contrast, it falls progressively in monkeys which consequently show more marked cardiovascular depression.[16]

The effects of enflurane were compared with those of halothane when administered with nitrous oxide to a group of unpremedicated volunteers breathing spontaneously.[17] Enflurane at approximately 1 MAC depressed mean systemic arterial pressure by 22 per cent, more than twice the fall induced by halothane. Myocardial contractility as measured by pre-ejection period and its derivatives was also depressed by enflurane but to a lesser extent than by halothane. However, this might not reflect the true action of enflurane on the myocardium for the mean $Paco_2$ measured in that group was approximately 1 kPa (7.5 mmHg) greater than in the halothane group.

Evidence of myocardial depression during anaesthesia is not necessarily a bad

sign; under certain circumstances the reduction in heart work can be beneficial. Furthermore, in the animal studies, despite myocardial depression there was no evidence to suggest that the oxygen supply to the heart[12] or to other tissues was inadequate and the oxygen tension in venous blood remained either normal or raised.[13] However, blood lactate did significantly increase and no adequate explanation for this is available at present.[12] Although myocardial depression might not in itself be harmful it is important to establish whether or not the cardiovascular system is capable of responding effectively to stress. The evidence both in man and animals suggests that the cardiovascular system does respond to hypercarbia[11] and to hypovolaemia[14] but that the response to the latter is impaired.

The large fall in mean systemic arterial pressure that is so consistently reported is a disadvantage because this could reduce critically coronary artery perfusion.

Enflurane may be a safer drug to use in the presence of raised blood catecholamines than halothane. The application of a solution containing adrenaline to mucous membranes and other tissues is less likely to induce dysrhythmias.[18,19] Although the administration of 2–20 ml adrenaline (1 in 100 000 dilution) either to mucous membranes or as a subcutaneous infiltration during enflurane anaesthesia increased blood pressure and heart rate in 20 per cent of patients, only 1.2 per cent developed premature ventricular contractions. These never exceeded five per minute. Additional doses of 20 ml solution could be injected hourly without inducing arrhythmias.[20] The evidence suggests that up to three times more adrenaline may be administered safely during enflurane anaesthesia compared with halothane anaesthesia.[18]

Enflurane depresses pulmonary ventilation in animals and man.[21] Recent studies in unpremedicated dogs have shown that enflurane, like halothane, did not result in increased $Paco_2$ when administered at 1 MAC but did so at 2 MAC.[22] Pulmonary ventilation is increased as a consequence of a raised $Paco_2$[22,23] but the response is not as effective as that in the awake animal. Furthermore, the ventilatory response to hypoxia is also reduced.[22] Normally if hypercarbia occurs at the same time as hypoxia the ventilatory response is augmented. This effect is abolished by both halothane and enflurane at 1 MAC.[22]

Enflurane dilates the bronchoconstriction induced by hypocapnia in an isolated denervated canine lung preparation. The dilatation is not as marked as that induced by halothane. This action does not seem to be mediated through the β receptor as β blockade does not affect it.[24] These findings may have some clinical significance. Morr-Strathmann and colleagues have shown that although enflurane slightly reduces lung compliance it also reduces airway resistance in healthy volunteers, the change being very similar to those measured with halothane.[25] The two drugs have been compared when used as the main anaesthetic agent in patients with chronic obstructive pulmonary disease.[26] The quality of anaesthesia was comparable between the two agents but there was a slightly higher incidence of coughing, wheezing, production of secretions and hypotension with enflurane.[26]

Clinical studies suggest that enflurane enhances muscle relaxation provided by muscle relaxant drugs.[27,28] Waud and Waud have shown in isolated guinea pig muscle that most volatile anaesthetic agents depress carbachol-induced depolarisation of the end plate region at a site distal to the acetyl choline-receptor

complex.[29,30] In man enflurane has been shown to depress the ability of muscle to sustain contracture in response to tetanic stimulation. Furthermore, with increasing doses it progressively augments the twitch depression induced by tubocurarine and prolongs the recovery time of twitch response.[31] Less non-depolarising muscle relaxant is required during enflurane anaesthesia than during halothane anaesthesia to depress the twitch response by 50 per cent.[31] However, this finding relates to very small doses of relaxant drug, and, judging from the slope of the dose response curves, may not apply to doses used in clinical anaesthesia.

Enflurane has been used in small concentrations (0.5–0.8 per cent) prior to delivery during anaesthesia for Caesarean section.[32] This did not significantly depress the Apgar score of the infants and was apparently not associated with excessive uterine haemorrhage. There was no evidence of maternal awareness during the procedure or recall afterwards.

Most enflurane is excreted through the lungs and less than 3 per cent is metabolised to inorganic fluoride.[34] This is less than that reported for other fluorinated anaesthetic drugs and probably reflects the greater chemical stability of the enflurane molecule.[34] It may also reflect the more rapid excretion of the drug which occurs as a result of its relatively low tissue solubility.[34,35] Rapid elimination reduces the time available for metabolism. Consequently the serum inorganic fluoride level does not remain elevated for as long after enflurane as it does after methoxyflurane. The mean peak level is normally less than 25 μ M/l[35,36] which is about half the concentration that is likely to cause renal damage.[37,38] There is no evidence to suggest that enflurane impairs renal function in otherwise healthy patients undergoing routine surgery and anaesthesia[35,36] or in volunteers undergoing prolonged anaesthesia (9.6 MAC hours).[39] However, high serum inorganic fluoride levels have been measured in a few instances[35,36] and are probably due to a delay in excretion of either enflurane, for example in obese patients, or of inorganic fluoride, for example in patients with impaired glomerular filtration. Some support for this suggestion comes from reports of nephrotoxicity following enflurane anaesthesia and surgery in patients with impaired preoperative renal function.[40,41] Another cause of raised serum inorganic fluoride might be its increased production as a result of induction of hepatic microsomal enzymes by drugs.[35,36] Enflurane itself has been shown to induce hepatic enzymes[42] so that previous exposure to the agent might lead to increased production of inorganic fluoride. Such a mechanism may have contributed to the renal failure reported following six hours of surgery and anaesthesia with enflurane in a patient with moderately severe heart disease who had been exposed to enflurane six weeks previously.[43] Urinary output returned spontaneously after three days and renal function gradually improved. The peak level of serum inorganic fluoride was not measured but the level two days post-anaesthesia was 93 μ M/l far in excess of the toxic threshold. It seems advisable to avoid enflurane in patients who have impaired glomerular function (i.e. raised blood urea or impaired creatinine clearance) or who have recently taken drugs that are known to induce liver enzymes. For the present this must include recent exposure to enflurane.

Apart from inorganic fluoride other biochemical variables have been measured following routine anaesthesia[35,36] and after prolonged anaesthesia without

surgery.[39] There was no evidence to suggest in either group of studies that liver function was impaired. However, SGOT was increased by three times the control value following prolonged anaesthesia and elevated significantly after routine anaesthesia.[35,39] This change is unexplained at present. Hepato-cellular dysfunction and jaundice have been reported in isolated cases after enflurane anaesthesia[44,45] but there is insufficient evidence to confirm that the anaesthetic agent was responsible.

Other small changes in serum electrolytes and other blood variables have been reported but are thought to be related to changes associated with stress.[35]

A marked and very variable increase in creatinine phosphokinase has also been measured in four volunteers following prolonged enflurane anaesthesia.[39] The clinical significance of this is not known at present. However, two cases of malignant hyperpyrexia have been attributed to enflurane.[46,47] In both of these patients suxamethonium was administered and therefore cannot be excluded as the responsible agent.

Enflurane administered in the absence of surgery does not significantly depress the immune response as measured by the ability of a volunteer's lymphocytes to transform in response to phytohaemagglutinin. It does induce a modest leucocytosis that persists until the first postoperative day.[48] In vitro studies have shown that enflurane has no mutagenic effect.[49]

The volatile anaesthetic enflurane has the advantage of inducing anaesthesia rapidly and allowing a fast recovery afterwards. It augments the action of non-depolarising muscle relaxants. It is a safer drug to use than halothane in the presence of raised blood catecholamines. It may induce seizure activity on the EEG and could under adverse conditions exacerbate and even induce renal failure. So far it has not been shown to cause liver damage. Otherwise many of its properties are similar to those of halothane.

ETOMIDATE

Etomidate is a potent rapidly acting intravenous hypnotic agent first introduced into clinical anaesthesia by Doenicke[50] in 1973 after animal studies by Janssen et al.[51] It is an ethyl-imidazole carboxylate derivative and consequently not related to any previous intravenous induction agent. It is a white crystalline powder, soluble in a wide range of solvents including water, ethanol and propylene glycol. The pH of the aqueous solution is 3.46 and its osmolality 254 mOs/kg.[52] Dissolving the drug in propylene glycol (the current solvent) increases the pH to 8.1 and the osmolality to 4640 mOs/kg.[52] Following intravenous administration, the plug is distributed approximately equally between red blood cells and plasma. Plasma binding in man is 76.5 per cent.[53] The dose is rapidly redistributed from the blood to other tissues. Animal studies show that only 2.5 per cent of the original dose remains in the circulation two minutes after intravenous administration.[54] In contrast peak levels are measured in the brain, heart, lungs, liver and kidney at that time and by 28 min only fat contains a high concentration of drug.[54] In man the fall in plasma concentration has been shown to fit a three compartment model with half times of the three phases being 2.8 min, 32.1 min and nearly four hours.[55] Studies in Wistar rats suggest that etomidate is metabolised in the liver

probably by capacity limited hydrolysis of the methylated ester. Peak blood level of metabolites were measured at 7 min though these had no anaesthetic activity.[54] The biological half life of the drug was shown to be 40 min.[54] About 50 per cent of a tritium labelled dose was excreted in the urine within four hours and 10 per cent of the dose excreted in the bile.

Studies in man of the renal excretion of labelled drug gave similar results; nearly 50 per cent of the administered dose was recovered within four hours and nearly 80 per cent by 24 hours.[56]

Etomidate rapidly induces hypnosis. Consciousness is lost within 10–65 seconds of administration, depending on the rate of injection, dose of hypnotic and type of premedication.[57,58] The time to loss of consciousness is similar to that after thiopentone.[59] The optimum dose that has been recommended for induction is 0.3 mg/kg.[50] This induces effective hypnosis for approximately 4–5 min with minimum cardiovascular changes.[60] Smaller doses within the range 0.12/0.16 mg/kg induce drowsiness but not necessarily hypnosis.[60]

Within the clinical range, the duration of unconsciousness depends on the dose of etomidate. 0.2 mg/kg induces sleep for 2–3 min whereas 0.4 mg/kg induces sleep for 6–7 min.[60,61] Premedication with narcotics increases the duration of hypnosis.[60,61] If etomidate 0.1 mg/kg is administered each time a patient awakes over a period of 30 minutes the duration of anaesthesia is not prolonged as the total dose rises.[62] However, cumulation, as judged by prolonged recovery time, has been noted when larger quantities of etomidate are administered as the principal anaesthetic.[61,63] Delayed recovery, i.e. more than 30 minutes after surgery, was recorded in 15 per cent of patients during an early study which used a continuous intravenous infusion of etomidate.[63]

Little work has been carried out to establish the relative potency of etomidate compared with other agents. However, using the criterion of duration of abolition of eyelash reflex 0.2 mg/kg etomidate is equivalent to 0.036 mg/kg Althesin (Table 1.1). This comparison was carried out double blind and in the same group of patients having repeated electro-convulsive therapy.[64] It is interesting to note that in a previous study carried out in a similar manner 50 mg methohexitone abolished eyelash reflex for the same period of time.[65]

Some studies have also been undertaken into the time to long-term recovery. Ten unpremedicated volunteers given 30 mg etomidate were asked to perform a vigilance test involving the recognition of numbers on a board. The mean time from induction to the achievement of a comparable performance with control was 24 min.[66] Kay has shown that ocular movements as measured by the Maddox wing had returned to control values some 30 min after the administration of etomidate 0.2 mg/kg.[62] Out-patients induced with either etomidate 0.3 mg/kg or propanidid 7 mg/kg and kept anaesthetised with nitrous oxide and halothane for minor surgical procedures woke at approximately the same time—some 6–8 min afterwards. They were able to stand and walk steadily within 17–20 min, the etomidate group taking slightly longer.[67] The quality of recovery after a single dose of etomidate is good with no 'hangover'.[68]

The EEG changes that occur during anaesthesia with etomidate (0.3 mg/kg) are broadly similar to those that occur with thiopentone or Althesin.[59,69,70,71] There is an initial increase in the overall energy level and then a progressive decrease

with burst suppression becoming established in some cases.[69] Frequency analysis shows that there is less fast β activity than is normally associated with intravenous anaesthesia.[59,70] Etomidate is similar to Althesin and different from the barbiturates in that slow activity (< 2 Hz) persists after induction.[70] This probably reflects the persistence of muscle activity that is characteristic of both these drugs.[70,72] The addition of diazepam or fentanyl at induction increases the rate of development of deep cortical depression and prolongs its duration.[69] The high incidence of myoclonic movements that occurs with etomidate anaesthesia is not associated with specific EEG changes or epileptiform discharges.[59,69,71] Furthermore, the drug has been administered to a group of patients with epilepsy and no specific

Table 1.1 Mean time from administration of drug to return of eyelash reflex (seconds). Adapted from O'Carroll, T. M., Blogg, C. E., Hoinville, E. A. & Savege, T. M. (1977);[64] Foley, E. I., Walton, B., Savege, T. M., Strunin, L. & Simpson, B. R. (1972)[65]

		S.D.
Etomidate (0.2 mg/kg)	252 s	(±87)
Althesin (0.36 mg/kg)	253 s	(±106)
Methohexitone (50 mg)	251 s	

adverse effects resulted.[73] It is presumed therefore that these movements originate in deep cerebral structures or in the brain stem.[59,69] The cerebral function monitor, which derives a trace from the EEG signal, indicates changes following etomidate that are similar to those induced by the barbiturates and Althesin.[74] However, the changes during a continuous infusion of etomidate are less obvious than those noted following Althesin. This makes control of the infusion less precise.

Although etomidate is an effective hypnotic it will not prevent movement in response to relatively minor stimulation.[59,62,75] Furthermore, the increase in blood pressure that is characteristically seen at the time of intubation is if anything more marked following etomidate than after methohexitone.[76] Anaesthesia with nitrous oxide, muscle relaxant and repeated bolus doses of etomidate does not suppress obvious clinical signs of increased autonomic activity during the noxious stimulation of surgery.[61] The paradox that deep cortical depression, as shown by burst suppression on the EEG, can be demonstrated at the same time as the patient responds with movement or autonomic changes to noxious stimulation has been reported previously with Althesin.[77,78] It emphasises the error of equating depth of cortical depression with adequacy of anaesthesia. Althesin and etomidate are potent depressants of the cerebral cortex but are far less effective at obtunding reflex responses to noxious stimulation. The administration of more hypnotic in an attempt to prevent autonomic changes or movement will merely depress the cortex further thus tending to prolong recovery without improving the quality of anaesthesia.[78]

There is wide agreement that etomidate exerts very little effect on the cardio-

vascular system of healthy patients.[57,58,67,79,80,81,82,83] Occasional dysrhythmias have been reported,[75,84] the incidence being approximately 1 per cent in adults and rather higher in children.[75,84] It is unlikely that this is a specific effect of etomidate, the incidence being comparable to that following thiopentone.[75,84] In healthy patients premedicated with atropine only, etomidate in doses between 0.15–0.3 mg/kg induces a small increase in heart rate, either no change or a small fall in systemic and pulmonary arterial pressure, a fall in systemic vascular resistance and either no change or a small rise in cardiac output.[82,85] Myocardial contractility, measured indirectly, is either unchanged[82] or slightly increased.[80] Myocardial blood flow, measured in five patients, rose, yet myocardial oxygen consumption only increased by a small amount which suggests that etomidate dilates coronary vessels.[82] A feature of many reports is that patients move during induction of anaesthesia with etomidate and may develop marked myoclonia. In the cardiovascular study of Kettler and colleagues,[82] measurements became difficult because of movement, and four out of five patients had to be held down. Rifat and colleagues[85] also noted muscle movement and myoclonia in 9/14 patients in their study. It is noticeable that the only other intravenous anaesthetic that does not overtly depress the cardiovascular system is ketamine which also induces increased muscle tone and movement. It is presumably to be expected that when patients become unconscious the cardiovascular system will show reduced activity unless the drug administered induces specific pharmacological stimulation. One suspects that central stimulation, with or without muscle movement and myoclonia, is the price that must be paid if 'depression' of the cardiovascular system is to be avoided at induction of anaesthesia. The tachycardia and movement following etomidate has been related to the incidence of pain that often accompanies intravenous administration of the drug[84] but it would be wrong to conclude that these effects are caused by pain; narcotic analgesics, which prevent these clinical signs, could do so by separate mechanisms. Whatever the mechanism, narcotic premedication is known to modify the incidence of myoclonia and movement[68] and as a result probably modifies the cardiovascular effects. In this context it is interesting to note that the cardiovascular changes following the administration of etomidate to heavily premedicated patients with heart disease were indistinguishable from those measured following Althesin 0.05 ml/kg.[86] In none of that group was there any complaint of pain on injection and no evidence of movement or myoclonia.

Comparison of the effect of etomidate with other agents is difficult because there is no agreed equipotent dose range. In general, etomidate alters cardiovascular activity less than all the other commonly used induction agents except ketamine and possibly methohexitone.[80,82,87] It is doubtful if the doses of different induction agents against which etomidate has been compared are always appropriate. In one study 0.15 mg/kg etomidate was compared with 1.5 mg/kg methohexitone.[80] Similarly in two other studies 0.3 mg/kg etomidate was compared with 0.075 ml/kg Althesin.[82,87] The doses used for comparison are probably of critical importance because the cardiovascular effects of the barbiturates and Althesin are dependent on the quantity administered per unit of time. Thiopentone was originally used in much larger doses which frequently had catastrophic effects on the cardiovascular system.[88] However, all these agents, if

administered slowly, in small doses, will induce hypnosis with little reduction in cardiovascular variables.

Changes in cerebral blood flow following the administration of intravenous induction agents have been measured in a group of healthy premedicated patients anaesthetised with propanidid, nitrous oxide and 0.1–0.4 per cent halothane and ventilated, using intermittent suxamethonium, to keep $Paco_2$ within the normal range. Etomidate 0.2 mg/kg reduced cerebral blood flow by 37 per cent, 30 sec after administration, but flow had returned to control value by 5 min. In contrast, the barbiturates and propanidid depressed flow by a greater percentage at 30 sec. By 10 min cerebral blood flow had returned to control values following both propanidid (5 mg/kg) and methohexitone (1 mg/kg) whereas after thiopentone (4 mg/kg) cerebral blood flow remained reduced and close to minimum values.[89] It is difficult to assess the clinical significance of such an investigation where so many other factors that alter cerebral blood flow were operating.

Famewo[90] has shown that etomidate 0.3 mg/kg reduced intraocular pressure in a group of premedicated patients by 33 per cent, a rather surprising finding in the face of the drug's minimum effect on the cardiovascular system and the high incidence of myoclonia and increased muscle tone that etomidate induces.

Etomidate slows respiratory rate for a short period following induction[61] and then increases it slightly.[58,59,81,91] Tidal volume increases for a brief period shortly after injection of the drug[59,81,91] and is followed by a short period of shallow ventilation.[91] Apnoea may occur but is less common than after thiopentone.[84] Its incidence is between 16–50 per cent[68,79,83,84,91] and is short lived.[79] Respiratory changes do not seem to be influenced much by premedication.[68,79,83] A fall in Pao_2 to a mean value of 66 mmHg was measured in a group of patients with heart disease breathing air and induced with etomidate (0.3 mg/kg) but this fall was less than that measured after Althesin (0.05 ml/kg).[92] $Paco_2$ and pH were not altered. However, in a similar group of patients premedicated with papaveretum and hyoscine, the $Paco_2$ increased by a mean maximum of nearly 1 kPa (7.5 mmHg) over the 10 minutes following the administration of etomidate 0.3 mg/kg.[86] Coughing, hiccough, and stridor seldom occur[64,68] and are not more frequent than after thiopentone.[84]

No consistent and marked changes have been detected in liver function tests, renal function tests or in plasma electrolytes at 24 hours and 7 days after etomidate.[93]

The principal complications of etomidate are muscle movement and pain at the site of intravenous administration. Much has been written about muscle movement and this has even been broken down into sub-headings such as myoclonus—mild or severe, spontaneous movement in response to noxious stimulation and generalised increase in muscle tone. Mild myoclonus is reported in 18–70 per cent of patients following induction.[57,59,64,68,67,75,79,81,83,84,90,91,93,94] Severe myoclonus or a generalised increase in muscle tone is less common (6–12 per cent).[68,79,81,84] The incidence of movement is far higher than after thiopentone (7.4 per cent),[84] Althesin (3.0 per cent)[64] or propanidid (0 per cent).[67] Movement is increased if the patient is stimulated and decreased by premedication especially if it contains narcotic analgesics.[68,79,83] Holdcroft and colleagues[68] demonstrated that papaveretum and hyoscine premedication reduced the incidence of movement

by approximately 40 per cent. Muscle movement is probably the result of two factors:

1. Central stimulation by etomidate at a level somewhere below the cortex.[59,69]
2. A reflex response to noxious stimulation.

The latter may be relatively mild, such as holding up the chin or placing a mask on the face. Pain on injection may also be a cause for movement.[84] It is difficult to assess how much the muscle movement limits the use of etomidate. Provided anaesthesia is effectively maintained movement rapidly subsides and so it is probably no more than an irritation for the anaesthetist. It also seems quite likely that this increased activity at induction is responsible for maintaining cardiovascular 'stability'.

The incidence of pain at the site of injection during the administration of etomidate is high, but there is wide variation in the reported incidence (15–81 per cent);[51,68] however, most studies describe an incidence of between 25–50 per cent.[59,67,75,79,83,94] The severity of pain can be modified according to the site of injection, the solvent used and the type of premedication.[95] Fast injection may be less painful[67,95] as is injection into a vein in the antecubital fossa compared with a vein on the back of the hand.[59,79] The aqueous solution of etomidate induces most pain and the solution made up in polyethylene glycol the least[52,94] the incidence of pain falling from 30 per cent to 4 per cent.[52] It is suggested that the improvement is due to the more physiological pH and osmolality of the latter solution.[52] Propylene glycol is the solvent currently used with etomidate and the incidence of pain during injection is slightly greater than that for the polyethylene glycol solutions.[94]

The occurrence of local reactions at the site of injection does not reflect the high incidence of pain. In 5–6 per cent of patients there is a local skin flush[64,83] and in several studies phlebitis has been reported in one or two patients.[68,79] Venous thrombosis observed three days after etomidate occurs in 8 per cent of cases.[95]

The incidence of nausea and vomiting is apparently rather higher than that following other induction agents. In a series of patients undergoing general surgical procedures the incidence was around 25 per cent with premedication making only small differences.[68] In a group of gynaecology patients, notorious for postoperative vomiting, the incidence was between 35–53 per cent varying slightly with the speed of injection and the solvent used.[94]

Doenicke and colleagues[96] demonstrated that etomidate does not release histamine when administered to volunteers unlike other commonly used induction agents.[96,97] In their study changes in plasma histamine also failed to develop in at least half of the subjects following the administration of Althesin or propanidid. It would therefore be useful to have the results for etomidate confirmed in a series larger than the eight subjects originally studied. Histamine release is initiated by a wide range of drugs used in anaesthesia without the development of clinical signs.[97] Another factor must be present to explain the severe clinical reactions that have been reported following the administration of other induction agents.[98] At this stage one cannot conclude that etomidate will never induce such a reaction. However, none has been reported to date despite many thousands of etomidate anaesthetics.