Review Article

New drugs – boon or bane? Premedication and intravenous induction agents

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Research on the benzodiazepines has shown that they have certain advantages over the opiates as premedicants. Diazepam, which produces good tranquilisation, is well absorbed when given orally though absorption is influenced by other drugs given at the same time. Oral lorazepam leads to more prolonged sedation and amnesia but the final elimination is more rapid.

Several new intravenous anaesthetics have been introduced during the last five years but none seems likely to replace thiopental. The theoretical disadvantages of thiopental are offset by its water-solubility, and the use of Cremophor EL in preparations of propanidid, alphaxalone, di-isopropyl phenol and one preparation of diazepam has led to many hypersensitivity reactions. Ketamine is gradually finding its rightful place in anaesthesia but its use is becoming limited to anaesthesia in difficult circumstances. The future concomitant use of other drugs and separation of isomers of ketamine may again broaden its applications. The new water-soluble steroid minaxolone has its own disadvantages, and the water-soluble benzodiazepine midazolam is as unpredictable for induction of anaesthesia as diazepam.

Key words

PREMEDICATION, diazepam, lorazepam; ANAESTHETICS, intravenous, minaxolone, di-isopropyl phenol, ketamine, midazolam.

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Premedication

The opiates remain the most widely used sedative premedicants and the most popular drugs are still the well-tryed morphine, papaveretum and meperidine. On the other hand the benzodiazepines have advantages over the opiates and are undergoing steady research and progress.

The superiority of diazepam as a premedicant as compared with morphine was shown soon after its introduction,¹ and diazepam sedates without causing significant nausea or vomiting. On the other hand the elimination half-life of about 50 hours² and conversion into the sedative metabolite N-desmethyl diazepam with an even longer half-life, gives diazepam distinctive dangers. The plasma level and clinical action of diazepam show a second peak five to six hours after administration, probably due to enterohepatic recirculation.

One of diazepam's advantages is that it is well absorbed by the oral route. Gamble *et al.*³ have shown that after a 10 mg oral dose the plasma level reaches a peak at 60 minutes (approximately 200 ng/ml⁻¹) and only begins to fall after a further 30 minutes. This compares favourably with plasma levels following administration by the intramuscular route which leads to particularly low levels if the injection is made into the gluteal region.⁴

The rate of absorption of oral diazepam can be considerably influenced by other drugs given parenterally at the same time.³ For instance atropine 0.6 mg i.v. or i.m. delays absorption and reduces the peak level reached. The opiates, especially morphine, have a similar effect, in contrast to metoclopramide which increases absorption to produce a peak at about 20 minutes, with a slow fall off. The influence of oral antacids is also significant

since they are frequently given in obstetrics to raise gastric pH.⁵ Aluminium hydroxide increases the rate of absorption, presumably by raising gastric pH to approach the pKa of diazepam and accelerating uptake from the stomach itself. Other antacids studied had little effect on absorption.

The clinical findings have broadly matched those for plasma levels and the highest scores for overall satisfactory effects are obtained 60–90 minutes after diazepam given by mouth.⁶ Again, clinical effects are enhanced by concomitant administration of aluminium hydroxide. The sedative action of intramuscular diazepam is somewhat less but one of its most undesirable effects is the intense and persistent pain that it causes at the site of injection.

Study of lorazepam as a premedicant⁷ has shown that it also was a better anxiolytic than the opiates. Galloon *et al.*⁸ found that while both diazepam and lorazepam were effective by the i.m. route, lorazepam had a slower onset and longer duration of action. It differs from diazepam in being somewhat better absorbed by the i.m. than by the oral route and the peak plasma levels occur at least two hours after injection.⁹ The onset of action parallels the plasma level but the advantages of better absorption after intramuscular injection is offset by the pain at the site. Clinically, 2–4 mg of lorazepam by mouth provides drowsiness and relief from apprehension, the full effect being reached in 90 minutes and lasting for about three hours. Blood levels following absorption from the stomach are reduced by the effects of rapid hepatic inactivation and the use of the sublingual route may lead to equally rapid absorption with higher peak effects. The elimination half-life is 12 hours and, as with diazepam, there is a second peak at 5–6 hours.

Amnesia following the benzodiazepines is well-recognised after their intramuscular¹⁰ and intravenous¹¹ administration. A dose-related amnesic effect has also been found¹² with diazepam 10 and 20 mg by mouth beginning about 20 minutes after administration and persisting for at least 90 minutes. Flunitrazepam, in this as in other respects, behaves similarly to diazepam, in doses of 0.5 and 1 mg. However with lorazepam 2 and 4 mg the time course was very prolonged, beginning in approximately 40 minutes and lasting for several hours (Figure 1). Kothary and Pandit¹³ confirmed that the duration of action of diazepam was about 90 minutes and of lorazepam about three hours but the amnesic effect is much more marked with the latter

FIGURE 1 Percentage frequency of complete or partial failure to recognise the previously seen stimulus at the times shown after the oral administration of lorazepam 1 mg, 2 mg and 4 mg. (From McKay and Dundee,¹² reproduced by permission of the Editor, Br J Anaesth.)

drug. Although patients may be aware of a visual or auditory stimulus, the ability to recognise or recall it later is closely related to the degree of drowsiness at the time. There is no good evidence that any of these agents can produce retrograde amnesia, that is amnesia for events before the drug was given, in the absence of hypoxia.

Benzodiazepine premedication has been used in obstetrics as well as general surgery. However diazepam does cross the placental barrier and may accumulate in the foetus.¹⁴ It could therefore cause prolonged depression of the infant. Lorazepam with its shorter half-life may be slightly safer for the infant but the intense anterograde amnesia is not always acceptable to the mother.

Intravenous anaesthetics

The steady influx of new drugs has continued but before analysing their properties the deficiencies of thiopentone should be considered. Only in the light of these can a role for new agents be considered.

Disadvantages of thiopentone

PHYSICAL PROPERTIES

Thiopentone is water-soluble but the solution is not stable for prolonged periods. Two weeks is recommended as a maximum safe time,¹⁵ which rules out marketing of the drug in solution, and most anaesthetists restrict the made-up solution to a much shorter shelf-life. The resultant 2.5 per cent solution has a pH of 10.5 which makes it irritant if injected extravascularly and carries the danger of arterial spasm and thrombosis if injected into an artery. It would be ideal if there were a water-soluble, neutral

TABLE I Anaesthetic and lethal doses of various anaesthetic agents given intravenously to male mice¹⁶

Agent	AD ₅₀ (mm/kg)	LD ₅₀ (mm/kg)	Therapeutic index (LD ₅₀ /AD ₅₀)
Thiopentone	13.2	90.5	6.9
Methohexitone	5.4	39.4	7.4
Propanidid	22.9	184.7	8.1
Ketamine	12.7	108.3	8.5
Althesin	1.8	54.7	30.6

and isotonic solution of an anaesthetic which could be rapidly absorbed from tissues as well as being useable intravenously.

INDUCTION CHARACTERISTICS

The onset of anaesthesia with thiopentone is rapid, predictable, and smooth and these must be regarded as prerequisites in any newly introduced agent. Hypotension and depression of cardiac output are disadvantages, particularly in patients with disease of the coronary arteries and many anaesthetists now use a high-dose narcotic induction technique. Respiratory depression following thiopentone is a minor problem since ventilatory assistance is easy to provide.

RECOVERY

Recovery following thiopentone is mainly due to translocation of the drug into the well-perfused tissues of the body and only to a small extent to metabolism. This means that full recovery can never be as rapid as following propanidid. However, metabolism is rapid enough to clear the drug to a clinically acceptable extent in hours rather than days. Certainly it is smooth and without hallucinations or (in the absence of narcotics) postoperative sickness.

SAFETY MARGINS

Animal experiments (Table I)¹⁶ have shown that thiopentone has the lowest therapeutic index of any of the currently used intravenous anaesthetics. Findings in man are less clear-cut but over a wide dose range the steroid combination Althesin has probably the greatest safety margin.

The steroid anaesthetics

Steroid anaesthesia has been known for over 25 years but it only became a satisfactory alternative to

older agents with the introduction of Althesin.¹⁷ Unfortunately the main constituent of this solution, alphaxalone, is sparingly soluble in water, and alphadolone acetate is added to enhance its solubility. In addition, the steroids require an organic solubiliser, and Cremophor EL has been used up to the present.

The introduction of Althesin renewed interest in the problems of hypersensitivity reactions which had first attracted attention following propanidid (reviewed by Clarke^{18,19}). The report of Clark and Cockburn²⁰ showed that reactions could occur with thiopentone but since then, evidence has increasingly implicated Cremophor EL.^{19,21} The frequency of reactions is approximately 1 in 1,000 with cremophor-containing anaesthetics compared with approximately 1 in 30,000 with thiopentone and, in addition, the studies of Glen and his colleagues²² have demonstrated in the "miniature pig" the role of a "short-term memory" for previous exposure to cremophor-containing drugs. They found that when such drugs are repeated within one to three weeks there was a marked liberation of histamine and distinctive clinical response.

Even before the introduction of Althesin, a range of steroids had been studied in an attempt to produce a drug which was both water-soluble and rapid-acting and had the high therapeutic index of this group. Minaxolone was introduced in 1979 and it was hoped that it would meet these requirements. Initial clinical trials²³⁻²⁶ have shown that 0.5 mg/kg⁻¹ does induce anaesthesia in one arm-brain circulation time. However, excitatory effects more marked than those with methohexitone occur in approximately 50 per cent of patients. These effects are accentuated when the drug is injected rapidly but are diminished with diazepam or opiate premedication. Recovery following anaesthesia with minaxolone/nitrous oxide/oxygen is slower than after anaesthesia with Althesin, methohexitone or thiopentone (Figure 2). This is contrary to the trend in other new anaesthetics and must be a definite drawback to its use. The drug was withdrawn from clinical trial in 1980 until animal toxicological findings could be re-checked, but it certainly does not appear to have the advantages of Althesin.

Di-isopropyl phenol

This is the newest of the non water-soluble anaesthetics to be solubilised in Cremophor EL, under the

FIGURE 2 Percentage incidence of patients unsafe (dark area) and safe with protective reflexes (cross-hatched area) two minutes after discontinuing nitrous oxide anaesthesia with various intravenous agents. Premedication: 0, none; D, diazepam; A, atropine; P/A, pethidine and atropine; P/H, papaveretum and hyoscine. (From H G McNeill *et al.*,²⁵ reproduced by permission of the Editor, *Anaesthesia*.)

name ICI 35,868 and has been in clinical use since 1977 when Kay and Rolly²⁷ described some early studies. However, clinical research has proceeded slowly because of doubts about this formulation. Initial studies^{28,29} indicate that 2.0 mg/kg^{-1} is a satisfactory induction dose when given over 20 seconds. The main advantage of this drug is the very low incidence of excitatory side effects in doses up to 3 mg/kg^{-1} but, against this, there is frequently marked respiratory depression even in the absence of sedative premedication.

All workers have noted a high incidence of pain on injection, amounting to approximately 39 per cent with hand or wrist injections. In fact the incidence only falls to acceptable levels when the drug is injected into a large antecubital vein or into a fast-running infusion. The pain is not, however, associated with late venous thrombosis. Recovery of consciousness appears to be smooth but no more rapid than after thiopentone.²⁹

However, the future of this drug must depend on a suitable vehicle being found as an alternative to Cremophor EL. One clear-cut hypersensitivity reaction with flushing, hypotension, and bronchospasm has been described following its use³⁰ and it seems likely that the incidence with this drug will be similar to that with propanidid and Althesin, approximately one in 1,000 administrations. Certainly the manufacturers of both Althesin and di-isopropyl phenol are investigating alternative solvents but the problem of producing one which is non-antigenic and non-irritant is still almost insoluble.

Ketamine

This is no longer a new drug but work is continuing to define its rightful place in anaesthesia and to reduce its undesirable effects. Its advantages are good local tolerance, rapid absorption from intramuscular injection, sympatho-adrenal stimulation and absence of muscular relaxation. Disadvantages include excessive hypertension and tachycardia during the first ten minutes after induction with hallucinations and delirium during the recovery phase, these being seen mainly in adults. Its main role would therefore appear to be for minor paediatric operations, in particular for investigative procedures and burns dressings. The drug has a more restricted place in adults for anaesthesia in difficult circumstances, e.g. at a major disaster, where anaesthetic facilities are primitive or when it is necessary to give anaesthesia in bed. The elevation of the arterial blood pressure suggests its use in the shocked patient but this indication has been doubted³¹ since some patients in this state experience a fall in mean arterial pressure or cardiac index and a rise in pulmonary capillary wedge pressure.

Ketamine is the only intravenous anaesthetic which produces definite and long-lasting analgesia^{32,33} and this has encouraged its use specifically for the relief of postoperative pain.³⁴ It has been used as a one per cent solution in an average dose of $25 \mu\text{g/kg}^{-1}/\text{min}^{-1}$ and effective clinical analgesia has been reported without serious side effects. The use of infusions for total intravenous anaesthesia has also been tried with satisfactory results.³⁵⁻³⁷ Induction has usually been with ketamine $1 \text{ mg/kg}^{-1}/\text{min}^{-1}$ depending on the state of the patient. However, it is pointed out that the requirement does decline with time as would be expected with a drug which is first translocated and only slowly metabolised³⁵ (Figure 3).

The marked hypertension and tachycardia with ketamine is probably a disadvantage in most patients and must be dangerous in those with cardiac disease. Attempts to control this action have been ineffective, though labetalol 1 mg/kg^{-1} given intravenously with the ketamine has proved the best.³⁸ Intravenous diazepam has also been used for many years to attempt to control postoperative delirium.³⁹ However, more recent studies⁴⁰ have shown that lorazepam 4 mg given intravenously before induction is more effective in preventing the delirium and dreams. Surprisingly few studies have

FIGURE 3 Dose of ketamine (mean $\pm$ SE) required to maintain anaesthesia over the first 50 minutes after premedication with lorazepam 4 mg orally and an initial dose of ketamine 1 mg/kg⁻¹. — Patients breathing spontaneously; --- patients receiving tubocurarine and controlled ventilation. (From Lilburn, Dundee and Moore,³⁵ reproduced by permission of the Editor, Anaesthesia.)

concentrated on the psychological approach in reducing the incidence of unpleasant dreams but Sklar *et al.*⁴¹ do show its value since any dreams encountered were pleasant. Unfortunately there is no control group in their study to show the nature of the dreams in the absence of psychotherapy, but clearly the overall approach seems appropriate.

The most promising breakthrough in the "taming" of ketamine has been in the separation of its optical isomers. White *et al.*⁴² have shown that the (+) isomer is approximately three times as potent as the (-) isomer, though the former produces less increase in blood pressure and heart rate. In addition, the analgesic potency is higher and the quality of anaesthesia better with the (+) isomer. It is also followed by fewer hallucinations, less delirium and less sickness than the (-) isomer.

Benzodiazepines

Evidence is now accumulating that not only does

FIGURE 4 Average plasma midazolam level ($\pm$ SE) after 5 mg (O—O—O) and 10 mg (●—●—●) given to the same subjects at a two-week interval. (From Dundee, Samuel, Toner and Howard⁴⁷ reproduced by permission of the Editor, Anaesthesia.)

diazepam (as Valium) cause pain on intravenous injection, but its use is followed by up to a 39 per cent incidence of venous thrombosis over the next 10 days.⁴³ These effects are probably related to the use of propylene glycol and benzoic acid as solvent and Cremophor EL was tested as an alternative for a short time. The resultant formulation (Stesolid MR) was found to be non-irritant,⁴⁴ but reports of reactions soon reached a similar frequency to those with propanidid and Althesin.⁴⁵ The preparation of diazepam in a soya-bean oil emulsion (Diazemuls: Kabi-Vitrum) has proved to have all the properties of Valium with a negligible incidence of pain on intravenous injection and subsequent thrombophlebitis (Table II).^{44,46}

Diazepam has proved to be an unpredictable induction agent but is a satisfactory sedative for endoscopies and for patients having prolonged operations under regional analgesia. The new water-soluble benzodiazepine, midazolam, appears to fill a similar role in anaesthesia with the additional advantage that recovery is faster. This stems from three factors: firstly, the more rapid conversion into hydroxy-metabolites as judged by a plasma half-life of 60–90 minutes,⁴⁷ compared with approximately 32 hours for diazepam; secondly, the fact that these metabolites are not themselves hypnotic compared with the temazepam, des-

TABLE II Frequency of venous sequelae 7–10 days after intravenous injection of various anaesthetics as induction agents. Findings from different sites of injection and sizes of vessel have been pooled

Drug	Concentration (%)	Main solvent	n	Pain on injection (%)	Venous sequelae (%)	Reference
Saline	0.9	Water	50	0	0	46
Thiopentone	2.5	Water	50	9	0	46
Methohexitone	1.0	Water	50	12	10	46
Di-isopropyl phenol	1.0	Cremophor EL	50	11	2	29, 46
Diazepam	0.5	Propylene glycol	50	37	36	46
	0.5	Soya bean oil	50	0	0	46
Flunitrazepam	0.1		43		5	43
Lorazepam	0.1	Propylene and polyethylene glycol	40		15	43
Midazolam	0.5	Water	100	1	6	46

methyl diazepam and oxazepam formed from diazepam; and thirdly, absence of entero-hepatic recirculation with midazolam — a phenomenon which leads to the undesirable "second peak effect" six hours after a dose of diazepam.⁴⁸ Midazolam is about twice as potent as diazepam and, as shown in Figure 4, plasma levels are negligible five and nine hours after typical clinical doses of 5 and 10 mg. Finally, midazolam, being water-soluble, lacks the irritant qualities of the standard diazepam solution and is similar to Diazemuls in its lack of venous irritation (Table II).^{46,49}

Etomidate

This drug has been in use in man for ten years but appears to have no clear place in intravenous anaesthesia. It has many disadvantages including the marked muscle movements on induction (which can be minimised by pretreatment with fentanyl) and a high incidence of venous thrombosis. As against these points it has no real advantages over those agents mentioned earlier.^{50,51}

Conclusion

There has been steady progress with the various groups of intravenous anaesthetics even if there are no drugs to supplant thiopentone. The drugs of low water-solubility cannot be used freely with safety until a suitable vehicle has been found. At present the soya bean oil emulsion appears the least toxic, but intensive research is in progress for alternatives. Certainly the most promising of the newer discoveries is midazolam — provided it is used as a basal hypnotic rather than as an induction agent.

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Résumé

Des études ont montré que les benzodiazépines ont certains avantages sur les opiacés comme agents de prémédication. Le diazepam, qui est un bon tranquillisant, est bien absorbé lorsqu'il est administré par voie orale, quoique son absorption soit influencée par d'autres médicaments donnés en même temps. Le lorazepam administré par voie orale produit une sédation et une amnésie de plus longue durée mais son élimination finale est plus rapide. Plusieurs nouveaux agents anesthésiques intraveineux ont été introduits au cours des cinq dernières années mais aucun ne semble pouvoir remplacer le thiopental. Les désavantages théoriques du thiopental sont compensés par son hydrosolubilité. L'emploi du crémosol EL pour les préparations de propanidid, d'alphaxolone et de di-isopropyl phénol ainsi qu'une préparation de diazepam ont provoqué de multiples réactions d'hypersensibilité. La kétamine va graduellement trouver sa propre place en anesthésie mais son emploi semble vouloir se limiter aux cas difficiles. L'usage concomitant d'autres médicaments et la séparation d'isomères de kétamine vont peut être amplifier ses applications. Le nouveau stéroïde hydrosoluble minaxolone a ses propres désavantages et l'hydrosoluble benzodiazépine midazolam est aussi incertain que le diazepam pour l'induction de l'anesthésie.