Comparative Analysis of Intravenous Anesthetics

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When thiopental was introduced into anesthetic practice it quickly became the most popular intravenous agent in most countries. Thirty-five years later, thiopental, as it is now known, still is probably the intravenous anesthetic most widely used. It might be assumed that brevity of action is the principal advantage of thiopental over pentobarbital and amobarbital, which it supplanted; however, rapidity of onset is more important, and is probably the main reason for its almost universal acceptance as an induction agent. In the mid-thirties many operations were performed using intermittent barbiturate anesthesia, and any delays in onset of action made it difficult to adjust dosages to patients' needs. Although the intravenous barbiturates are rarely used alone for anesthesia, rapidity of onset remains a desirable property of any agent used primarily for induction.

Barbiturates

The mechanisms that determine speed of onset are complex. It is difficult to conceive how a barbiturate and a thiobarbiturate could differ in their transport to brain, apart from differences in the amounts bound to plasma proteins. However, the protein bonds are loose and are unlikely to affect the time to onset of sleep. 1, 2 Non-drug factors can influence the transport time, by changes in either cardiac output 3 or caliber of vessels. 4, 5 In clinical studies the latter may be minimized in healthy patients by rapid injection of the drug during the period of reactive hyperemia following transient occlusion. 5, 6 Speed of onset may be increased by methylation or sulfuration. These substitutions increase the lipid solubility of the unionized forms of the drugs. The partition coefficients between lipid solvent and aqueous buffer at pH 7.4 (C 2 value) for thiopental and thiamylal are 16 and 21 times as high as those of their corresponding barbiturates, pentobarbital and secobarbital. The difference between the coefficients of hexobarbital (methylated) and nor-hexobarbital (nonmethylated) is of the same order. 7 Methylation of pentobarbital, secobarbital and amylobarbital produced similar effects on the C 2 values. 8

The rate at which barbiturates penetrate the central nervous system can be correlated with the lipid solubility of the unionized molecules or the partition coefficient between lipid solvents and aqueous buffer. 5, 9 There is a marked delay in onset of soporific action following intravenous injection of barbital (diethyl barbituric acid) because of the slow penetration of the drug into the brain. 11 The onset of action (penetration into the brain) is quicker after administration of the more lipidsoluble ethyl-n-hexyl barbiturate. The difference between the hypnotic actions of pentobarbital and thiopental can be explained by the different partition coefficients of the two drugs and is supported by actual analyses of their rates of passage into brain. 12 In practice, the "blood–brain barrier" is nonexistent so far as rates of transfer of clinically used intravenous barbiturates are concerned.

The presence of a CH 3 side-chain in the N-1 position increases the "convulsive" actions of a barbiturate. Such a radical is present in the rapidly-acting barbiturate, hexobarbital (Evipal), which achieved some popularity for a few years prior to the introduction of thiopental. However, spontaneous muscle movements, including tremors and hypertonus, were so common with hexobarbital that it was abandoned in favor of thiopental. Since methohexital also has a CH 3 radical in the N-1 position, this drug also may produce excessive extraneous muscle movements.

Irrespective of the drug used, three factors increase the incidence and severity of excitative phenomena. The quicker the rate of in-

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jection, the higher will be the incidence and the greater the severity of extraneous muscle movements.\textsuperscript{12} At a constant rate of injection the incidence of excitatory phenomena also increases with dosage.\textsuperscript{14} Finally, certain premedicants such as scopolamine, promethazine, and cyclizine may increase the incidence of excitatory phenomena resulting from barbiturates, while opiates may lessen it.\textsuperscript{12}

Other phenomena such as hiccupping and coughing occur most frequently with buthialtal, medital and methohexital. As with other excitatory phenomena, the incidence and severity increase with dosage and rate of injection.

Data from a variety of publications are presented in Table 1 to show the influence that a premedicant may have on the incidence of complications during induction of anesthesia. This underscores the importance of standardizing premedication in trials of new drugs.

**Pharmacokinetics**

Drugs which quickly penetrate into brain will also diffuse out rapidly and soon be distributed to skeletal muscle and other tissues. It is now well recognized that redistribution, rather than metabolism, accounts for the rapid recovery from clinical doses of thiopental.\textsuperscript{16} Price\textsuperscript{15, 18} has presented a mathematical analysis of the kinetics of thiopental distribution, revealing that the course of anesthesia depends passively upon a competition between nervous and non-nervous tissues for the drug. A minute after injection, the blood has given up 90 per cent of the injected dose, principally to the central nervous system, heart, liver, and other richly perfused viscera. During the subsequent half hour these organs in turn are depleted as the result of further redistribution. About 80 per cent of the thiopental initially contained in richly perfused viscera is distributed to the other aqueous tissues of the body, while the remainder enters fat. The blood supply of fat is so low relative to other tissues that it cannot begin to store thiopental to any significant degree until the central nervous system has lost more than 90 per cent of its peak content.

Until recently, very little attention has been paid to the role of metabolism in reducing the plasma thiopental concentrations. Brodil\textsuperscript{18} calculated that 10–15 per cent of the drug was broken down per hour, but Price\textsuperscript{19, 20} ignored this in his calculations. Animal experiments and observations in humans, however, have shown the action of thiopental to be prolonged in the presence of hepatic dysfunction. This pointed to the positive role of the liver in its breakdown, and its importance in recovery from doses in excess of those rapidly removed from the brain by redistribution. Studies in vivo by Mark and his colleagues\textsuperscript{21} showed that the liver, by removing as much as 50 per cent of the thiopental from the hepatic blood flow, shortened the duration of action. Recently, Saidman and Eger determined the arterio-hepatic venous thiopental differences in the dog and found that metabolism was of major importance in the early reduction of arterial levels, and hence played a major role in the early awakening seen with this anesthetic.\textsuperscript{22} They concluded that although uptake in muscle still played the dominant role in the early decline in the arterial concentration, the additional effects of metabolism and uptake in fat were important.

The biotransformation of thiopental is mediated primarily by microsomal enzyme systems, mainly in the liver. The reserve capacity of the liver is such that functional impairment must be great before the effect is manifested clinically. Side-chain oxidation is the major mechanism of inactivation in vivo, but 5-de-methylation plays some part.

Patients "waken" from barbiturate anesthesia with an appreciable amount of unmetabolized drug in the body. Thus, complete recovery is delayed for an appreciable time after even small doses. Although they may behave and speak normally, patients should be advised against taking alcohol or other drugs on the same day, since their effects may be markedly augmented by the subhypnotic concentrations of barbiturate still present.\textsuperscript{23} This caution also applies to methohexital, which is metabolized slightly more quickly than thiopental.\textsuperscript{25, 26}

Even thiophexital (sodium d1-5-1-(1-methyl-2 pentynyl)-5-allyl-2-thiobarbiturate), the most rapidly metabolized barbiturate yet studied in man, is not truly short-acting, particularly when considered in relationship to the eugenols.\textsuperscript{27}
COMPARATIVE ANALYSIS OF INTRAVENOUS ANESTHETICS

**Table 1. Percentage Incidences of Excitatory Phenomena* and Respiratory Disturbances† after Approximately Equivalent Doses of Thiopental (4.0 mg/kg) and Methohexital (1.6 mg/kg) Given after Various Premedications**

<table>
<thead>
<tr>
<th>Preanesthetic Medication</th>
<th>Thiopental</th>
<th>Methohexital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excitative Phenomena (Per Cent)</td>
<td>Respiratory Disturbances (Per Cent)</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Atropine, 0.6 mg</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Meperidine, 100 mg</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Morphine, 10 mg</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Scopolamine, 0.4 mg</td>
<td>37</td>
<td>52</td>
</tr>
<tr>
<td>Promethazine, 50 mg</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine, 100 mg/scopolamine, 0.6 mg</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Meperidine, 100 mg/promethazine, 50 mg</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Promethazine, 50 mg/scopolamine, 0.4 mg</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

All figures are based on series of at least 100 observations except when, on ethical grounds, numbers with thiopental were limited to 80,† and with methohexital to 10.‡

* e.g., tremors, spontaneous involuntary muscle movements, or hypertonus.
† e.g., cough, hiccup, or marked depression.

Two other points regarding the actions of barbiturates are worthy of consideration. Subnarcotic doses of barbiturates increase the sensitivity to somatic pain produced by tibial pressure but have an analgesic action with respect to painful stimuli applied to the skin. Increased sensitivity to somatic pain has also been demonstrated in the postoperative period following moderate doses of thiopental. The mechanism of this hyperalgesia—a term which is preferred to the original “analamgesia” has been studied in some detail. Its clinical importance lies in the fact that dangerously large doses of thiopental may be needed to obtund reflex responses to surgery when this agent is used as the main or sole anesthetic. Thus, thiopental is not suitable for use alone in many instances in which a rapidlyacting easily administered drug would otherwise be ideal.

The sequelae of an intra-arterial injection of concentrated thiopental are well documented and may be very serious. A survey of cases published prior to 1956 suggested that the higher the concentration of thiopental used, the greater is the risk of permanent damage following its intra-arterial injection.

Many theories have been put forward to explain the sequelae, but the most fascinating pertinent observation was that of Waters. He demonstrated that when thiopental is injected into blood with a pH of 7.4, crystals of relatively insoluble acid form in the blood stream, and these can occlude small vessels. The greater the concentration of the solution used, the greater will be the production of crystals. In subsequent studies, Brown, Lyons and Dundee have demonstrated that erythrocyte hemolysis and platelet aggregation also occur, and that both these effects are accentuated by the acid crystals. A study of the crystal-forming ability of aqueous solutions of clinically used drugs showed that this was less likely to occur with dilute solutions. Release of adenosine triphosphate (ATP) from damaged erythrocytes or platelets and an area of endothelial damage at the puncture site were adequate reasons for the initiation of thrombosis. Oxybarbiturates appear to be less likely to form crystals than thiobarbiturates, but dilution is the main factor in preventing crystal formation. This is particularly important for the thiobarbiturates, which are sometimes used in high concentrations, e.g., 5 per cent thiopental or thiamylal. Crystal formation also occurs in veins, but it is unimportant because of the ever-increasing diameter of the vessels and subsequent resolution of the crystals. As new barbiturates are developed, the above facts suggest a preference for the more potent drugs, which can be used in dilute solutions.
Of the many newer barbiturates that have been studied as induction agents, methohexital is the only one which offers any challenge to thiopental or thiamylal. Methitural and buthalital cause unacceptably high incidences of respiratory disturbances, while the clinical use of thiopental has not yet been reported in detail.

Being an oxybarbiturate, methohexital is less likely to cause damage to the interiors of blood vessels than thiopental, and being 2.5-3.0 times as potent as thiopental, it can be used in a more dilute solution, which enhances its safety with respect to sequelae after accidental intra-arterial injection. However, a few patients complain of pain on injection of 1-2 per cent solutions.

Evidence for more rapid recovery after methohexital compared with thiopental is lacking. The absence of "hangover" has been commented on by Wyant and his colleagues, who used methohexital in volunteers and in patients undergoing minor gynecologic procedures. A direct comparison between thiopental and methohexital was made by Green, using a Miles Trainer Car and Recording Gear. Volunteers were given comparable doses of either drug and their driving skills and abilities compared after each agent. Recovery times, as judged by ability to perform certain tests accurately, were significantly shorter after methohexital than after thiopental.

Mention should be made of the Scandinavian compound, enibomal (Narcodorm, Narkotal), introduced in Germany two years after hexobarbital, which contains a bromine atom in the 5 side-chain. It has the advantage of remaining stable in solution for at least three years, but despite this it has not achieved much popularity outside Scandinavia. This may be due to commercial rather than pharmacological considerations, particularly since Lunding and Moller found recovery from enibomal to be as prompt as that after methohexital. Since it is a methylated oxybarbiturate, with the potential for causing a high incidence of excitatory phenomena, judgement on its ultimate value will have to be reserved until more comprehensive investigations have been carried out.

Eugenols

This group of induction agents is derived from oil of cloves. These drugs are phenoxyacetic amines and, hence, are chemically different from the barbiturates. Although several of these drugs have been subjected to clinical study, only one, propanidid, is now in clinical use. Although not commercially available in this country, the eugenols represent a completely different type of drug which may be the basis for further developments in the field of intravenous anesthetics. Effective doses cause sleep in one circulation time. Hence, they can be classed as "rapidly-acting" compounds, but they differ from the barbiturates in several important respects.

All the eugenols are relatively insoluble in water, and either organic solvents or "solubilizing agents" must be used. Propanidid is a yellowish oil which can be dissolved to form a 5 per cent aqueous solution by the use of 20 per cent Cremophor El. In fact, the solution currently available (Eponol), uses as solubilizer 16 per cent of the hydrophobic part of Cremophor El, a mixture of higher fatty acids. This substance appears to act by "enveloping" the molecules of propanidid. The resulting product, though moderately viscous, is miscible with water and with most anesthetic adjuvants, but any mixture should always be freshly prepared.

A distinctive property of the eugenol anesthetics is respiratory stimulation. When propanidid is given repeatedly at short intervals, hyperventilation occurs with each injection. It is followed by a period of hypoventilation, and with large doses both phases are exaggerated. Opiate premedication in these circumstances suppresses the hyperventilation and increases the incidence of subsequent respiratory arrest. However, apnea necessitating ventilatory assistance is much rarer after propanidid than after equivalent doses of thiopental. Respiratory stimulation may result from desensitization of the pulmonary stretch receptors, though it may also be secondary to the decrease in arterial blood pressure.

In contrast to thiopental and other barbiturates, propanidid is rapidly metabolized in the blood stream by the removal of the C₆H₄ group to form the corresponding acid.
cent work has shown that serum cholinesterase plays a part in splitting the ester linkage, and the use of anticholinesterases or low serum levels of the enzyme could delay the breakdown of propanidid. Recovery would then occur as the result of redistribution.

The promptness of recovery after propanidid has been noted in clinical studies. In minor dental surgery performed using propanidid alone, it was found that, although time of awakening was similar to that after methohexitol, the time before the patient was fit to go home was much shorter with propanidid. When given intermittently, propanidid has much less cumulative action than either thiopental or methohexitol. In fact, doses are required more frequently to make this technique unsuitable for anesthesia lasting more than ten minutes. The duration of sleep has been studied in groups of patients given 0.5–1.5 mg/kg prior to surgery. There was an almost linear relationship between dosage and duration of anesthesia with normal doses of propanidid which differed from the progressive increase in sleeping time that can be expected with large doses of thiopental. However, the individual variations in effect were such that it was impossible to predict the exact amount needed to produce sleep for a short procedure of known duration. Clarke found that the doses needed for four to five minutes of narcosis ranged from 225 to 1,000 mg (3.8–17.6 mg/kg).

Although other clinical studies have supported the view that propanidid is metabolized rapidly in the body and that it behaves quite differently from the barbiturates, this is shown most clearly by the work of Doenicke and his colleagues from Munich. They have shown not only that recovery from propanidid is more rapid than recovery from the commonly used barbiturates, but that with the barbiturates there is a greater tendency for return to “sleep periods” during the subsequent hours. They also showed that 11 hours after methohexitol the effects of alcohol (0.5 liter of beer) were potentiated, whereas at the same time after propanidid there were only the usual mild symptoms.

There is no evidence that hyperalgesia such as occurs after barbiturates, occurs after small doses of propanidid. Although patients may not overreact to surgical stimuli, anesthesia can lighten very quickly and the clinical picture be similar to that produced by methohexitol.

Early in its clinical use it was found that propanidid intensifies the paralyzing action of succinylcholine. This effect is not consistent, but the author has encountered the unpleasant situation of patients who quickly regained consciousness, yet had residual paralysis. It would appear that this effect is related to the breakdown of propanidid by cholinesterases. In practice, one finds propanidid a little short-acting. When it is used simply as an induction agent, there can be no delay in the administration of supplementary agents. However, the advantages of a detoxicated anesthetic are such that one hopes newer agents with similar actions will be found. It is in this area, rather than among the barbiturates, that advances in intravenous anesthesia are likely to be made.

**Diazepam**

This drug is not primarily an anesthetic agent, but a minor tranquilizer with useful sedative and amnesic properties. It is widely used in psychiatry, particularly in treating anxiety–tension states, and this may explain, in part, the favorable reports of its use for preanesthetic medication. Diazepam is an effective oral hypnotic. Adult doses (20–30 mg) produce light sleep. This action is more marked when the drug is given intramuscularly. When given intravenously, there is a delay of one to two minutes before its maximum depressant action becomes evident, and there is great individual variation in responses.

Doses in the region of 0.5–1.0 mg/kg are necessary to induce anesthesia, and even these have remarkably few side-effects. However, the period of sleep is very long, and dizziness may persist for 24 hours after operation. This technique has little to commend it over others currently available. Diazepam enhances the effect of nondepolarizing muscle relaxants and can produce some muscular relaxation by its depressant effect on the neurons of the spinal cord, but alone it is of no clinical value as a muscle relaxant during general anesthesia. Although diazepam has no analgesic action, it does not cause hyperalgesia.
Some European workers have used diazepam as part of neuroleptanesthesia combined with dextromoranamide (Dimorlin) or meperidine. Others have given a single rapid injection of 20–30 mg followed by local blocks of neuroleptanesthesia.

Diazepam is most useful in surgery as a sedative or tranquilizer, either given alone to produce amnesia or in combination with regional anesthesia. The usual adult dose is 5–15 mg. Amnesia usually lasts about half an hour, but there is no evidence that diazepam causes retrograde amnesia. Diazepam can be used in small doses as a “cover” for any form of local anesthesia, and is also useful for sedation of patients receiving mechanical ventilation. The sedative–amnesic actions of diazepam also make it useful for endoscopic examinations, for which it can be given alone or with an opiate.

Diazepam is also used to reduce the discomfort of cardioversion. In one study in which the effects of thiopental and diazepam were compared, Muenster and colleagues induced sleep with a slow infusion of 1 per cent thiopental (250–400 mg) or with 15–20 mg diazepam. All patients had received their usual maintenance doses of digitalis during the preceding 48 hours. The cardiac status of the patients was similar in the two groups. Each group included some patients with rheumatic, ischemic, or hypertensive heart disease. The electrocardiograph records showed no premature ventricular beats in either series prior to the onset of sleep. Both drugs produced unconsciousness within three minutes and, although a few patients momentarily groaned with the countershock, none recalled the event. After induction of anesthesia, the incidences of premature ventricular beats in the two series were strikingly different. In the half minute preceding countershock they were observed in 11 of 18 patients given thiopental, but in none of the 17 given diazepam. The incidences were similar in the two series in the ten seconds immediately following countershock, but later arrhythmias were recorded in 12 of the patients receiving thiopental and in only four who were given diazepam. The eventual conversion rate was unaffected by the anesthesia.

In the postoperative period, diazepam's amnesic actions may be useful. McClish and his colleagues found that about a third of patients developed psychiatric complications when subjected to postoperative mechanical ventilatory support following open-heart surgery. However, in another group of patients who received the usual postoperative analgesic medication supplemented by intravenous doses of 2.5 to 5.5 mg diazepam six times a day, the incidence was less than 5 per cent. The latter group had better patient behavior and improved patient–nurse and patient–doctor relationships. Because of its amnesic properties, diazepam has been recommended for use in intensive care units.

Neuroleptanesthesia

This attractive term is applied to the state induced by the administration of a suitable dose of a narcotic analgesic and a hypnotic neuroleptic (major tranquilizer) drug. These drugs may be used alone (neuroleptanalgesia or “wakeful anesthesia”) or as adjuncts to inhalation anesthesia. There is nothing mysterious about this drug combination, which was the basis of the “artificial liberation” technique popularized in France about 20 years ago. Then, meperidine was combined with chlorpromazine and/or promethazine.

Now, a short-acting analgesic, fentanyl, is usually given with the butyrophenone, droperidol, although phenoperidine and dextromoramide are also used as analgesics, while haloperidol may be used in place of droperidol. A premixed combination of one part fentanyl with 50 parts droperidol (Innovar) is most commonly used, and to many, “Innovar” and “neuroleptanesthesia” are synonymous. In this brief survey only Innovar will be discussed. The use of this fixed drug combination may be criticized but it has proven most satisfactory in clinical use. Larger amounts of opiate cause too much respiratory depression, while smaller amounts result in too much drowsiness from the neurolept agent.

Innovar is no routine substitute for thiopental, since it is not primarily an induction agent, but rather a potent hypnotic–narcotic mixture. It has marked respiratory depressant effects and mild alpha-adrenergic blocking and antiarrhythmic actions which may produce hypotension and tachycardia. Despite its
widespread use for about ten years, the pharmacology of the individual drugs in the mixture or the combination itself has not been fully investigated.

There is no standard technique for induction of neuroleptanalgesia, but generally one injects a predetermined dose of Innovar and then waits for several minutes to observe its full effect. This is followed by small incremental doses as necessary to produce the desired state of analgesia or anesthesia. Neuroleptanalgesia is combined with nerve block or topical anesthesia as required. The full induction can take half an hour. Cardiovascular depressant effects are minimized by slow injection. Droperidol has a vasodilatory action which may benefit some poor-risk patients by increasing tissue perfusion. Equally important is the fact that it may enhance any existing hypovolemia before the onset of surgery and possibly lead to the need for liberal use of balanced salt solutions or blood transfusion.

Respiratory depression is not a serious problem provided one is aware of its existence. Although patients are very drowsy, they will breathe deeply on command and oxygenation can be easily maintained. Occasionally fentanyl causes rigidity of the chest wall, resulting in respiratory difficulty and difficulty in inflating the lungs. This condition responds rapidly to muscle relaxants. In neuroleptanalgesia assisted or controlled ventilation is essential, and muscle relaxants should be used as needed.

It has been claimed that droperidol prolongs and potentiates the analgesic effect of narcotics, but there is no evidence to support this. It may make patients less likely to complain of pain, but it has no true analgesic action. There is no scientific basis for the view that patients require less analgesics in the postoperative period after neuroleptanesthesia than after other techniques. The use of any opiate analgesic during anesthesia reduces the need for postoperative analgesics. Although it may be pure coincidence, it is worth noting that Innovar is used more widely in the United States, where opiate premedication is the exception rather than the rule, than in Britain, where opiates are given almost routinely before major surgery.

Neuroleptanalgesia without the subsequent use of general anesthetic agents has been used satisfactorily for such procedures as bronchoscopy, burn dressings, ophthalmic surgery, and radiologic procedures. Large doses of opiates, which do little or nothing to allay the anxiety of the patient, are avoided, and the antiemetic action of droperidol is also very useful.

A warning should be given concerning the intravenous use of droperidol alone for its sedative action. Although patients appear placid, drowsy and indifferent to their surroundings, they may be agitated and ill at ease. This has been found when droperidol has been used as a premedicant. However, a recent report showed that Innovar produced better preoperative sedation than morphine, coupled with a considerable reduction in postoperative emesis.

One must also be aware of the risk of extrapyramidal effects of droperidol, which can cause hypertonus and a typical parkinsonian crisis. Small (10 mg) intravenous doses of promethazine will control these effects, but these may have to be repeated, since droperidol has a fairly long duration of action. Care must also be taken in the administration of droperidol and Innovar to patients currently taking the monoamine oxidase inhibitor, phenelzine.

It is unfortunate that neuroleptanesthesia is looked on as a separate technique rather than an application of the basic principles of balanced anesthesia. It has certainly made many anesthesiologists aware of the potential value of large doses of narcotic analgesics and their safety if given properly. One hopes that there will be a further search for better analgesics and safer neuroleptic drugs, rather than an evaluation of the use of predetermined drug mixtures.

**Ketamine**

This interesting drug is chemically similar to phencyclidine (CI-395), whose use in anesthesia was abandoned about ten years ago because of psychotic effects, and cycloheximide (CI-400). It bears no chemical relationship to either the barbiturates or the eugnols. It is available in forms suitable for intravenous (10 mg/ml) or intramuscular (50 mg/ml) administration. It is a definite de-
parture from orthodox general anesthetics, and its actions are not similar to those of Innovar or diazepam.

The site of action of ketamine is claimed to be the midbrain, in contrast to the barbiturates, which act on the reticular formation.107 Its pharmacology was reported by Chen108 and by McCarthy and associates,109 who described it as being a compound with epi-leptic, analgesic and anesthetic action but without hypnotic properties. Chen later defined cata-
lepsy as “a characteristic akinetic state with a loss of orthostatic reflexes but without impair-
ment of consciousness in which the extremities appear to be paralysed by motor and sensory failure.”110 The early clinical pharmacologi-
cal studies by Domino, Chodoff and Corssen led to the drug’s being used in anesthesia.111 The manufacturer calls it a “rapid-acting non-
barbiturate general anesthetic,” but Corssen and Domino term it “dissociative anesthesia,” characterized by complete analgesia combined with only superficial sleep.112

Apart from hypertonus, a tendency to keep the eyes open, and some degree of nystagmus, patients under the influence of ketamine are indistinguishable from those having other forms of anesthesia. Consciousness is lost within ten minutes after the usual dose, 2 mg/kg, intravenously, in adults. Detectable analgesia often continues for a further half hour. It is not known whether ketamine is “rapidly-acting” in the same manner as thiopental and propanidid, and clinically one has the impression that the onset of sleep takes much longer than after these two drugs. Ketamine is unique in that it is not irritating to tissues and is rapidly effective after intramuscular injection, with onset of sleep occurring in two to eight minutes.

One of the most interesting effects of ket-
amine is its cardiovascular stimulating action. Blood pressure increases and tachycardia occurs. This effect is not related to dosage and, contrary to some early reports,113 is not less in hypertensive than in normotensive patients.114 The severity of hypertension is unrelated to the rate of injection.115 Possible explanations for the circulatory changes include central stimulation of the vasomotor center or depression of baroreceptor reflexes.116 Circulating catecholamines may be increased following its administration. The pressor effect may be diminished or abolished by alpha-adrenergic blocking drugs in animals117 and man.118 With increases in mean pressure of 25–30 per cent some reports of cerebrovascular accidents might have been expected, yet this has not occurred in what must now amount to more than 20,000 administrations. It is not yet clear whether ketamine is a drug of choice for induction of anesthesia in the “poor cardiac risk” or otherwise hypotensive patient.

In adults, recovery from ketamine anesthesia can be accompanied by delirium or excite-
ment, especially when no depressant pre-
anesthetic medication or other anesthetics are given and when the operative procedure is short.119 This is probably more likely to occur in women than in men.120 The time of estab-
lishing verbal contact with patients varies, but they can usually be calmed by talking to them. It is in the period between opening the eyes and waking fully that trouble is most likely to arise. Small doses of diazepam (2.5 mg) will usually control delirium, but care should be taken lest the patients lapse back into a deep sleep. Most patients have no memory of the immediate emergence upset, which is more disturbing to those in contact with them. Emergence delirium is less common in children, and rarely occurs with other types of intravenous anesthetics.

More troublesome are the perceptual alter-
ations which patients experience during re-
covery from ketamine anesthesia. Occasional patients have hallucinations and dreams, which can be morbid and terrifying. Again, these generally occur in lightly premedicated adults undergoing short operations. Garfield and his colleagues have compared the incidences of this problem after ketamine and halothane.121 They have also investigated the effects of detailed preoperative “briefing” of patients regarding what untoward reactions might occur. Briefing of patients increased the incidence of postoperative complications with halothane, but the incidence with ketamine, which was already high, was not increased. Thus, one can incriminate ketamine specifically as the cause of these sequelae. They can be reduced by the administration of diazepam at the end of the operation.122 Although unpleasant dreams may occur for as long as six
weeks after ketamine, it is necessary to note that Albin and his colleagues found no long-term personality disturbances in patients subjected to ketamine.\textsuperscript{113}

The place of ketamine in anesthesia is gradually being defined. It is certainly an unusual drug, with unique and frightening side-effects. It is important that its use be limited to the proper indications. Its greatest usefulness has been in pediatric anesthesia, particularly for neuroradiologic procedures.\textsuperscript{112} However, ketamine may cause an increase in cerebrospinal fluid pressure.\textsuperscript{113} This drug is especially useful for surgical procedures requiring multiple, frequent anesthetics, such as the changing of dressings in the burned patient. Reports of its use in obstetrics are also encouraging.\textsuperscript{114, 115}

Perhaps ketamine's main value in adults will prove to be in circumstances in which an anesthesiologist is not readily available, as in some underdeveloped countries.\textsuperscript{116} Patients usually maintain good control of their airways and can usually be left alone after administration of ketamine. Here, it would indeed fill a great need.

Other Drugs

Gamma-OH (gamma-hydroxybutyric acid-4 hydroxybutyrate) has been studied periodically for the past ten years and is no nearer being a useful intravenous anesthetic than when it was first studied. The drug can be converted to gamma-aminohydroxybutyrate (GABA), a well-known neuroinhibitor.\textsuperscript{117} Although it has probably justified the claim that it is a nontoxic hypnotic, the onset of sleep is not smooth, the volume of solution needed is large, and recovery may be prolonged. Its most likely future appears to be as a basal hypnotic for patients on ventilator therapy.

The steroid anesthetic, hydroxydione (Vivadril, Presurex) is rarely used now because of the very slow onset of action, damage to veins, and delayed recovery, but a new steroid compound known at present as CT 1341 appears very promising. This drug is a mixture of two steroids (3a-hydroxy-5a-pregnane-11,20-dione and 21-acetoxy-3a-hydroxy-5a-pregnane-11,20-dione), prepared for clinical use in cremophor E1. Preliminary experience of about 200 administrations by the author and colleagues shows this to be a promising agent. Induction is rapid and smooth and recovery prompt, with a low incidence of nausea and vomiting. This may well replace propofol and find an even larger field of use in minor operations or outpatient surgery.

Too many of us equate intravenous anesthesia with thiopental. From this survey it is apparent that many intravenous agents are available to the anesthesiologist. It is hoped that a broader view of the potential of nonbarbiturate anesthetics will be taken. Proper understanding and use of these drugs require the special skills of an anesthesiologist who, in this context, is truly an "applied pharmacologist."

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COMPARATIVE ANALYSIS OF INTRAVENOUS ANESTHETICS

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