New Accessory Drugs Used in Anesthesia

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The classes of drugs that will be discussed are as follows: the tranquilizers, barbiturate antagonists, narcotic antagonists, and antagonists to muscle relaxants. The curariform action of antibiotics will also be discussed.

Tranquilizer is a term which has been introduced to denote a new group of drugs such as the phenothiazines, rauwolfia derivatives, and meprobamates. This term is used by some to imply control of psychomotor excitement without excessive cortical depression, that is, without the loss of rational or discriminate thought. Tranquilizers are presumably distinct from the barbiturates or sedatives in that they are supposed to produce quiescence without producing as much impairment of performance. However, simply defined, a tranquilizer is a drug that produces peace of mind. The tranquil state can be accomplished by a host of drugs such as the barbiturates, alcohol and the narcotics. Therefore, the recommendation1 has been made that the term tranquilizer be discarded and that this group of drugs, instead of being called tranquilizers, should be classified according to their effect on the central nervous system. Following such a scheme, the phenothiazines and rauwolfia derivatives which produce suppression of sympathetic nervous system and are active in the hypothalamic area would be called central sympathetic suppressants. The meprobamates (Equinil or Miltown) which produce skeletal muscle relaxation and are active in the thalamus would be central muscle relaxants.

The Phenothiazines

The phenothiazines which have been used extensively in anesthesia are shown in Table I. The first phenothiazine used to any extent in medicine was promethazine (Phenergan).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose - mg.</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
</tr>
<tr>
<td>Promazine</td>
<td>Sarpine</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Compazine</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
</tr>
<tr>
<td>Mepazine</td>
<td>Pacatal</td>
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</table>

It was used as a long acting antihistaminic. It was soon realized that this agent potentiated the effects of barbiturates and narcotics. Therefore, a search for other compounds related to promethazine was started. In 1952, chlorpromazine (Thorazine) was introduced. Chlorpromazine has a wide variety of effects and is probably the most versatile drug of the group. However, it has a very serious draw-
back—the production of hypotension and tachycardia.

Chlorpromazine. The hypotension produced by chlorpromazine is difficult to reverse. It is probably due to peripheral vasodilatation and suppression of the vasomotor center. It produces reversal of the action of epinephrine. That is, in a patient who has received chlorpromazine and is hypertensive, epinephrine may cause a further fall in pressure. The hypotension does respond to norepinephrine, neosynephrine, Vasoxyl, and Methedrine in doses greater than ordinarily used clinically. It is not recommended that chlorpromazine be used in conjunction with spinal or epidural anesthesia because profound hypotension difficult to reverse may ensue.

Thorazine by itself does not produce any respiratory depression. However, the respiratory depression of narcotics is intensified. When chlorpromazine first was introduced, we used 25 mg. intramuscularly as preoperative medication in a patient who was sensitive to morphine sulfate and other narcotics. It was found that the patient simply would not breathe enough to become fully anesthetized. Intubation of the trachea was accomplished with a relatively low blood level of cyclopropane and the help of a muscle relaxant.

Chlorpromazine does not have so great a tendency to produce convulsions and extrapyramidal stimulation as do some of the other phenothiazine derivatives. It has been found useful to control the agitation of alcoholism or the excitement after hypoxia. It has been combined with Seconal and scopolamine to provide sedation and to control psychomotor activity during labor. It has also been used for the control of postpartum hypertension which may result from the combined effect of a vasoconstrictor and an oxytocic drug given within three to six hours of each other. A subarachnoid hemorrhage due to rupture of an intracranial aneurysm occurring in a patient who had received a vasoconstrictor prophylactically before caudal anesthesia for delivery and an oxytocic at the time of delivery of the placenta has been reported.

Knapp and Beecher found that a dose of 50 mg. of chlorpromazine given immediately postoperatively was effective in reducing nausea, vomiting and wretching for 24 hours. However, it took twice as long for the patients who received chlorpromazine to awaken as compared to those that had not. Furthermore, hypotension of a serious degree resulted in many patients.

Two Danish anesthetists evaluated the use of 50 mg. of chlorpromazine as compared to 10 mg. of morphine sulfate as preoperative medication. They made careful observations on two groups of patients subjected to abdominal hysterectomy. The anesthetic management was standardized, that is, the same dose of thiopental and succinylcholine was used for induction. The anesthetics were given by the same two anesthetists. Maintenance was with nitrous oxide and succinylcholine. Under these conditions, the drugs were remarkably similar. The degree of sedation was identical. Chlorpromazine produced a decrease in the incidence of nausea and emesis. However, recovery was prolonged. Residual neuromuscular blockade or respiratory insufficiency and lethargy was more noticeable with chlorpromazine. These workers tended to favor morphine sulfate to a slight extent.
Promethazine. Promethazine does not seem to have as profound a hypotensive effect as chlorpromazine. Yet, almost half of the normal volunteers given 50 mg. of promethazine intramuscularly and tilted on a table, fainted; that is, became hypotensive. However, transient hypertension following promethazine given intravenously, has been reported. On several occasions, we have given promethazine intravenously in a deliberate attempt to lower blood pressure but it was ineffective. Furthermore, it has been used intravenously during spinal anesthesia, apparently without much of a hypotensive effect in contrast to chlorpromazine.

The effect of 50 mg. of intramuscular promethazine on the respiration of normal adult males has been studied. The respiratory minute volume was found to be increased and the end expiratory carbon dioxide tension was found to be decreased. This stimulation of respiration was probably due to the restlessness that the volunteers developed. When Phenergan is used in conjunction with other drugs or anesthetics, then it has a depressant effect on the respiration.

I have used the combination of Demerol, Phenergan and scopolamine as preoperative medication for tonsillectomy. It appeared that some of the children had lost their sense of equilibrium and were afraid that they would fall when they were being transferred from the bed to the litter. Even though the medication was given according to weight, it was difficult to obtain a uniformly successful effect; that is, some were too lightly and some too heavily medicated. The children were then given Vinethene and ether by the open technique. Some of the children would simply not breathe sufficiently to become anesthetized and the inductions were slow and tedious. During the procedure, apnea was encountered occasionally when the mouth was opened or when the tonsils were grasped. Furthermore, the children did not seem to struggle against an obstructed airway.

In addition to producing merely restlessness and Parkinsonism, promethazine has produced convulsions in a patient with a history of epilepsy. Therefore, we do not recommend that it be used alone or in the patient with agitation, eclampsia or history of epilepsy.

Promethazine has been used as a premedicant and as an adjuvant during anesthesia. By adjuvant, it is meant that promethazine was given during anesthesia, for example, thiopental-nitrous oxide, to reduce the amount of thiopental necessary in the hope of shortening the awakening time. This, however, did not work out. At the present time there seems to be little justification for the routine use of promethazine for premedication or as an adjuvant during anesthesia.

Promazine. Promazine (Sparine) is less likely to produce hypotension than chlorpromazine. Some authors say that it is relatively ineffective when used alone for the treatment of excitement, agitation, or nervous tension. Agranulocytosis and extrapyramidal motor activity simulating Parkinsonism are seen less often than with chlorpromazine. However, convulsions following the use of promazine have been reported. Some obstetricians prefer promazine to promethazine. Also, it has been found useful to control the agitation of alcoholism.

Prochlorperazine and Perphenazine. Prochlorperazine (Compazine)
and perphenazine (Trilafon) are effective anti-emetics. As anti-emetics they are best used in the immediate postoperative period. They are also effective in the treatment of senile agitation. One of the serious complications resulting from their use even in therapeutic doses is extrapyramidal stimulation to an alarming degree. Dislocation of the jaw and a death from the tetanic contraction of respiratory muscles have been reported.

THE BARBITURATE ANTAGONISTS

Megimide. Megimide was introduced by Shaw in 1954 as a specific antagonist to the barbiturates. However, subsequent workers, notably the group from Copenhagen, were not able to substantiate this. If Megimide were a chemical antagonist or competitive inhibitor, it might be expected that patients would regain consciousness despite a high blood level of barbiturate. But it was found that in patients with severe barbiturate poisoning, Megimide changed neither the blood level at which consciousness returned nor the duration of the coma. Megimide, therefore, should be classified as an analeptic or central nervous system stimulant similar to picrotoxin but with a somewhat wider margin of safety.

Megimide quite consistently stimulates respiration depressed by barbiturate overdosage. The Danish School has successfully restored respiration to normal in patients made apneic by an overdose of barbiturate. Others have successfully used Megimide to stimulate respiration after thiopental anesthesia. Since 1955 there have been many reports describing the use of 50 mg. to 100 mg. of Megimide to shorten the awakening time after thiopental anesthesia. Several reports, one utilizing a double blind technique, could show no significant difference in the waking times between those patients receiving Megimide and those who do not. However, the bulk of the evidence seems to favor a shortening of the awakening time after thiopental anesthesia by Megimide.

Megimide is not without its side effects. Convulsions have been produced in man by doses of 200 mg. or more. Visual hallucinations consisting of black specks, smoke, fire, or colored patterns occurred in 15 out of 50 patients suffering from barbituric acid poisoning who were treated with Megimide. Vomiting and spasm of the masseter muscles may occur. This may lead to aspiration of vomitus if an endotracheal tube is not in place. If an endotracheal tube is in place, bucking and bronchospasm may result.

Ritalin. The literature on methylphenidate (Ritalin) has not been so profuse as that on Megimide. It also is considered to be a non-specific stimulant of the central nervous system, that is, an analeptic. It has been used for the treatment of depression following the use of Reserpine or other tranquilizers, in various depressed mental states, and following thiopental-nitrous oxide anesthesia. In patients who had a dilatation and curettage, the recovery time as measured from the removal of the anesthetic mask to response to verbal command was, for the group receiving Ritalin, about one half as compared with those who had not. The optimal dosage was found to be 0.10 mg.-0.19 mg./lb. Ritalin also has been noted to stimulate the respiration of patients moderately depressed with barbiturates, meperidine or both. Side effects that have been noted are: mild transient rise in blood
pressure, nausea, retching or emesis, restlessness, tremors, relapse and insomnia.

Summary. These analeptics should be used with great caution if at all in the patient with severe barbiturate poisoning. First, because of the excellent results obtained by Nilsson, with merely supportive treatment and with attention to maintenance of respiration and blood pressure, and avoidance of pulmonary and renal complications. Second, because the length of the coma is not shortened despite a rousing effect.

In the moderately depressed patient or one overdosed with thiopental, they may be given a trial in the hope of stimulating respiration and also producing a state of wakefulness. The dose should be limited and if an adequate response is not obtained, then other measures should be used.

In the patient who is only slightly depressed, these drugs can be very useful to establish a quicker return to consciousness and thus an easier nursing problem. Branch has been using Ritalin in ambulatory dental anesthesia patients and believes its benefits outweigh the disadvantages.12

THE NARCOTIC ANTAGONISTS

The narcotics do have a true antagonist. That is, the respiratory depression, hypotension, nausea and emesis produced by the narcotics can be blocked by these antagonists. There are two narcotic antagonists in common use. Nalorphine (Nalline) which is identical to morphine except for the side chain on the nitrogen which has an allyl group instead of a methyl group. Levallorphan (Lorfan) is related to levo-dromoran as Nalline is to morphine. Lorfan is more widely used because: its use is not restricted by the Harrison Antinar-

The combination of a narcotic and narcotic antagonist can be used for preoperative medication and as an adjuvant during anesthesia.18 I use the combination of Lorfan, Nisentil and scopolamine for premedication in children for tonsillectomy. I also use the combination for procedures during which I do not desire to control the respiration. The sedative effects of the narcotic and the antagonist seem to be additive, so larger doses of narcotic need not be used for preoperative medication even though it is combined with a narcotic antagonist. If controlled respiration is employed, the narcotic alone can be used before and during the anesthetic

Table 2.
The Following Ratios of Narcotic to Antagonist Have Been Recommended:

<table>
<thead>
<tr>
<th>Narcotic</th>
<th>Antagonist</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levo-Dromoran</td>
<td>Lorfan</td>
<td>10/1</td>
</tr>
<tr>
<td>Morphine</td>
<td>Lorfan</td>
<td>20/1-50/1</td>
</tr>
<tr>
<td>Demerol</td>
<td>Lorfan</td>
<td>60/1-100/1</td>
</tr>
<tr>
<td>Nisentil</td>
<td>Lorfan</td>
<td>25/1-50/1</td>
</tr>
<tr>
<td>Demerol</td>
<td>Nalline</td>
<td>20/1</td>
</tr>
</tbody>
</table>

The point that is very intriguing, as well as interesting, is that by selecting the proper ratio of the antagonist to the narcotic, the above undesirable effects can be blocked without significantly blocking the analgesic properties. The ratios for Lorfan that have been worked out by several workers are given in Table 2. The narcotic antagonists have been used for the treatment of depression due to narcotic overdosage including neonatal respiratory depression. If it is used in the narcotic addict, typical withdrawal symptoms will result.
process to help induce apnea and to provide analgesia. The respiratory depressant effect of the narcotic is reversed with the narcotic antagonist at the end of the operation if necessary.\textsuperscript{14} Foldes has used the combination of Nisentil and Lorfan in a ratio of 50 to 1 during obstetrical labor. It produced good analgesia without respiratory depression of either mother or newborn. The combination is also effective for postoperative pain.\textsuperscript{15}

**Antagonists to Muscle Relaxants**

Before we discuss the antagonists to the muscle relaxants, let us briefly review the pharmacology of the muscle relaxants. They have been classified into two groups: the nondepolarizing and the depolarizing agents. The nondepolarizing agents fill the receptor sites at the motor end plate which would normally be occupied by acetylcholine. This prevents acetylcholine from depolarizing the end plate and so the contraction of the muscle. The depolarizing agents also fill the receptor sites, but, because they are similar to acetylcholine, they cause depolarization of the end plate and contraction of the muscle. This is the twitching seen with the injection of succinylcholine. However, unlike acetylcholine, they stay at the receptor sites and prevent the repolarization of the end plate, therefore, the muscle cannot contract again. D-tubocurarine is a member of the nondepolarizing and succinylcholine is a member of the depolarizing group. Recently, there has been some evidence to suggest that succinylcholine, after prolonged usage, acts as a depolarizing agent, and as a result of this, the antagonists to reverse the paralysis of d-tubocurarine, have been used for succinylcholine.\textsuperscript{16} The antagonists to d-tubocurarine are prostigmine and edrophonium (Tensilon). These drugs act primarily as cholinesterase inhibitors. Cholinesterase is the enzyme that breaks down acetylcholine and renders it ineffective. So, cholinesterase inhibitors allow a higher concentration of acetylcholine to accumulate at the end plate. Before either one of these drugs is used, however, atropine should be given, preferably a few minutes before. Atropine is used to prevent the bradycardia, bronchospasm and excessive secretions that may result when acetylcholine is allowed to accumulate. The trend has been to give the antagonist routinely at the end of the procedure when d-tubocurarine is used. The dosage is atropine 0.4 mg. to 1.2 mg. followed by prostigmine 0.5 mg. This is repeated if necessary. The British are a little more generous with the dosage, using as much as 2.5 mg. of prostigmine. Edrophonium (Tensilon) has a more fleeting action and there is a real danger of re-appearance of the paralysis in ten or fifteen minutes, so one should follow edrophonium with prostigmine. The dose of edrophonium ranges from 5-20 mg. Cases of prostigmine resistant curarization have been reported. These have occurred primarily in debilitated patients and those with fluid and electrolyte imbalance, for example, carcinoma of the lung and intestinal obstruction.

As far as antagonists to succinylcholine are concerned, one is not on as safe ground as with d-tubocurarine. If one uses the cholinesterase inhibitors, that is, prostigmine and edrophonium, then one has to assume that the succinylcholine is no longer acting as a depolarizing but rather as a nondepolarizing agent. Just when, and if, this occurs cannot be determined.
clinically. However, if other measures fail then one can give a small test dose of edrophonium and observe the result. If a beneficial response is obtained, then prostigmine can be given. Prostigmine should not be given first because marked prolongation of the apnea may result.  

THE CURARIFORM ACTION OF ANTIBIOTICS

Neomycin has been reported to have a neuromuscular paralytic effect similar to curare. It is potentiated by ether. Several deaths due to respiratory paralysis following the intraperitoneal installation of neomycin during ether anesthesia have been reported. This effect can be partially antagonized by prostigmine. Calcium has also been reported to be effective. To avoid respiratory paralysis, cyclopropane, which does not potentiate the effects of neomycin, should be used to anesthetize patients receiving neomycin parenterally.

Streptomycin and polymixin B have also been shown to have a curariform action. However, with the doses used clinically, no cases of postoperative apnea have as yet been ascribed to streptomycin or polymixin B.

BIBLIOGRAPHY