Newer Agents For The Anesthesiologist

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At the time man began to look for agents which would produce pain relief and allow surgical procedures to be painless, he also became interested in methods of administering these agents. As we see our patients preoperatively most of them usually have two requests. First, they want to be "asleep" and second they want this "sleep" to be produced by an intravenous agent. Many specifically ask for pentothal. Some medical historians are already calling this present period "The Era of Intravenous Anesthesia."

We have been interested in finding the safest anesthetic agent for the patient; one which gives the surgeon the best operative conditions and still is pleasant for induction and has no after effects. To date, no one agent meets these criterion. Needless to say, the perfection of an anesthesia does not lie in a drug alone. A great deal lies in the skill and artistry with which it is administered.

During the past 20 years we have been using intravenous agents more and more. Much has been learned about the metabolism of the ultra-rapid acting barbiturates. Brodie and co-workers have shown that it is redistribution of these barbiturates which makes them ultra-short acting. Body fat, in this instance, acts as a reservoir in which the drug is stored and from there it is gradually released to be detoxicated relatively slowly by oxidation. The fat acts as a buffering mechanism which influences slightly the intensity of anesthesia, and much more the duration of anesthesia with these agents. The more fat there is in the body the more efficient is the buffering action, and the briefer the effect of a single injection of these agents. Recent work has substantiated earlier evidence that the liver is the primary site of metabolism of these agents. Other tissues are quantitatively unimportant. Using thiopental containing S it has been shown that the breakdown of the molecule seems to be at the side chain. Oxidation of the side chain converts the molecule to a carboxylic acid derivative. This derivative has none of the central nervous depressant action of the parent drug. The metabolism of these ultra-short barbiturates is slow and with large doses or repeated small doses, the resulting plasma level equilibrium is above the anesthetic level and is maintained by the reservoir of fat. The post-anesthetic somnolence seen is due to persistance in the plasma of the barbiturate itself which is coming out of the fat reservoir. This is the reason why unsupplemented use of these agents as anesthetics should be restricted to selected surgical operations of brief duration where only small doses are needed. It is safer to maintain the relatively stable barbiturate at a low plasma level for basal anesthesia, and to obtain depth of anesthesia with other agents when long surgical procedures are contemplated.

Because of the occasionally protracted period of somnolence and the tired weak feeling that some patients complain of due to the presence of the barbiturate in low concentration in the blood for 24-48 hours, the search goes on for other agents. One of these agents which is of interest and may have promise is hydroxydione (trade-name Viadril-Pfizer Lab.)

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Selye and others during their work in animals on hormone action noted depression and anesthesia with various steroids. Merryman reported sleep in humans by the intravenous injection of progesterone. Recently a group of water soluble steroids were tested for anesthetic activity. 21-hydroxy pregnanedione sodium succinate had the widest margin of safety, produced no hormonal effects, no salt retention, no pathological changes in organs but did produce anesthesia. Figure 1 shows the relationship of hydroxydione, a water soluble steroid with anesthetic activity dissociated from the hormonal activity, to progesterone and also to hydrocortisone.

![Figure 1](image)

The relationship of hydroxydione to progesterone, and to cortisone.

It is structurally related to hormonally active steroids. This same configuration is similar to the substance in some of the tars which have been used to cause carcinoma in animals. It is a white crystalline material obtained as a free acid made water soluble by neutralization with sodium carbonate. Hydroxydione has been tested for estrogenic, androgenic, anabolic, progestational, corticoid, adrenal corticotrophic, thyrotropic and gonadotropic activities and these are absent. In animals and humans it effects cerebral metabolism like barbiturate anesthesia, namely reducing oxygen consumption of the brain when anesthesia is produced. The electroencephalographic picture is also quite similar to deep thiobarbiturate levels. When the drug is made up in 2.5 per cent solution it has a pH of 8.5-9.8 and direct injection into a vein causes pain and a high incidence of thrombosis. Injecting the drug slowly into an intravenous of 5 per cent glucose which is running rapidly has resulted in only mild burning of the arm in the occasional patient. With this technique the incidence of thrombosis or thrombophlebitis is no greater than when barbiturates are used.

Hydroxydione has definite anesthetic properties and its effects clinically are of interest. Injection of 0.5 to 1 gram intravenously produces unconsciousness in about 5 minutes and anesthesia in 7 to 10 minutes. There is practically no respiratory depression and little or no fall in blood pressure in the supine individual. No studies are reported of the effects of posture on the circulatory effects of the drug. The pulse rate remains unchanged with slow injection. With 0.5 gm. doses anesthesia lasts 30-45 minutes and on wakening patients appear wide awake, conscious and do not have the hangover effect produced by the barbiturates. The incidence of
nausea and vomiting has been remarkably low. Patients are pleased with its effect. The drug appears to produce some retrograde amnesia. In patients without the usual premedication of morphine or demerol and scopolamine there is retrograde amnesia of about 30 minutes.

An interesting feature of this drug is the obtundation of the pharyngeal reflex. It is possible to expose the larynx with ease and without gagging or coughing in most patients who receive one gram of Viadril intravenously. The vocal cords are not however insensitive and will adduct if stimulated. They do not stay in spasm long and normal respiration occurs quite promptly. We use the drug to produce unconsciousness for suspension laryngoscopy and if the larynx is cocaineized this method has proved very satisfactory.

As with barbiturates, if the anesthesia begins to wear off, more drug can be injected. The second dose is smaller and I am certain there is a cumulative effect.

Animal work with this drug has shown that heptacyclazine has no effect on duration of anesthesia or depth of anesthesia. The method of metabolism of the drug in the human has not been reported, but repeated daily anesthetic doses in monkeys has not shown any liver or kidney damage and no bone marrow depression.

Further evidence that the drug has anesthetic properties is that if meperidine is used to supplement it, as we usually do when we are using thiopental, much less meperidine is used than with the before mentioned drug. It produces a definite analgesic state far greater than that produced by barbiturates.

This latter property has given us an opportunity to use a new drug of the opiate series called heptacyclazine. Heptacyclazine is an analog of meperidine. Figure 2 shows that it contains a seven numbered heterocyclic ring in place of piperidine in meperidine. To date, it has had modest clinical trials. Several properties are of interest. It definitely raises the pain threshold and is effective in treating clinical pain of postoperative patients. Its effectiveness seems to be somewhere between codeine and meperidine. The drug that does not produce euphoria, sedation, amnesia or a sense of well being and thus differs from all the other opiates. Because of this, addiction to the drug is said to be absent. If this proves to be true it is the first opiate to have this property. Another interesting action is the lack of respiratory depression when this drug is given.

![Figure 2](image-url)

**Figure 2**

Formula of Heptacyclazine which is an analog of meperidine.
We have been using Viadril and heptacyclazine in combination and are pleased to have a patient with a pleasant and unexcited induction plus amnesia of this event. We have an anesthetized patient without respiratory depression plus an insensitive pharynx and finally a patient who, on wakening, is alert, cooperative, and not sleepy and groggy for the next 24 hours.

Heptacyclazine may be useful in potentiating the effect of thiopental-nitrous oxide-oxygen anesthesia, similar to the way in which we use meperidine at present. It would produce analgesia without respiratory or cardiovascular depression. Its place in the treatment of pure pain is being evaluated. Here it may fail because of its lack of sedative effect.

At present, the only complication with these drugs is their irritation properties which necessitates an intravenous be running for their administration. The 5-7 minutes which are needed before the patient is unconscious and in a surgical plane of anesthesia also deters their use in a busy operating schedule.

Another intravenous anesthetic agent which does not appear to cause somnolence after operation is a thio-barbiturate called Baytenal. It is sodium 5,5-allyl-(2-methyl-propyl)-thiobarbiturate. The drug is stable in solution for about 36 hours. It is a white powder readily soluble in water and used in 10 per cent solution. Baytenal acts rapidly and produces little respiratory or circulatory depression in therapeutic doses. Four hundred milligrams produces unconsciousness with recovery in 5 minutes and ability to be ambulatory in 10 minutes with no demonstrable after effect. Because of its rapid elimination or detoxification (and no storage in fat) it may prove useful as a constant intravenous drip for longer surgical procedures, similar to the way we now use succinylcholine or thiopental.

My experiences with the newer thiobarbiturates have not been too satisfactory. Many have worked well on animals but in humans we have seen several side effects, namely venous thrombosis, thrombophlebitis, coughing, sneezing, hiccups and vomiting. This was true also during the early synthesis of thiopental and thioallyl. It may be due to impurities or contaminants and some of these newer drugs may come into clinical use.

Recent work has also been done with intravenous analeptics which seem specific for barbiturates. N-allyl-normorphine (Nalline) is not effective in the treatment of barbiturate overdose. It is effective in treating all opiate derivative intoxication. Recently, Boyd, from the Pharmacology Department in Kingston, again showed both its ineffectiveness and possible harmful effects in the treatment of barbiturate overdose.

Reports from the Australian as well as the British literature have revealed some interesting studies with two drugs, one of which seems specific for barbiturate intoxication, the other being a respiratory stimulant against any type of respiratory depression. These two new substances, bb-methylethyl-glutarimide (NP13) and 2:4—Diamino-5-phenylthiazole hydrochloride (D.A.P.T.) used in conjunction with the resuscitative regime advocated by Nilsson may further reduce the death rate in barbiturate intoxication.

The chemical structure of NP13 indicates a definite resemblance to the barbiturate ring as seen in Figure 3. In therapeutic doses this drug appears to exert a direct antagonism to the barbiturate. If this drug is given intravenously in high dosage
and rapidly it will cause convulsions. Much of this drug is excreted in the urine unchanged. I know of no reports as to what effect it has on barbiturate blood levels or brain barbiturate content.

A di-substituted barbiturate

\[ C_6H_5 - C - S \]
\[ NH_2 - C - C - NH_2 \cdot HCL \]

BB-methylethylglutarimide (NP13)

2: 4-Diamo-5-phenylthiazole hydrochloride (D.A.P.T.)

Figure 3

Chemical structure of bb—Methylethyl-glutarimide (NP13) and of 2:4-diamo-5-phenylthiazole hydrochloride. (D.A.P.T.) antagonists of and similar in structure to barbiturate.

These same investigators have studied a large number of drugs reported to have analeptic properties against opiates. All of these drugs have either a muscarine-like action or are anti-choline esterase drugs and a common chemical linkage is the phenylthiazole radical. Testing drugs with this linkage it was found that 2:4-Diamo-5-phenyl-thiozole hydrochloride (D.A.P.T.) was active in the stimulation of respiration in both opiate- and barbiturate-medicated animals with respiratory depression.

Using a combination of these two drugs intravenously the Australian investigators report success in bringing deeply comatose, areflexic barbiturate-intoxicated patients to what they call a "safe state" in a matter of two hours. They then remove the endotracheal tube and treat them as though the patient were recovering from light anesthesia. These investigators feel this has the advantage of obviating prolonged endotracheal intubation or tracheotomy, minimizing possible complications of prolonged coma and is economical in preventing prolonged strict nursing care.

Time alone will tell whether this will be an advance in therapy since now on a careful medical regime alone the mortality rate in barbiturate poisoning is about 1.6—4 per cent.

Still another antidote is an analeptic drug which is said to have marked stimulant effects on both respiration and circulation with an improved margin of safety over the commonly used analeptics. Metrazol, nikethamide and picrotoxin tend to produce convulsions, this tendency being counteracted, if the analeptic dosage is not too large, by the anti-convulsant effect of the barbiturates. They are not as effective in narcotic poisoning.

Figure 4 shows the structure of this new analeptic. Structurally it does not resemble the other analeptics. NN-Dibutylethylene diamine NN dicarboxy bismorpholide is effective in counter-acting the respiratory and circulatory depression caused by both barbiturates and opiates. It has the advantage of not producing convulsions except in excessively large doses. This drug given intravenously, in therapeutic dosage,
is said to also stimulate respiration in the normal unpremedicated subject. It does not have any "amphetamine-like" stimulant action on the central nervous system and does not produce insomnia.

![Chemical structure of a new antidote for barbiturates.](image)

**N N' Di butylethylene diamine N N' dicarboxy bismorpholide**

Figure 4

Chemical structure of a new antidote for barbiturates.

In subjects depressed with overdosage of either narcotic or barbiturate it will stimulate respiration and raise the blood pressure. The recommended dose is 15 mgm. intravenously. Onset of action is brief, the peak activity is reached in 5-8 minutes and lasts for about 1 hour. How successful this drug will be must await further clinical trials.

Antidotes are also being used with the muscle relaxants. With muscle relaxants most of the anesthetist's attention is focused on respiration and how it is altered, but another important and adverse effect these drugs have must not be overlooked. As well as blocking activity at the neuromyal junction, and producing muscle relaxation with inadequate respiratory exchange, they have inherent in them the ability to block sympathetic ganglia with resultant deleterious effects on the circulation. Occasional patients develop unexplained hypotension of a severe degree. Some have profound circulatory collapse with doses of curare that do not necessarily paralyze the respiratory muscles. Curare may on occasions also have a central nervous system depressant action. While not producing unconsciousness it may block the passage of impulses from centers important in maintenance of both respiration and circulation.

Because of the antidotes, todays anesthetist is probably more liberal with his doses of relaxants. But in some instances the antidote fails to outlast the relaxant or at times the anesthetist is surprised to see adverse effects in the patient following injections of neostigmine, atropine, or nikethamide. The anesthetist is at a loss to explain why the patient suddenly develops an asthmatic attack, a marked tachycardia, an elevated temperature, has a convulsive seizure of just simple atelectasis. Intravenous agents affect people in various ways and should not be used empirically. The antidote may be producing all of these complications.

As regards curare antidotes one which may be used to counteract the apnea occasionally seen after succinylcholine should be mentioned. Of the two enzymes in blood (true cholinesterase in the red cells and pseudocholinesterase in the plasma) the pseudocholinesterase is reportedly responsible for the hydrolysis of succinylcholine. It has been suggested that unduly prolonged succinylcholine apnea be treated with transfusion of whole blood. Fresh blood is preferable, but even after storage whole blood contains some 30 units of pseudocholinesterase per ml. of plasma. There is now a commercial preparation available for clinical trial which is an ethanol fraction of concentrated human plasma and is a subtraction of Cohn's globulin fraction IV-6.
This is said to be a specific antidote for succinylcholine apnea. There are, however, cases reported who have had prolonged apnea from succinylcholine whose serum, when tested, revealed normal enzyme levels. These people were suffering from cancer and inanition. They had altered electrolyte values in the serum, primarily low potassium. It may be that in patients like these, muscle paralysis is difficult to reverse because of a loss of excitability. Antidotes are of no use.

In concluding I want to repeat the statement made by a leading pharmacologist and physiologist with whom I was associated 20 years ago. He still makes it to his students today. "Inhalation anesthesia is the safest anesthetic method, since the patient's own vital processes keep him alive; intravenous anesthesia depends on the patient's ability to detoxify or excrete the anesthetic agent and this may be quite variable, and once the agent is injected you can't get it back". We are developing antagonists and antidotes, it's true, but an anesthetic administration has always been a dangerous experience for the recipient, and the over-all picture would appear that it has become, with the spread of the newer methods, a more dangerous experience. I'm reminded of the modern Dante's (Geoffrey Kay's) poem in which he is describing the type of pit into which the unwary anesthetists may be drawn through putting their trust in false gods, be they new intravenous anesthetic agents, antidotes, or indicator soda lime.

Here rests beneath this grassy plot,
My patient, Mrs. Geer,
Who, being curarized, could not
Exhibit hyperpnoea.
If we could meet a second time,
Less confident I'd be
In "indicator" soda lime:
I'd measure her B.P.!

BIBLIOGRAPHY