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Noninhalational Anaesthetics

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1 Introduction

Attempts to define the sites of action and mechanisms involved in general anaesthesia continue to excite experiment and philosophical discussion (Miller *et al.*, 1965; Halsey and Kent, 1972; Miller *et al.*, 1972b; Anderson and Amaranath, 1973; Eyring *et al.*, 1973; Mullins, 1973; Halsey *et al.*, 1974). With the inhalational anaesthetics there is general recognition that potency can be correlated with lipid solubility, but the search for new anaesthetics still depends upon an empirical approach. This is particularly the case with noninhalational compounds where the possession of lipid solubility is no guarantee of anaesthetic activity. Such compounds must have the right structure as well as being lipid soluble. There is great diversity among the various classes of noninhalational compounds which produce

anaesthesia, and their particular properties are the sum of many interacting factors which include lipid solubility, structure, degree of ionization, and the rate and route of metabolism and elimination. These in turn determine potency, speed of onset, duration of action, and degree of cumulation. The qualities which make a compound an acceptable anaesthetic are often not its anaesthetic properties *per se*, but other factors such as its actions on the cardiovascular, respiratory and central nervous systems, and on the body tissues, as well as its stability, and the nature of its degradation products. The noninhalational anaesthetics will be considered predominantly from a pharmacokinetic point of view, but details of clinical activity in animals and man will be included especially with the newer classes of compounds.

Since classical times there have been repeated attempts to produce insensibility during surgery, with alcohol, the opiates, and mandrake, and more recently with chloral hydrate and trichloroethanol. The successful introduction of inhalational anaesthetic agents during the last century eclipsed all these methods. The first real alternative to inhalational anaesthetics occurred with the introduction of the intravenous barbiturates in the 1930s. The intravenous barbiturates were used originally to induce anaesthesia rapidly before transferring to an inhalational agent. More recently, injectable compounds have been developed which alone provide surgical anaesthesia, and some can be used by both the intravenous and intramuscular routes.

The major advantage of an intravenous induction agent is the rapid loss of consciousness after a simple injection. The patient is not subjected to the potentially unpleasant experience of breathing through a face mask while still conscious, which may be resisted by children and animals. The rapidity of onset of anaesthesia is not influenced by breath-holding.

The major disadvantages are that the anaesthetic effect cannot be cut short and a suitable vein must be found. Here again, children and animals may not be cooperative. An intramuscular agent avoids the second problem but speed of induction is sacrificed.

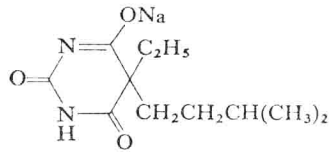
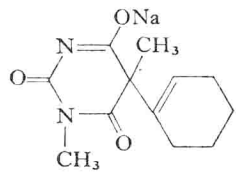
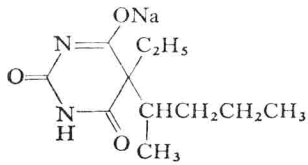
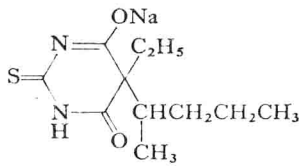
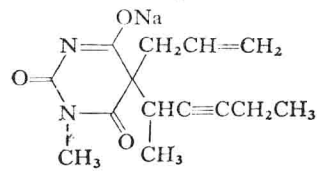
It is easy to list the ideal properties of an intravenous induction agent but difficult to achieve. An ideal anaesthetic would have to have the following properties and be administered in a stable solution containing the human dose in 5 to 10 ml; no pain on injection, local tissue or vascular damage; rapid induction; a wide safety-margin; no cumulation of effect; no respiratory or cardiovascular depression; no laryngospasm or bronchospasm; no twitching or other stimulant activity during induction, sleep or recovery; no dreams or hallucinations; no nausea, vomiting or anorexia; some degree of analgesia; compatibility with all other agents used in anaesthesia. No existing compound satisfies all these criteria.

2 Barbiturates

The sodium salts of amylobarbitone, hexobarbitone and pentobarbitone (Table 1) were the first barbiturates used as intravenous induction agents but were soon succeeded by thiopentone sodium, the thio-analogue of pentobarbitone (Lundy, 1935). Thiopentone has remained the standard induction agent for nearly forty years despite many attempts to displace it. Methohexitone sodium has been the only barbiturate to compete with

TABLE 1

Rapidly acting barbiturates used for induction of anaesthesia by the intravenous route

Name and formula	Structure
Amylobarbitone sodium: sodium 5-ethyl-5-isopentylbarbiturate	
Hexobarbitone sodium: sodium 5-(cyclohex-1-enyl)-1,5-dimethylbarbiturate	
Pentobarbitone sodium: sodium 5-ethyl-5-(1-methylbutyl)-barbiturate	
Thiopentone sodium: sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate	
Methohexitone sodium: sodium α-(±)-5-allyl-1-methyl-5-(1-methylpent-2-ynyl)barbiturate	

it, and only in recent years have any practical alternatives to the barbiturates appeared.

2.1 THIOPENTONE

The major advantage of thiopentone is the rapidity and smoothness with which it produces loss of consciousness. The time taken is essentially the vein-to-brain circulation time. Spontaneous muscle movement is seen only occasionally after induction and recovery is normally rapid.

Thiopentone has many deficiencies though most are overcome in skilled hands. The aqueous solution of the sodium salt is not very stable and has to be freshly prepared. The solution is very alkaline (about pH 11 for a 5 per cent solution) and this may contribute to the tissue irritation it causes if injected perivenously. The nature of the aqueous solution complicates the effects of accidental intra-arterial injection with thiopentone. It causes severe pain, temporary arterial spasm, and occasionally tissue necrosis in the affected vascular bed (Cohen, 1948a and 1948b). When thiopentone solution is mixed with blood some of the anaesthetic is precipitated from solution (Waters, 1966). In addition, haemolysis and platelet aggregation can occur leading to intravascular thrombosis (Brown *et al.*, 1968). Presumably, by the intravenous route, any precipitated material is soon redissolved by further dilution as its passes into the larger vessels. After accidental intra-arterial injection, the precipitate is swept into vessels of decreasing calibre.

The normal human dose of thiopentone is between 150 and 500 mg but the safety margin is limited. Excessive dosage to overcome the effects of surgical stimulus leads to depression of the respiratory and cardiovascular systems and provides a serious hazard with this anaesthetic (Dundee, 1965a). Safe doses of thiopentone used alone do not provide sufficient analgesia to permit surgery, and some workers consider that with light anaesthesia sensitivity to pain is increased (Clutton Brock, 1960; Dundee, 1960). The laryngospasm that can occur spontaneously or following attempts to intubate the airway may be a result of this increased sensitivity (Paton and Payne, 1968). Post-operative hiccough, nausea and vomiting are no more frequent than after other anaesthetics. The only absolute contraindication to the use of thiopentone, as to other barbiturates, is in patients exhibiting porphyria (Dundee, 1965b).

2.1.1 *Distribution and elimination of thiopentone*

The rapidity of onset, duration of action, safety margin and cumulative properties of thiopentone are determined by the nature of its tissue distribution and eventual elimination from the body, and will therefore be discussed

in some detail. They reflect the physicochemical properties of thiopentone, its metabolism, and differences in the blood supply of the various body tissues.

Thiopentone has a pK_a of 7·4 (Bush, 1961) so that about 50 per cent is present in the nonionized form in the blood. The nonionized fraction has high lipid solubility (Bush, 1963) which permits it to pass rapidly into the brain (Price *et al.*, 1957; Mark *et al.*, 1958). Price *et al.* (1960) showed that in man the brain takes up 10 per cent of an intravenous dose of thiopentone within 1 minute of injection. The brain then loses thiopentone so that after 5 minutes only half the peak concentration remains, and falls to one tenth by 20 minutes. The brevity of action of small doses of thiopentone was originally attributed, on presumptive evidence, to rapid metabolism (Jailer and Goldbaum, 1946), but Brodie *et al.* (1950) showed that metabolism is slow, and that redistribution into nonnervous tissue, especially fat, is the more probable explanation (Brodie *et al.*, 1952). Redistribution of thiopentone occurs as its equilibrates between the water and fat phases of the tissues. However, the rate of uptake of thiopentone by adipose tissue is too slow to account for the speed with which consciousness is regained (Price *et al.*, 1960), and redistribution initially into other tissues such as muscle has been proposed. It is difficult to obtain direct evidence of the concentration of thiopentone in many tissues at all times during anaesthesia. From the isolated observations available, Price (1960) constructed a mathematical model which predicts the kinetics of thiopentone redistribution. This model provides a satisfactory explanation for all the properties of thiopentone which reflect its disposition and elimination. He suggests that within 1 minute of an intravenous injection of thiopentone, 90 per cent of the dose is distributed into the brain and other organs which receive a rich blood supply. Thereafter the thiopentone is redistributed to other tissues, firstly into lean tissue and then into fat. The rate at which a tissue takes up thiopentone is dependent on the blood supply to the tissue, and the maximum level achieved is dependent on its lipid content. As Price (1960) has suggested, the rate at which the central nervous system loses thiopentone depends predominantly on the rate at which the poorly-perfused tissues gain it. Fat is so slowly perfused that it cannot begin to concentrate thiopentone to an important degree until the central nervous system has already lost over 90 per cent of its peak content. After a single small dose of thiopentone the concentration of thiopentone in the brain falls rapidly below anaesthetic levels as it equilibrates with the blood, and long before equilibrium between the aqueous and lipid tissues is established. Consciousness returns whilst a high proportion of the original dose is still in the body. With repeated doses or slow infusion, more and more tissues approach equilibrium with the thiopentone in the blood

during the period of unconsciousness. The capacity of the body tissues to remove thiopentone from the brain is gradually lost (Price, 1960). In such a situation, thiopentone is no longer short-acting, and this explains why repeated doses are increasingly cumulative.

It is generally accepted that eventually thiopentone is eliminated by metabolic degradation in the liver, and that little is excreted unchanged in the urine (Brodie *et al.*, 1950; Mark, 1963). Brodie *et al.* (1950) studied the plasma thiopentone decay curves in human subjects from 1 to 5 hours after intermittent doses of 1 to 4 g. They concluded that the 15 per cent per hour decline in plasma concentration was attributable to metabolic transformation. This assumed negligible urinary excretion, and that equilibrium between the plasma and tissues is established 1 to 2 hours after the original dose. However, the rate of fall of the plasma concentration may not reflect the rate of metabolism accurately. If the tissues were still moving towards equilibrium, the rate of disappearance of thiopentone from the plasma would overestimate the real situation. Alternatively the muscle and fat could provide a reservoir of thiopentone which could, at least in part, replace the metabolized drug, and the rate of disappearance would be underestimated. Despite such considerations, Mark *et al.* (1969) still consider that the plasma decay curves indicate the maximum rate of metabolism of thiopentone. With such an uncertain situation, full balance studies are necessary to discover the true rate of metabolic degradation. One such study in rats (Shideman *et al.*, 1953) indicated that during the first 6 hours, thiopentone was metabolized at a rate of 10 per cent per hour.

How much metabolism influences the duration of anaesthesia with thiopentone is a matter of dispute. Saidman and Eger (1966) have criticized Price (1960) for ignoring it as a factor in the early decline of thiopentone plasma concentrations. They cited studies on the hepatic arterio-venous differences in thiopentone level several hours after dosing, when it was assumed that the tissues were in equilibrium. In their work on dogs, differences of 6·6 and 15·1 per cent were found at 3 and 5 hours respectively, but no information was given about the concentrations measured. Mark *et al.* (1965) showed a 0 to 50 per cent extraction rate by the liver in human patients suffering from various forms of liver disease. Saidman and Eger (1966) concluded from their own results that metabolism plays a significant role in early wakening from anaesthesia. This would appear to be an unsupported conclusion. The ability of the liver to remove an unspecified amount of thiopentone when the concentration is low, gives no indication of its capacity to do so in the early stages of anaesthesia when the concentration is high. There is little evidence that thiopentone is more potent, or has a longer duration of action in patients with liver damage.

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Mark *et al.* (1972) referring back to their earlier work (Mark *et al.*, 1965) pointed out that the duration of sleep after thiopentone was similar in all patients regardless of the ability of their livers to remove the drug. There is no direct or circumstantial evidence to suggest how much thiopentone is metabolized in the early stages of anaesthesia. Although liver damage would probably reduce the rate at which thiopentone is metabolized, this is unlikely to influence the duration of anaesthesia after a single dose. It could prolong post-anaesthetic depression and increase the cumulative properties of thiopentone.

Thiopentone is highly protein bound—about 75 per cent at typical plasma concentrations (Brodie *et al.*, 1950). This probably plays a part in the rapid redistribution of thiopentone from the central nervous system and blood into other tissues. Mark *et al.* (1969) suggest that the biodegradation of barbiturates is aided by the high degree of weak protein binding which serves as a transport mechanism to the liver where the barbiturate is easily detached. The slow elimination of the last traces of thiopentone may reflect the increase in protein binding to 90 per cent found when plasma concentrations fall below 5 $\mu g\ ml^{-1}$ (Dayton *et al.*, 1967).

It is difficult to predict what effects changes in blood pH will have on the course of thiopentone anaesthesia. Whilst lowering of the pH will increase the proportion of the anaesthetically active nonionized form of thiopentone present in the blood, this is the form which is readily lipid soluble. Brodie *et al.* (1950) showed in the dog that lowering the blood pH several hours after induction of anaesthesia with thiopentone reduced its concentration in the plasma. It is probable that changes in blood pH would influence anaesthesia differently at the early and late stages. Immediately on induction, when the brain and blood concentrations are high, a lowering pH could intensify anaesthesia by increasing the proportion of the active nonionized material available. In the later stages of anaesthesia or during recovery, any lowering of the pH when blood thiopentone concentrations are low, whilst encouraging distribution into fat, would be unlikely to have much influence on the depth of anaesthesia.

2.2 METHOHEXITONE

Methohexitone (Table 1), the only barbiturate to become established as an alternative to thiopentone, is a mixture of the D- and L-α-isomers of sodium 5-allyl-1-methyl-5-(1-methylpent-2-ynyl)barbiturate (25398) (Stoelting, 1957; Gibson *et al.*, 1959). With the original mixture of α- and β-isomers (22451) (Gibson *et al.*, 1955; Gruber *et al.*, 1957) there was a clinically unacceptable occurrence of hiccoughs and muscle tremors. The clinical properties of methohexitone have been described by Taylor

and Stoelting (1960). It shares many of the properties of thiopentone but is about three times as potent and has a shorter duration of action. Pain on injection and muscular twitches are the major disadvantages but the incidence of vein damage is possibly less than with thiopentone. Respiratory depression is present at effective anaesthetic doses and may be greater than with equivalent doses of thiopentone. Laryngospasm and coughing are no more frequent than after other barbiturates but the incidence of hiccough is greater. Subsequent work has confirmed the original impressions of methohexitone including the 3:1 potency compared with thiopentone (Clarke *et al.*, 1968) though Barry *et al.* (1967) have pointed out the problems of comparing potency when duration of action is different. The low incidence of vascular damage with methohexitone may be a consequence of higher potency, as a 1 per cent solution can be used compared with the usual 2·5 per cent solution of thiopentone. It is less cumulative than thiopentone in man (Clarke and Dundee, 1966) and in mice (Child *et al.*, 1971).

The higher potency, shorter duration of action, reduced cumulation and more rapid inactivation of methohexitone probably reflect slight differences in its physicochemical properties compared with thiopentone (Brand *et al.*, 1963). The pK_a of 7·9 and protein binding of 73 per cent for methohexitone compare with 7·4 and 75 per cent for thiopentone. These differences, though slight, mean that more of the active nonionized form of methohexitone is available at blood pH and may explain its higher potency. Further, methohexitone is less lipid soluble than thiopentone and therefore less concentrated in body fat, a site where it would be protected from metabolic transformation. Thus methohexitone has several marginal advantages over thiopentone though these may be outweighed by the greater tendency of methohexitone to produce excitatory phenomena.

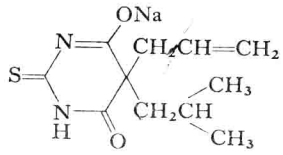
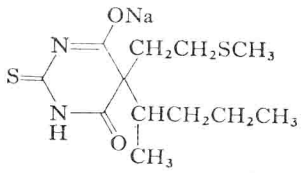
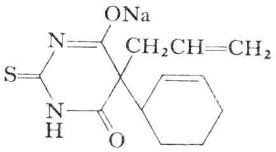
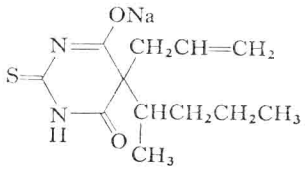
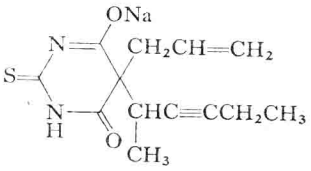
2.3 MISCELLANEOUS BARBITURATES

Among the predecessors of thiopentone only pentobarbitone is still in regular use as an intravenous anaesthetic, mainly in animals. It is slightly slower in onset and of longer duration than thiopentone but has an advantage in being formulated as a solution ready for use. Buthalitone, methitural, thialbarbitone and thiamylal (Table 2) have all been claimed to have advantages over thiopentone but none has proved sufficiently different to displace it (Dundee, 1963, 1971).

Thiohexital (Table 2), the desmethyl thio-analogue of methohexitone is the most recent barbiturate to be examined clinically (Mark *et al.*, 1968). It is considered the most rapidly metabolized barbiturate (25 per cent per hour in man) and has a shorter duration of action than methohexitone. Side effects in man include twitching, tremors and hiccough, and it has been

TABLE 2

Miscellaneous rapidly acting barbiturates used for induction of anaesthesia by the intravenous route

Name and formula	Structure
Buthalitone sodium: sodium 5-allyl-5-isobutyl-2-thiobarbiturate	
Methitural sodium: sodium 5-(1-methylbutyl)-5-(2-(methylthio)ethyl)-2-thiobarbiturate	
Thialbarbitone sodium: sodium 5-allyl-5-(cyclohex-2-enyl)-2-thiobarbiturate	
Thiamylal sodium: sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate	
Thiohexital sodium: sodium 5-allyl-5-(1-methylpent-2-ynyl)-2-thiobarbiturate	

suggested that, as was found during the development of methohexitone, one of its stereo isomers might produce less of these undesirable effects.

2.4 CONCLUSIONS ON BARBITURATES

The relative failure to improve upon thiopentone, despite the testing of many thousands of barbiturates, testifies to the difficulty in finding the perfect anaesthetic in this class of compounds. The necessity to use strongly

alkaline solutions is an important disadvantage of the barbiturates. However their major flaw—cumulation of action with repeated doses—arises because their duration of action is controlled by redistribution rather than metabolism. Unless a new barbiturate is developed which is metabolized at a very much faster rate than existing compounds, there will be no real advance in this class of intravenous anaesthetics.

3 Gamma-hydroxybutyric acid

Gamma-hydroxybutyric acid (sodium 4-hydroxybutyrate) (**1**), commonly known as Gamma OH, was introduced into anaesthesia by Laborit *et al.* (1960). They considered it might act by entering into the metabolic pathway of the putative central nervous system inhibitor gamma-aminobutyric acid (GABA) (**2**). Gamma OH produced sleep when given by the oral and by the

$HOCH_2CH_2CH_2COONa$ (1)

$H_2NCH_2CH_2CH_2COOH$ (2)

intravenous routes but it has not become widely accepted as an anaesthetic except in France (Vickers, 1969). The dose of Gamma OH is high (4 to 6 g), the onset of unconsciousness is slow (10 to 20 minutes even after intravenous injection), and it does not produce true surgical anaesthesia when used alone. It is best regarded as a basal anaesthetic and clearly has none of the essential properties of an induction agent.

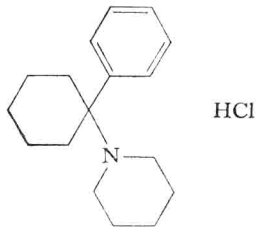
4 Phenylcyclohexylamine derivatives

The quality of anaesthesia produced by the phenylcyclohexylamine derivatives differs from that of all other anaesthetics. They produce a state resembling catalepsy rather than sedation or hypnosis particularly in lower doses. It has been suggested that the reactivity of the central nervous system to sensory stimuli is altered but not truly blocked. Although sensory input may reach cortical areas, they fail to be perceived in some of the association areas which are depressed. The state produced by the phenylcyclohexylamine anaesthetics therefore has been called "dissociative anaesthesia" (Corssen and Domino, 1966). This difference in action makes comparison with conventional anaesthetics difficult as some of the usual criteria for assessing depth of anaesthesia are not present.

4.1 PHENCYCLIDINE

Phencyclidine, 1-(1-phenylcyclohexyl)piperidine hydrochloride (**3**), was the first compound of this class to be evaluated in animals and man. In

most species, phencyclidine produces a combination of stimulation and depression, stimulation being most prominent with lower doses in mice and rats. A gradation of effect from catalepsy towards a state of general anaesthesia is seen in cats, dogs and monkeys, though convulsions are seen with



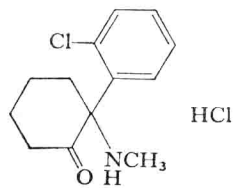
(3)

higher doses in these species. (Chen *et al.*, 1959). Blood pressure is usually slightly raised, respiration is depressed only at the higher doses, and there is some local anaesthetic effect. Phencyclidine is active by the intravenous and the intramuscular routes. It was used particularly in the management of monkeys (Chen and Weston, 1960) and, despite its long duration of action, it was used in a wide range of zoo animals (Kroll, 1962).

In man, phencyclidine proved unsatisfactory because of marked psychotomimetic actions and often prolonged post-anaesthetic confusion (Johnstone *et al.*, 1959).

4.2 KETAMINE

Ketamine (2-(*o*-chlorophenyl)-2-methylaminocyclohexanone hydrochloride) (**4**) succeeded phencyclidine. Ketamine is less potent, is of shorter



(4)

duration, and less stimulant than phencyclidine yet possesses the same type of anaesthetic action. McCarthy *et al.* (1965) compared the properties of phencyclidine and ketamine with those of two barbiturates, pentobarbitone and thiamylal, in laboratory animals. They found that with ketamine the

central nervous system was predominantly depressed. The animals passed through a state of catalepsy into general anaesthesia with increasing doses though the effects were different from those of conventional anaesthetics. Induction was rapid though slightly slower than with the barbiturates. Cats and dogs showed muscular rigidity, salivation and urination. Their eyes were usually open, dilated, and showed nystagmus. Pharyngeal reflexes were not depressed. Monkeys were the species in which ketamine produced the best quality of anaesthesia. In unanaesthetized dogs, ketamine produced dose-related rises in blood pressure, and little respiratory depression except at the highest dose levels. Cardiovascular collapse and respiratory depression were marked when ketamine was injected into animals already anaesthetized with pentobarbitone or chloralose. This is an effect similar to that reported with steroid anaesthetics (Lerman and Paton, 1960; Child *et al.*, 1972a).

The first use of ketamine in man was described by Corssen and Domino (1966). As well as recognizing qualitative differences in the responses to ketamine, they found induction slightly slower than with conventional rapidly acting anaesthetics. Adequate anaesthesia was obtained in 1 to $1\frac{1}{2}$ minutes after the start of an intravenous dose of 1 to 2 mg kg^{-1} and lasted for 5 to 8 minutes. Arterial pressure rose, particularly if the injection rate was rapid and this also increased the slight initial respiratory depression. The rise in blood pressure varied from "trivial" in some patients to "alarming" in others. The protective pharyngeal, laryngeal, eyelid and corneal reflexes, as well as pronounced muscle tone, were present throughout anaesthesia but analgesia was presumed to be quite adequate. Recovery was moderately rapid, and was accompanied in a significant number of patients by vivid dreams or hallucinations some of which were unpleasant. By the intramuscular route, an acceptable degree of anaesthesia and analgesia was obtained with doses of 4 to 5 mg kg^{-1} in about 5 to 8 minutes and lasted for 20 to 30 minutes.

All subsequent studies in man have confirmed these initial findings. Virtue *et al.* (1967) remarked on the excellent analgesic action of ketamine, and showed that despite rises in blood pressure the myocardium was not sensitized to the effects of adrenaline. Szappanyos *et al.* (1969) found ketamine particularly useful for children in whom they found a much lower incidence of psychic side effects than in adults. They also found little cumulation with ketamine as it was possible to give repeated doses of half the initial dose without prolongation of action. The latter finding is not in agreement with that of Corssen *et al.* (1968) who found recovery prolonged after multiple supplementary doses. Dundee *et al.* (1970) found that half the patients induced with 2 mg kg^{-1} of ketamine intravenously as the sole agent required further doses but this was not necessary after 3 mg kg^{-1}.

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