Intravenous Anaesthetic Agents

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General preface to series

The current rate of increase of scientific knowledge is such that it is recognized that '. . . ninety per cent of all the existing knowledge which can be drawn upon for the practice of medicine is less than 10 years old'.*

In an acute specialty, such as anaesthesia, failure to keep abreast of advances can seriously affect the standard of patient care. The need for continuing education is widely recognized and indeed it is mandatory in some countries.

However, due to the flood of new knowledge which grows in an exponential fashion greatly multiplying the pool of information every decade, the difficulty which presents itself is that of selecting and retrieving the information of immediate value and clinical relevance. This series has been produced in an effort to overcome this dilemma.

By producing a number of authoritative reviews the Current Topics Series has allowed the General Editors to select those in which it is felt there is a particular need for a digest of the large amount of literature, or for a clear statement of the relevance of new information.

By presenting these books in a concise form it should be possible to publish these reviews quickly. Careful selection of authors allows the presentation of mature clinical judgement on the relative importance of this new information.

The information will be clearly presented and, by emphasizing only key references and by avoiding an excess of specialist jargon, the books will, it is hoped, prove to be useful and succinct.

It has been our intention to avoid the difficulties of the large textbooks, with their inevitable prolonged gestation period, and to produce books with a wider appeal than the comprehensive, detailed, and highly specialized monographs. By this means we hope that the Current Topics in Anaesthesia Series will make a valuable contribution by meeting the demands of continuing education in anaesthesia.

Westminster Hospital
London

Stanley A. Feldman
Cyril F. Scurr

* Education and Training for the Professions.
Sir Frank Hartley, Wilkinson Lecture,
Delivered at Institute of Dental Surgery, 30.1.78
University of London Bulletin, May 1978, No. 45, p. 3.

Preface

This is not a textbook on intravenous anaesthetics, neither is it an updating supplement to the 1974 edition of *Intravenous Anaesthesia.* Rather, as the title conveys, it is intended to be a survey of what were considered to be topical items during the three months of its writing (January-March 1978).

The author has been engaged in the study of intravenous anaesthetics for over a quarter of a century and this has provided useful background knowledge against which to consider the current topics. To give these relevance in relation to established knowledge it has been necessary to include a brief survey of the present status of the barbiturates and eugenols. Such a review would have been impossible with althesin, as there is no established view on its place in anaesthesia; rather an attempt has been made to suggest a rational approach to its use to make the most of the many excellent qualities and to limit its dangers.

Most will agree that anaphylactoid reactions to intravenous anaesthetics is the major current talking point. This subject has been reviewed in depth by my colleague Richard Clarke in what is the longest chapter in this book. As one of the authors of a published report on a survey of 100 cases of sensitivity to intravenous anaesthetics, he has the necessary knowledge to put this subject into its true perspective. One hopes that this survey will help readers to clarify their views on hypersensitivity and be aware of this most dangerous aspect of the action of intravenous anaesthetics.

It is inevitable that a book of this nature reflects some of my personal current interests. This may partly explain the space devoted to ketamine. Ken Lilburn's collaboration in this has enabled me to draw on his experience of two years full-time research with this interesting drug. Some may feel that enough time and effort has already been given to 'taming' it and that it should join bromethol, vinesthene and ethylene. An apology is offered to those who feel that my knowledge of research in this field could have been put to better advantage.

This element of personal choice may be reflected in the inclusion of a lengthy discussion on the benzodiazepines and a briefer review on balanced techniques.

What of etomidate? To have omitted it or give it just brief mention may not have detracted from the value of the book to the average reader. However, there is no extensive review of it in the English language and the current one has given us an opportunity of comparing our findings with those of continental workers. Matthew Zacharias, who collaborated on this chapter, has undoubtedly more personal experience with etomidate than anyone in Britain and in the light of our finding it is hard to envisage a bright future for it.

There are three clinical fields in which there is much disagreement as to the place of intravenous anaesthetics. I have been fortunate to get the views of three experienced colleagues, on paediatrics (Sam Keilty), obstetrics (James Moore) and cardiac surgery (Ian Carson). Each of these has given his own views, rather than reviewing the literature and this should help clarify the position of intravenous drugs in the relevant fields.

A book on current topics must be written in a hurry and published before it is out of date. For this reason the bibliography has been kept to a minimum except in the major topics. It is an interesting experience to have a 'longhand-to-Editors' interval of about three months and this has not allowed time for rewriting or lengthy corrections. Such speed has only been possible with the cooperation of many colleagues and particularly the junior department staff who corrected tables, prepared diagrams, checked references etc. Above all an experienced typist, capable of reading my corrected manuscript and making sense of it has been an essential. To Noelle Collins I am particularly indebted for perfectly filling this role.

Belfast April 1978 John W. Dundee

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J.W.D.

Contents

1

Classification of intravenous anaesthetics

Although this book includes drugs other than those used principally to produce intravenous anaesthesia, it is useful to consider the manner in which the intravenous anaesthetic agents have been classified because it reveals an interdependence of three pharmacological activities:

1. Pharmacokinetics.
2. Chemical structure.
3. Clinical acceptability

Duration of action

The terms 'ultra-short-acting' and 'short-acting' are often applied indiscriminately to intravenous anaesthetics. These terms are not only confusing but may also be misleading and may have serious consequences for those not aware of the pharmacokinetics of the drugs. 'Ultra-short-acting' and 'short-acting' should be reserved for drugs which are rapidly broken down in the body and from which rapid recovery is not dependent on redistribution to non-nervous tissues. On this basis the terms are only applicable to:

Ultra-short-acting	propanidid (Epontol, Fabontal)
Short-acting	Althesin (Alfatesine; CT 1341)

In contrast with these truly short acting drugs, the termination of action of intravenous barbiturate (thiobarbiturate or methylbarbiturate) and the return of consciousness occur when there is a large amount of active drug remaining in the body. There is therefore always the possibility that these patients may relapse into unconsciousness if left undisturbed, especially if drugs given in the early postoperative period themselves lead to some depression of consciousness.

Onset of action

It is desirable for induction agents to have a rapid onset of action. Ideally, in adequate doses they should produce sleep in one arm–brain circulation time, so that dosage can be accurately titrated against the patient's requirements. Drugs with a slow onset of action are essentially basal hypnotics.

In general, drugs with a rapid onset of action have a shorter duration of action than more slowly acting compounds. The primary induction agents

(rapidly acting) also produce fewer side effects — excluding immediate cardiovascular and respiratory depression — than the slower acting (basal hypnotic) drugs. These latter drugs should be used only when specifically indicated. The following classification separates the various groups of drugs according to the rate of onset and their chemical constituents, rather than according to their duration of action (the more usual but less appropriate classification).

Rapidly acting

Induction agents:	thiobarbiturates, methylbarbiturates eugenols Althesin (steroid) etomidate sulphate (imidazole)

Slower acting

Basal hypnotics:	phencyclidines (ketamine) tranquillizers (diazepam, etc.) neuroleptic drug combinations and intravenous analgesics
others:	sodium oxybutyrate (Gamma-OH), chlormethiazole (Heminevrin), barbiturates

It should be noted that the barbiturates (such as pentobarbitone), which are generally employed as oral hypnotics, can be used intravenously — when they will have a moderately rapid onset of action.

Barbiturates

In addition to the above, these rapidly acting drugs can be classified either according to their chemistry or according to their clinical acceptability.

Chemistry (see Table 2.1)

Thiobarbiturates	thiopentone, thiamylal, thiobutobarbitone, buthalitone*, methitural*, thialbarbitone
Methylbarbiturates	hexobarbitone*, methohexitone, enibomal (Narkotal)

Clinical acceptability

Very satisfactory	equally acceptable	thiopentone, thiamylal, thiobutobarbitone, thialbarbitone
Unsatisfactory	too high an incidence of side effects	buthalitone*, methitural*, hexobarbitone*
Compromise	unique advantages, side effects	methohexitone, enibomal (Narkotal)

*These have been withdrawn from clinical use because of side effects.

Reference

Dundee, J. W. (1975). Classification of intravenous anaesthetics. In: *Recent Progress in Anaesthesiology and Resuscitation,* Proceedings of the IV European Congress of Anaesthesiology, Madrid, 5—11 September 1974, pp. 77—8. Ed. by A. Arias, R. Llaurado, M. A. Nalda and J. N. Lunn. Excerpta Medica, Amsterdam and Oxford; American Elsevier, New York.

2

The present status of the barbiturates

Barbiturates were the first successful intravenous anaesthetics and they remain the most popular anaesthetic induction agents. It is helpful to look at the reasons for their early acceptance and continuing clinical popularity — which has been achieved in spite of dangerous and occasionally lethal complications — since these drugs are the standards against which all new intravenous drugs are judged.

It has to be appreciated that, historically, not only were the intravenous barbiturates a new type of drug but also a completely new concept, viz. loss of consciousness induced by agents given intravenously. Perhaps just as important was the fact that it coincided with the development of the technique of 'balanced' anaesthesia — which restricted the use of the intravenous barbiturates to the production of hypnosis and thus limited the early abuse which followed their introduction. This, in fact, also resulted in the use of safe doses by the avoidance of the toxicity of large cumulative doses.

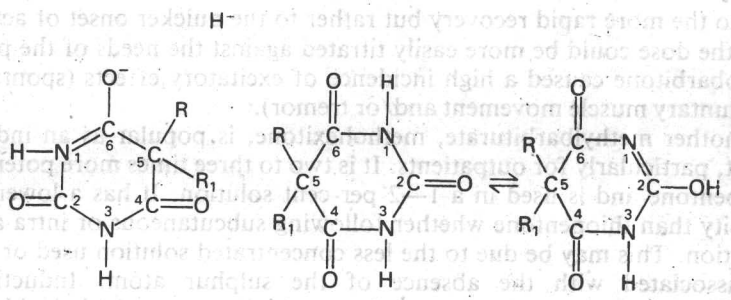
Barbiturates

Four chemical groups of barbiturates have been used, and Table 2.1 shows the relationship of the 1 and 2 position side chains to their group characteristics when given intravenously. The methyl thiobarbiturates are not used clinically and are included in the Table solely for the sake of completeness.

In practice, the (oxy)barbiturates are used mainly as night-time hypnotics adminstered by mouth. Occasionally they are used in psychiatric practice in small doses as basal sedatives. The absence, in Britain, of a commercially available stable solution of any of these drugs has hampered their use as a preanaesthetic medication, an indication for which they are widely employed in North America. The very active Campaign for the Use and Restriction of Barbiturates (CURB) propaganda of 1976—1977 was aimed at reducing the overprescribing of barbiturates as sedatives and reducing the incidence of dependence on these drugs. This is not likely to have much effect on their very limited use in the preoperative period, although it may have lessened the incidence of their prescription as a night sedative. However, in general, the benzodiazepines (diazepam, nitrazepam and, more recently, lorazepam) are widely considered to be the drugs of choice for patient sedation on the night before operation.

There is available a preparation containing pentobarbitone sodium 60

Table 2.1 Relationship of chemical grouping to clinical action of barbiturates



Pyrimidine derivative | Keto form | Enol form

Cyclical ureide of malonic acid

Group	Substituents position 1	Substituents position 2	Group characteristics when given intravenously
(Oxy)barbiturates	H	O	Delay in onset of action, degree depending on 5 and 5′ side chains. Useful as basal hypnotics. Prolonged action
Methyl barbiturates	CH_3	O	Usually rapidly acting with fairly rapid recovery. High incidence of excitatory phenomena
Thiobarbiturates	H	S	Rapidly acting, usually smooth onset of sleep and fairly prompt recovery
Methyl thiobarbiturates	CH_3	S	Rapid onset of action and very rapid recovery but with so high an incidence of excitatory phenomena as to preclude use in clinical practice

mg/ml (Nembutal) made up with propylene glycol (20 per cent v/v) and alcohol (10 per cent v/v). Although intended as a veterinary preparation, it has been used as a sedative in intensive care work and, to a lesser extent, for premedication. This solution causes an unacceptably high incidence of persistent pain at the i.m. injection site (which does not occur with freshly prepared aqueous solutions). Although it has a greater soporific effect than the same dose of pentobarbitone given by mouth, it has a poor anxiolytic action and is inferior to diazepam as a premedicant.

Methylbarbiturates

Amylobarbitone and pentobarbitone were the earliest barbiturates to be used as intravenous anaesthetics. They were later replaced by hexobarbitone (Evipan, Evipal), a methylated barbiturate. The success of this drug was not

due to the more rapid recovery but rather to the quicker onset of action so that the dose could be more easily titrated against the needs of the patient. Hexobarbitone caused a high incidence of excitatory effects (spontaneous involuntary muscle movement and/or tremor).

Another methylbarbiturate, methohexitone, is popular as an induction agent, particularly for outpatients. It is two to three times more potent than thiopentone and is used in a 1—2 per cent solution. It has a lower tissue toxicity than thiopentone whether following subcutaneous or intra-arterial injection. This may be due to the less concentrated solution used or it may be associated with the absence of the sulphur atom. Induction of anaesthesia with methohexitone is followed by an appreciable incidence of extraneous muscle movements although these are less marked than with hexobarbitone. The factors which influence the frequency and severity of these movements have been studied in detail and it has been shown that both the total dose of drug and the speed of injection affect the incidence and severity of the muscle movements. The incidence is reduced by the use of an opiate premedication (or the administration of fentanyl immediately before the induction of anaesthesia) but increased by the preoperative use of promethazine or hyoscine (Table 2.2). Respiratory complications (cough and hiccough) are often troublesome with methohexitone but can be minimized by injecting the drug slowly and by using a small total dose.

Table 2.2. Percentage incidence of excitatory phenomena (spontaneous involuntary muscle movement, hypertonus or tremor) following equivalent doses of thiopentone and methohexitone given after different premedicants

Preanaesthetic medication	Thiopentone $4\ mg \cdot kg^{-1}$	Methohexitone $1.6\ mg \cdot kg^{-1}$
Atropine or nil	4	17
Hyoscine	18	46
Promethazine	25	70
Pethidine	4	7
Pethidine—hyoscine	6	25
Promethazine—hyoscine	46	87

Atropine premedication is also helpful in this respect. Another disadvantage of methohexitone is the sensation of pain on injection but figures as to its frequency or severity vary. Methohexitone is also more likely to induce epileptiform convulsions in susceptible patients than the other intravenous induction agents.

It is surprising that, despite these disadvantages and the fact that early claims concerning its lesser cardiovascular toxicity have not been confirmed, methohexitone continues to be used and is considered by many to be the induction agent of choice in certain situations (Whitwam, 1976). One of these is when early ambulation and a rapid turnover of patients are required; here the relatively rapid recovery which occurs after methohexitone, as compared with other intravenous anaesthetics, is the reason for its popularity.

Although early reports claimed that recovery was significantly shorter than after equivalent doses of thiopentone, it was hard to be sure if this was a true finding or only an illusion (because of the problems involved in assessing true recovery times). Objective evidence in support of this rapid recovery was provided by Carson, Graham and Dundee (1975) who also found a more rapid recovery after methohexitone than after Althesin.

Despite early claims that methohexitone is inactivated more rapidly in the body than thiopentone, it has been generally assumed that all intravenous barbiturates have a similar pharmacokinetic profile; i.e. rapid redistribution to non-nervous tissue with ultimate location of large amounts in body fat and a slow rate of metabolism. Qualitative differences between drugs are attributed principally to differences in lipid solubility rather than to metabolism. However, Breimer (1976), using sensitive chromatographic methods of measurement, has recently confirmed the more rapid metabolism of methohexitone which was found to have the relatively short half-life of 70—125 minutes. With this rapid metabolism there are smaller amounts of drug available for storage in fat and for eventual release into the blood. This work provides scientific evidence to justify the use of methohexitone in circumstances where a rapid return of consciousness is desired.

Whitwam (1976) has judged methohexitone against his criteria for the ideal induction agent and concludes a survey of its advantages and disadvantages by stating that 'methohexitone is the best drug currently available for the routine induction of anaesthesia by the intravenous route'. It is hard to disagree with his arguments if one accepts the overriding importance of an early recovery of complete consciousness. Furthermore, one would hesitate in recommending its use in large doses as sole agent even for minor procedures as the unpleasant sight of the patient sitting up in bed and periodically hiccoughing during recovery, or the occasional occurrence of severe spontaneous muscle movement, must be considered. Nevertheless, 20 years after its introduction, methohexitone is the only intravenous barbiturate which offers a serious challenge to thiopentone. In Chapter 1 it is classified as a barbiturate whose 'advantages outweigh its disadvantages' and this would seem to be an apt description.

Thiobarbiturates

Six thiobarbiturates have been used extensively in clinical anaesthesia and two of these (buthalitone and methitural) caused such a high incidence of complications on induction that they are no longer used. Methitural embraced an interesting concept in its formulation by including a sulphur atom in a thioethyl side chain in the hope that this would accelerate its breakdown and at the same time liberate methionine which would protect the liver from the toxic effects of the barbiturates. It is perhaps timely to recall that pharmacologists and anaesthetists were at one time concerned about the potential hepatotoxic effects of intravenous anaesthetics. We are acutely aware of the potential dangers of inhalational agents in this respect but should not forget that large doses of intravenous agents may be equally

toxic. This is discussed later in relation to total intravenous anaesthesia (Chapter 11).

Four thiobarbiturates are acceptable as induction agents but thiopentone is by far the most popular of these. Thiamylal is slightly more potent than thiopentone (estimated as 1.1 : 1.0), but otherwise the two drugs are clinically indistinguishable. Thiamylal is not commercially available in Britain. Thiobutobarbitone is only about 70 per cent as potent as thiopentone (w/w); it is commercially available in parts of continental Europe under the trade name of Inactin (Inaktin). Thialbarbitone is only half as potent as thiopentone, and for some years it was used in 5 and 10 per cent solutions which were clinically equivalent to 2.5 and 5 per cent thiopentone. These high concentrations created solubility problems and caused an increased risk should accidental arterial injection occur. Another interesting point about thialbarbitone (Kemithal) was its distinct odour which pervaded the hands of its users for several days. At the time of writing it is not commercially available in Britain but is still used in South America. Thialbarbitone was the only drug in this series which was synthesized and evaluated in Britain.

One could readily dismiss thiopentone in this chapter by saying that it is the world's most popular induction agent and that familiarity with its use has contributed to its overall safety. It is by no means a perfect intravenous anaesthetic, yet we have learned to live with its failings. At a time when much interest is being shown in new intravenous induction agents, it is the yardstick against which these should be judged (Table 2.3).

Like its immediate predecessor, hexobarbitone, it causes sleep in one arm—brain circulation time. However, in contrast to hexobarbitone which caused an unacceptably high incidence of involuntary movements, thiopentone usually produces a smooth, quiet induction. In some patients there may be minor limb movements but these are not troublesome. They occur more frequently after the rapid injection of large doses of drug and, like methohexitone, their incidence and severity are affected by the nature of the premedication, being reduced by opiates and increased by phenothiazines such as promethazine, by hyoscine or other non-analgesic drugs. The smoothness of induction by thiopentone, as compared with methohexitone, is shown in Table 2.2, which is a comparison of the incidence of excitatory effects found in several very large series of patients following the administration of equivalent doses of the two induction agents. Laryngospasm was once considered to be a dangerous complication of thiopentone but this has lost its terrors since suxamethonium became available. However, this complication is rarely encountered in adequately atropinized patients unless there has been a minor degree of regurgitation of gastric contents or a direct irritation to the larynx.

Much has been written about the absence of analgesic action of thiopentone (an antanalgesic activity has even been ascribed to it). There appears to be much confusion as to what this term implies. Perhaps this is due to the word 'antanalgesic' which perhaps might be better replaced by 'hyperalgesia' — i.e. the increased appreciation of a painful stimulus. Subnarcotic doses of thiopentone increase the patient's sensitivity to somatic pain and

Table 2.3 The advantages and disadvantages of thiopentone

	Advantages	Disadvantages
Physical properties	Soluble in water Easily injectable solution No pain on injection	Not stable in solution Highly alkaline solution Irritant on subcutaneous or arterial injection
Induction	Rapidly acting Consistent effect Smooth induction Low incidence of hypersensitivity reactions Minimal cardiovascular and respiratory depression in small doses No interference with action of neuromuscular blocking drugs	Antanalgesic action in small doses No analgesic action, even in large doses Unpredictable response to painful stimuli Potential hazard of laryngospasm Unfit patients show an exaggerated response to its depressant effect
Anaesthesia	Adequate duration of induction dose to allow gaseous or volatile supplementation Can be given intermittently	Not a 'sole anaesthetic' Readily crosses placental barrier Cumulative effect on intermittent injection Potential hepatotoxic effects of large doses
Recovery	Usually smooth No emetic effects	Due to redistribution rather than detoxication Delay in return of full mental faculties Prolonged sensitivity to pain after large doses Not suitable for unaccompanied outpatients

this state of antanalgesia, which is associated with a low brain concentration of thiopentone, occurs during induction and during recovery from large doses of the drug. It appears to apply only to the pain of deep pressure (such as that produced by pressure on the tibia) since small doses of thiopentone have been shown to reduce the ability to appreciate a painful stimulus applied directly to the skin. Small doses of thiopentone appear to antagonize the analgesia produced by nitrous oxide and pethidine in experimental situations. This seems to contradict the established clinical experience that the addition of nitrous oxide enhances the action of thiopentone; in fact, the nitrous oxide—oxygen administered is used to compensate for the missing analgesic component in thiopentone anaesthesia. As long ago as 1938, Organe and Broad demonstrated that much smaller doses of thiopentone were required to produce satisfactory anaesthesia when the drug was injected intermittently than when nitrous oxide was also being administered.

Even large doses of thiopentone appear to be devoid of a specific analgesic action. With the barbiturates, perhaps more than any other drugs used widely in anaesthesia, the clinical level of anaesthesia is related to the intensity of the surgical stimulus as well as to the degree of cerebral depression. After thiopentone, an undisturbed patient, with depressed respiration and abdominal and masseteric relaxation, may give a picture of moderately

deep surgical anaesthesia, but on application of a surgical stimulus the respiration is stimulated, relaxation lost and there may be reflex movement of a limb. If this patient is given sufficient thiopentone to produce surgical anaesthesia in the presence of strong stimulation, a dangerous degree of respiratory depression and prolonged unconsciousness may occur when the stimulation ceases.

While the analgesic drugs will reduce the dose of thiopentone required to produce surgical anaesthesia, because they also depress respiration and most are long acting, a similar state can be produced to an excessive dose of thiopentone, especially if a large dose of analgesic is given too near to the end of the operation. With the use of nitrous oxide—oxygen to supplement thiopentone it is possible to produce a satisfactory pattern of anaesthesia without excessive dosage of thiopentone or analgesics and without causing dangerous and prolonged depression of vital functions.

Although much emphasis has been placed on the cardiovascular and respiratory depressant effects of thiopentone, in practice these are minimal in fit patients. Perhaps it is hoping for too much to find a drug which will not produce these untoward effects in ill patients, but in practice the slow administration of small doses of thiopentone are well tolerated by most patients. The correction of hypovolaemia and the avoidance of opiate or phenothiazine premedication, together with preoxygenation, can further increase the safety of this procedure.

Many claims have been made for the lesser cardiovascular toxicity of the newer intravenous anaesthetics in poor-risk patients. In general, significant advantages have not been substantiated for these agents. Lyons and Clarke (1972), Lyons, Clarke and Dundee (1974) and Clarke and Lyons (1977) gave equivalent doses of several intravenous induction agents to heavily premedicated patients prior to cardiac surgery. Five minutes after injection a similar fall in blood pressure was found after thiopentone 4 $mg \cdot kg^{-1}$, methohexitone 1.5 $mg \cdot kg^{-1}$, propanidid 4 $mg \cdot kg^{-1}$, Althesin 0·05 $\mu l \cdot kg^{-1}$, diazepam 0·36 $mg \cdot kg^{-1}$ and flunitrazepam 0.032 $mg \cdot kg^{-1}$. This fall occurred most rapidly with propanidid and most slowly with the two benzodiazepines. Methohexitone caused the highest incidence of tachycardia.

While it is feasible to give thiopentone by intermittent injection, this is not recommended except in short procedures. Large doses produce enzyme changes which are consistent with liver dysfunction and should be avoided. The potential of 'total intravenous anaesthesia' as a means of eliminating theatre pollution is attractive but, for reasons which are discussed fully in Chapter 11, thiopentone and similar drugs are not recommended for this purpose.

It has been fairly well established that recovery from thiopentone is due to redistribution in the body rather than to rapid detoxication, although drug metabolism by liver mitochondria is probably more important than originally envisaged (Saidman and Eger, 1966). Even allowing for the effects of metabolism, there is no justification for considering thiopentone to be an ultra-short-acting drug. A large amount of unmetabolized drug remains in the body for at least 12 hours after its administration and this may potentiate the action of alcohol or other barbiturates taken post-