TWO YEARS' EXPERIENCE USING THE PHENOTHIAZINE AMINE DERIVATIVES IN ANAESTHESIA AND ARTIFICIAL HIBERNATION WITH SPECIAL MENTION OF THE NEW DERIVATIVE "PACATAL"*

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THE phenothiazine amine derivatives form a relatively new chemical family which has aroused considerable interest in medical therapeutics, particularly in anaesthesia, psychiatry, and internal medicine.

Their discovery dates back to 1944 (1) when two investigators, Gillman in the United States and Charpentier in France, had the same idea of uniting in one molecule the phenothiazine nucleus, whose anthelmintic properties were well known, and the aminated chain, similar to that of the molecule of the anti-malaric drugs. Each investigator's work was unknown to the other because of the disruption of war.

Disappointed by their poor anthelmintic properties, the American school soon abandoned the study of these new compounds. The French school, on the contrary, investigated them extensively and produced a large series of related drugs. Because of the very close corroboration between laboratory and clinical trials, the discovery of the phenothiazine amine series rapidly found a tremendous clinical application, first in anaesthesia (2, 3, 4), and then in psychiatry, later a multitude of uses appeared helpful in other fields of medicine.

In 1945, Halpern and Ducrot in France described the powerful antihistaminic properties of one of the new group, promethazine.¹ They also pointed out the many secondary effects of this compound, in particular its hypnotic action, its antishock properties, its neurovegetative stabilizing effect, and its potentiation of local and general anaesthetic agents. These beneficial effects were incorporated into anaesthesia by Laborit in 1946, who thus gave rise to "Potentiated Anaesthesia"

Two years later, a new compound of the series, chlorpromazine² was proven to have lost the antihistaminic properties of promethazine but to have increased much farther the analgesic-sedative-neurovegetative stabilizing and antishock properties. In association with promethazine and pethidine, the "lytic cocktail" was established and with it "Artificial Hibernation." Then in some very acute and desperate state of illness, man could now benefit from the reduced life of the poikilotherm being, by submitting himself temporarily to an acute stress,

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¹Promethazine Poulenc registered trade mark of Phenergan Poulenc (3 277 R P), the chlorhydrate de dimethylamino-3-dimethyl 2-2-propyl-1-N-phenothiazine

²Chlorpromazine Poulenc registered trade mark Largactyl in Canada, the chlorhydrate dichloro 3 (dimethylamino 3-propyl)-10 phenothiazine (4560 R.P.).

he could survive. The new family of drugs clinically seemed to give a lysis of the autonomic nervous system, mostly the adrenergic part which is responsible for homeothermia. Clinical application proved to be helpful in surgery either as potentiated anaesthesia or as artificial hibernation, when combined with hypothermia. It also proved helpful in medicine for maintaining life in the very sick patient. Recently American research reproduced some of the experiments of Laborit and collaborators and demonstrated once again the antishock properties of chlorpromazine both in traumatic and haemorrhagic shock (5, 6).

The presentation of this small series of patients treated over the last two years with the phenothiazine derivatives stresses the clinical value of these drugs. On the same occasion, a new phenothiazine derivative, "Pacatal," on clinical trial for the last six months, is discussed in comparison with chlorpromazine and promethazine.

The latter, Pacatal,³ has properties similar in some ways to those of chlorpromazine but the hypnotic effect is somewhat less, consciousness being retained even under hibernation. Also the drug could, unlike chlorpromazine, be given intravenously undiluted without causing tachycardia or hypotension.

CLINICAL DATA (Table I)

This study includes 84 cases of artificial hibernation and 500 cases of potentiated anaesthesia. In 14 of the 84 cases of artificial hibernation, Pacatal was used and in the rest Chlorpromazine, in 100 of the 500 cases of potentiated anaesthesia Pacatal was used and in the remainder Chlorpromazine

TABLE I
CLINICAL DATA

I	ARTIFICIAL HIBERNATION	84 cases	No of cases
	<i>Surgical Cases</i>	Cerebral aneurysm Commando (radical neck dissection with resection in continuity of the primary cancerous tumor) Thyrotoxicosis Poor surgical risks In prevision of severe operative blood loss	6 15 3 14 7 45
	<i>Medical Cases</i>	Cerebrovascular accidents Cerebral traumatism Postneuro-surgery hyperthermia Severe infection diabetics tetanus peritonitis Post-extensive surgery	8 8 9 2 1 2 2 32
	(a) patients "in extremis" <i>because of shock due to</i>		
	(b) <i>therapeutic sleep</i>	Psychoneurosis Ulcerative colitis Recurrent infections Light tetanus	4 1 1 1 7
II	POTENTIATED ANAESTHESIA* over 500 cases		

³Warner-Chilcott registered trade mark of N-methyl-piperidyl-(3) methyl phenothiazine

I. ARTIFICIAL HIBERNATION

These cases have been discussed in previous presentations (7, 8), therefore only a brief summary will be given.

A. Surgical Cases

For surgical cases, hibernation has been used on poor risk patients or those presenting a special problem such as anticipated severe operative blood loss, extensive radical surgery—brain surgery where hypothermia was desirable because of possible need for cerebral blood flow occlusion.

Hibernation is begun the night before surgery by the oral administration of promethazine with a barbiturate.

When chlorpromazine is used, two hours before surgery, chlorpromazine and promethazine are given intramuscularly in doses varying between 10 to 50 mgm of each according to the general condition and age of the patient, one hour before surgery, 25 to 75 mgm. Demerol with small quantities of atropine are given subcutaneously. Upon arrival in the operating room, the patients are usually asleep, many snoring, but they can be aroused by painful or vocal stimuli. Oxygen is administered for a few minutes and intubation can be effected under local analgesic spray alone or with a few cc. of pentothal with or without a small dose of relaxant.

The pharyngeal and laryngeal reflexes are depressed; they usually tolerate an oropharyngeal airway without coughing. Once the patient is intubated, anaesthesia is maintained by N_2O+O_2 , 2 to 1 liter and later, 1 to 1 liter per minute and an intravenous drip of 0.02 per cent Demerol. Ice bags are applied on the praecordium and great vessels of the axilla and groin.

In most cases light hypothermia is sufficient and temperatures of 90 to 94°F are attainable. Towards the end of the surgical procedure, the Demerol drip is stopped. When the anaesthetic gas is withdrawn, the patient usually awakens immediately. Postoperative analgesia is prolonged and very little opiates, if any, are necessary. Mild analgesics such as aspirin are usually sufficient.

In cases of radical neck dissections with resection in continuity of the primary cancerous mass there was much benefit from artificial hibernation. The vascular system of these patients was very stable during this long and drastic surgery. The effects of surgical trauma seemed absent and early ambulation was possible. Even after 6 to 8 and sometimes 10 hours of surgery, these patients, who were usually elderly (7 were over 70 years, 4 over 80 years and 1 over 90), could sit up in bed the day of operation and all were up the next day.

These results would seem to be due to the protective action of the hibernating drugs combined with light N_2O anaesthesia. After operation, care should be taken not to overheat the room and the patient should be covered with only one sheet. Neglect of these precautions could cause a rise in body temperature.

For the correction of *cerebral aneurysm*, where deeper hypothermia is desired, we found use for the new drug Pacatal.

The same premedication is given the night before. On the morning of operation about four hours before surgery, promethazine and Pacatal are given intramuscularly, 25–50 mgm. of each, and active cooling with ice bags is

initiated. The patient's reaction to cold is treated by instituting an infusion of promethazine and Pacatal in doses varying from 100 to 300 mgm. of each per 500 cc. of 5 per cent dextrose in water. Demerol is given in divided doses intravenously as indicated by the respiratory rate. When the rectal temperature is about 90–93°F, the promethazine-Pacatal drip is stopped and the patient is intubated with a minimal dose of succinylcholine, anaesthesia is maintained with N_2O+O_2 and a 0.02 per cent Demerol drip. No pentothal is used, in order to avoid cardiac arrhythmias (9, 10). The "relaxed brain" was a very good operative field, hypotension was easily obtainable by about 10° Fowler position and a very small amount of 0.1 per cent Arfonad drip. The heart was constantly monitored by an electrocardiograph machine. In only one case was any arrhythmia noted, which was an auricular flutter without any modification of the blood pressure. The arrhythmia subsided by itself in the immediate postoperative period.

All these patients had spectacular postoperative recoveries. They were conscious and moving on the operating table. They complained of cold when the N_2O and Demerol were stopped, if the body temperature was still low at this time.

The only systemic manifestation was a transient tachycardia up to 140, which disappeared by raising the body temperature quickly. One patient was given more "cocktail" and he ceased complaining of cold and felt comfortable even when the rectal temperature was still in the neighbourhood of 83°F.

Some of the patients who were conscious before operation were able to sit up and eat their breakfast on the first postoperative day, even though inconvenienced by a large periorbital haematoma. Those who came to surgery in an unconscious state made a slower but uneventful recovery, except in one instance. This was a case of a large diffuse aneurysm which had to be closed by a muscular graft. Twenty hours after operation the patient, having regained partial consciousness, developed signs of intracranial hypertension and died suddenly. Post mortem examination revealed a small intracranial haematoma and necrosis of the pituitary.

B. Medical Cases

For medical cases, hibernation has been used as a resuscitative measure on patients in extremis, where the other classical means had failed. We also had a small series where mitigated hibernation or therapeutic sleep had been used for psychic and neurovegetative sedation.

Induction of hibernation is done with injection of the "lytic cocktail," consisting of 25 mgm. of chlorpromazine or Pacatal with 25 mgm. each of promethazine and Demerol. It is given in a slow intravenous infusion of 250 cc. of 5 per cent glucose in water, while the same dosage of the same drugs is given intramuscularly in undiluted form. Maintenance of the hibernating state is done by alternating administration of the "lytic cocktail" with that of milder neurovegetative lytic drugs such as procaine, magnesium sulfate, hydergine, etc. Great care must be taken during hibernation to follow the reactions of the patient. The vital signs such as pulse, blood pressure, respiratory rate, and body

temperature are followed and charted as a graph at the head of the bed every 15 to 30 minutes. Because close observation is so important, a specially trained nursing staff is a necessity. The "lytic cocktail," owing to its adrenolytic effect, may require replacement of blood volume or temporary maintenance of vascular tone by nor-epinephrine drip.

In these 84 cases of artificial hibernation, 32 patients were in extremis when treated and all other treatment had failed. Ten of these patients died and post mortem examination revealed findings sufficient to account for their deaths. The technique and the drugs used were not felt to be incriminated in any of these cases, and the excellent results in the remaining cases would suggest great advantages in this technique.

It is felt that hibernation aided in fluid and electrolyte control because of reduced metabolism and minimal loss of water. In fact, there is slow breathing and no perspiration whatsoever. In diabetics, even though the blood sugar remained elevated, it was easier to control the acetonuria and correct electrolyte imbalance. Cases where death seemed imminent due to neuro-endocrine imbalance were allowed to survive by lysis of the autonomic system. These patients were changed from a state of hyperpyrexia, agitation, marked tachycardia, to that of restful hypothermia in which there was sufficient time to correct the fluid and electrolyte imbalance and, at times, the causal pathology.

II. POTENTIATED ANAESTHESIA

By definition, potentiated anaesthesia is light Pentothal, N_2O , and Demerol anaesthesia supplemented by phenothiazine derivatives. This type of anaesthesia was used in cases of plastic surgery around the mouth and neck where vomiting had to be avoided, for example pharyngeal flap, and in cases where epinephrine was used extensively for haemostasis. In these latter cases, the hypertension caused by the epinephrine might have been dangerous as many of the patients were elderly and arteriosclerotic.

The combination of chlorpromazine and promethazine was very effective against vomiting. Pacatal alone was less effective in this respect. In this series, the potentiation effect of chlorpromazine on the general and local anaesthetic agents seemed more pronounced than that of Pacatal.

Chlorpromazine caused a reversal of the epinephrine-induced hypertension and a marked tachycardia when given intravenously. This was a worry in the elderly hypertensive patient. Pacatal given intravenously prevented epinephrine-induced hypertension without reversal effect and without tachycardia.

CONCLUSION

The final role of the phenothiazine derivatives has not been determined, but the experience described above would suggest that they have great therapeutic value in anaesthesia for the poor surgical risk and in the resuscitation of patients in extremis from many causes. Chlorpromazine has proved to be the most potent of the phenothiazine drugs used. Pacatal would seem to have some definite indications, especially where intravenous medication is necessary; it therefore deserves further investigation.

RÉSUMÉ

Ces dérivés nouveaux sont obtenus à partir de l'union dans une même molécule de deux composés différents: les anthelminthiques et les antimalariques. L'idée de cette conjugaison est née en même temps en France et aux Etats-Unis vers 1944. Les Américains ont bientôt abandonné l'étude alors que les Français l'investiguaient à fond. Les dérivés obtenus avaient des propriétés nouvelles d'un intérêt considérable en anesthésie et en réanimation: en particulier, les propriétés antihistaminiques, antishock, antispasmodiques et de stabilisation du système nerveux autonome.

Dans notre étude, nous présentons la série de malades qui ont bénéficié de ces agents nouveaux; ils sont au nombre de 84, soumis à l'hibernation artificielle pour réanimation médicale ou chirurgicale et au-delà de 500 où la stabilisation neuro-végétative obtenue par ces médicaments a grandement aidé à l'administration de l'anesthésie et aux suites opératoires. Nous mentionnons également les possibilités de l'hibernation avec hypothermie allant jusqu'à 80°F dans les cas de neuro-chirurgie, en particulier les anévrysmes cérébraux.

Le Pacatal, dernier employé des dérivés de la phénothiazine, dans notre étude s'est avéré moins puissant que le largactyl dans son action anti-émétique post-opératoire, mais d'usage plus facile par voie intraveineuse. Son étude mérite d'être poussée davantage.

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