PACATAL* IN ANAESTHESIA: A PRELIMINARY REPORT**

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THE INTRODUCTION of the lytic cocktail into clinical use by Laborit and Huguenard in 1951 (1), and the excellent results claimed, stimulated interest in so-called "ganglio-plegic" drugs and "Thibernation artificielle." Whatever one's opinion may be regarding the usefulness and rationale of such techniques, it must be agreed that new, powerful, and interesting drugs have been added to the anaesthetist's armamentarium. One of these, chlorpromazine has been the cause of lively controversy, mainly because some investigators seized on the unusual properties of the drug to sustain hypotheses of their own making (2). That at least 2,000 papers have been published on chlorpromazine proves the widespread interest in this drug. In Canada, these include valuable papers by many investigators.

The concept of tranquillizing action, apart from any effects of hypnosis or analgesia, has emerged. Recently the term "Ataraxia" meaning "calmness, untroubled by mental or emotional excitement" has been used by Fabing (3, 4). Many well-established drugs such as the narcotics and barbiturates may produce this effect in addition to their other well-known properties.

Because of the stress and strain of present-day living, drugs having a predominately tranquillizing effect have extensive clinical application. The narcotics, barbiturates, and hypnotics because of undesirable effects have limited therapeutic usefulness when only a tranquillizing effect is desired. Drugs such as Serpasil (5, 6), Miltown or Equanil (Meproamate) (7, 8) and more recently Suavitil (Benactyzine HCC) (9, 10), in spite of some disadvantages, have been found very useful clinically in producing relief of nervous tension. As a result of these successes, drugs of a similar nature can be expected to flood the market. Because the tranquillizing properties of these drugs may be used to advantage by our specialty, anaesthetists should maintain an interest in the investigation of such drugs in the hope that eventually an ideal one may be found.

The phenothiazine derivatives deserve special consideration as members such as chlorpromazine, promethazine, Diparcol, and Avomine have already found a place in medicine.

In a search for less toxic phenothiazine derivatives, Schuler and Nezel synthesized eight compounds each having a terminal piperidine ring attached to the nitrogen atom of phenothiazine. These compounds were investigated by

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Nieschulz in 1954 and the most promising one, P 391 or Pacatal, was subjected to an exhaustive and detailed study (11)

Pacatal is N-methylpiperidyl-3-methylphenothiazine and its structural formula is shown in Figure 1

CHLORPROMAZINE

PROMETHAZINE

DIPARCOL

PACATAL

FIGURE 1 Structural formulae of some phenothiazine derivatives

PHARMACOLOGY

Pacatal has been extensively investigated in various laboratory animals by many workers including Nieschulz (12), Gadermann (13), Donat (14), and Horatz (15) and their findings are briefly summarized.

Pacatal was absorbed and eliminated quickly

LD₅₀ varied from 20 mg/kg i.v. in rabbits to 750 mg/kg s.c. in mice. Daily administration of up to 20 mg/kg. orally to dogs for six months produced no untoward effects.

Circulatory effects included decreased capillary permeability, vasodilatation, and vasodepression. In anaesthetized dogs, doses of 5 mg/kg produced moderate depression of blood pressure (20 mm.Hg) which could be reversed by vaso-pressor agents, but was accentuated by Pendiomid or Arfonad. The main effects on the heart were "intravascular anaesthesia," protection against epinephrine-induced and hypothermic arrhythmias, and coronary vessel dilatation in the isolated guinea-pig heart.

Pacatal seemed to depress the sympathetic nervous system producing partial adrenergic blockade and some measure of adrenolytic activity, in that the pressor, but not the local vasoconstrictor or hyperglycaemic effects of adrenalin was inhibited. Blood sugar levels were not usually affected. Nor-epinephrine was not blocked. The carotid sinus reflex was inhibited.

Parasympathetic activity was apparently depressed as salivary secretions were lessened, gut activity was reduced, vasodepression from vagal stimulation was inhibited, gastric secretions were reduced, and the incidence of experimentally produced gastric ulcers was lessened. The effects of acetyl choline were unchanged. Mydriatic action was slight.

Action on the central nervous system was a predominantly quieting effect and marked sedation was seen only following higher doses. Pacatal was a mild anti-convulsant. The hypnotic activity of barbiturates was prolonged without a decrease in the rate of fall of the plasma concentration of the barbiturates. The anaesthetic action of ether was markedly increased. Pacatal is a mild analgesic and the analgesic properties of morphine, Demerol, and phenacetin were potentiated. Pacatal was an effective local anaesthetic agent. The action of succinylcholine was potentiated.

Pacatal in large doses (50 mg./kg. in rabbits) lowered normal body temperature only slightly, but had strong antipyrexial properties. The basal metabolic rate was reduced up to 23 per cent.

Pacatal administration was not followed by albuminuria but haematuria was produced by large doses (as by chlorpromazine). Liver damage was not reported. Pacatal is a mild anti-histamine.

The pharmacological activities of Pacatal are summarized and compared with some phenothiazine derivatives in Table I.

TABLE I
SUMMARY OF PHARMACOLOGICAL ACTIVITY OF SOME PHENOTHIAZINE DERIVATIVES
(after Horatz, 17)

	Phenergan	Diparcol	Largactil	Pacatal	
Antihistamine	+++	+	+	++	
Parasympathetico-lytic	++	+	+	++	
Sympathetico-lytic	+	+++	+++	++	
Blood pressure lowering	+	+	++	++	
Blood pressure stabilizing	++	+	++	++	
Analgesic	+	+	++	++	
Metabolism lowering	+	++	++	++	
Temperature lowering	+	++	+++	+	
Local anaesthetic	+++	+	+++	+++	
Anticonvulsant	++	+++	+++	+	
Strong action	+++	Medium action	++	Weak action	+

CLINICAL STUDIES BY OTHER INVESTIGATORS

It must be remembered that accurate inferences cannot always be made from the results of experiments with animals (16). Apart from species differences,

much higher doses may be given to animals with apparently different results. Also animals may be under barbiturate anaesthesia to facilitate some recording, such as blood pressure changes.

Horatz first reported the clinical use of Pacatal in 439 cases (17) and later in 1,144 patients undergoing surgery (18). Premedication was with repeated 50 mg. doses of Pacatal, morphine being withheld except in the case of severe pain. The total dose and route of administration depended on the severity of the procedure but his dose schedule included barbiturates, Dolantin and in children atropine. This series included 403 pulmonary, 21 cranial, and 20 cardiac operations. Minor cases were "pretreated" and in major cases Pacatal was used for "potentiation of narcosis." Horatz later enlarged his series to over 5,000 cases (19). He combined Pacatal with Pendiomid for controlled hypotension, and with refrigeration in place of the "lytic cocktail," claiming that using a single drug is advantageous. He used Pacatal for many hours preoperatively. Good results were claimed but hypersecretion after thoracic surgery, hyperpyrexia (easily controlled by amidopyrine), and increased difficulty in judging the patient's postoperative condition were occasional disadvantages. Toxic potentiation of narcotics was noted.

OTHER REPORTED USES

Pacatal has been used successfully in combination with barbiturates in "Schlaftherapie" or therapeutic sleep (20).

In psychiatry encouraging results were obtained with 50 patients suffering from mild anxiety states (21) but hypochondriacal schizophrenics were not affected (22). Manics showed a wide variation in response and best results were claimed in anxiety states and drug addiction (23).

Lindsay (24) has used Pacatal in more than 50 psychiatric patients in office practice and noted its good sedative action. The treatment was later modified because of occasional complaints of "blurred vision," found to be caused by difficulty in accommodation.

Good results have been reported by Kline (25), but complications including hyperpyrexia, dryness of the mouth, urinary retention, and lack of therapeutic benefit were reported.

Pacatal has been used to potentiate the analgesic action of morphine in cases of inoperable carcinoma (26).

The drug has aroused wide interest mainly in Germany. At least thirty papers have been published and more can be expected in the near future.

CLINICAL STUDY

Pacatal is at present available as tablets containing 50 mg. or 25 mg. of Pacatal base (as Hydrochloride), and as ampules (2 cc.) containing 25 mg. Pacatal base (as Acetate) per cc. The pH of the solution is 5.6 to 5.8 at 25°C. The solution is not physically compatible with solutions of Pentothal, Demerol, chlorpromazine, promethazine, muscle relaxants, or with normal saline, but can be diluted with distilled water or 5 per cent Dextrose water.

LOCAL EFFECTS

Pacatal, like most phenothiazine compounds, is irritating to tissues. Early in the series, Pacatal was given intravenously undiluted to 35 patients and a transient phlebo-thrombosis occurred in two patients. Since we began diluting Pacatal solution with at least three times its volume, no phlebo-thrombosis has resulted from its use. Following intramuscular injection in 106 patients, 84 complained of sore buttocks after operation. This was particularly noticeable in children when relatively large doses had been given. Because of this, oral administration is preferred for premedication, particularly since this route gives equally satisfactory results. Oral administration produced no nausea, vomiting or gastric discomfort.

DOSAGE

Early in the series, Pacatal was given intravenously to adult patients in doses ranging from 25 to 250 mg. It was found that the small doses produced no obvious effects, and that the large doses used produced no more of the desirable effects than moderate doses.

The usual dosage evolved for adults was 100 to 200 mg (about 1 mg per pound of body weight) and relatively larger doses for children (about 1½ mg per pound of body weight) by whatever route was chosen.

In our present series, Pacatal was given to 352 patients ranging in age from 2 to 86 years. There were 204 children and many of the adults were "poor risk" patients. The drug was used in the following ways:

PRESENT INVESTIGATION

1. H.S. Sedation—56 cases
2. Premedication either alone or in various combinations with Atropine and Demerol—204 cases
3. Following usual premedication, in conjunction with anaesthesia, either immediately preceding induction or during the course of anaesthesia—148 cases.
4. Postoperatively—42 cases

RESULTS

Of the 56 patients who had received Pacatal orally at bedtime, 47 slept well. Patients who had received the usual dose of Pacatal about 1 to 1½ hours previously usually arrived in the operating room in a tranquil frame of mind. A few were asleep when left undisturbed, but awoke readily. Most rested peacefully and though alert mentally, they appeared to be unusually calm in the acceptance of their surroundings. This was particularly noticeable in the case of children who would tolerate venipuncture for Pentothal administration with unusual equanimity.

Sedation was considered excellent in 26, good in 142, and poor in 37.

In most cases salivary secretions were greatly reduced, particularly in adults, and although the mouth was not completely dry, excessive secretions were not troublesome during subsequent anaesthesia. Secretions, when present, were of

normal consistency and not tenacious. In children, particularly during ether anaesthesia, secretions were sometimes troublesome. Consequently in addition to Pacatal, atropine was given in half the usual dosage and this combination was satisfactory in most cases.

In 53 cases, Demerol (in dosage $\frac{1}{2}$ – $\frac{3}{4}$ mg per pound) was given as well as Pacatal. Sedation was better than would be expected from the use of either drug alone, but no potentiation of the toxic effects of Demerol was seen, suggesting that the increased sedative effect was one of "combination" rather than potentiation. No respiratory or cardiovascular depression was seen, even in elderly subjects.

Whenever the drug was given immediately before operation, alone or after the usual premedication with atropine and Demerol or morphine, the patients within three minutes become more sedated without increased respiratory depression. Even intravenous doses up to 250 mgm given rapidly produced little effect on blood pressure or pulse rate.

No peripheral anti-sympathetic effects were seen. The size of the pupil was not affected, there was no congestion of nasal mucous membrane; no venous dilatation, no warm dry flushed skin and sweating, if present when Pacatal was given, was not abolished.

No amnesic effects were attributed to the drug. Hyperexcitability did not occur.

EFFECTS DURING ANAESTHESIA

Central Nervous System Effects

The induction dose of Pentothal to the loss of the lid reflex was usually reduced by about 20 to 30 per cent of anticipated dose, and this estimated reduction of Pentothal dosage was confirmed in 9 patients who had received Pentothal for induction a short time previously.

All inhalation anaesthetic agents commonly used were slightly potentiated in that the course of anaesthesia was unusually smooth and patients could be maintained in light anaesthesia with minimal amounts of agents. So-called "automatic" anaesthesia was usual. If reflex activity returned during too light a level of maintenance, the patients' reactions were slight, and not a vigorous protest. Return to an adequate level of anaesthesia was easily accomplished. This was particularly noticeable during tonsil dissections. There was no increased respiratory depression and it was felt (as in the case of narcotics) that Pacatal increased the duration of action of agents rather than their depression of vital functions. When Pacatal was given during anaesthesia, similar results were noticed and the level of anaesthesia apparently deepened. The action of muscle relaxants did not appear to be affected.

Cardiovascular Effects

During anaesthesia changes in blood pressure or pulse rate were seldom seen and could usually be attributed to definite operative or anaesthetic causes. However, the hypotensive effect of Pentothal was sometimes exaggerated particularly

in elderly hypertensive subjects. In 9 such cases, a normal response to small doses of Methedrine was obtained. Protection against untoward reflex activity was hard to evaluate as Pacatal was not used to cover errors in anaesthetic technique and any excessive blood loss was replaced

POSTOPERATIVE PERIOD

Increased postoperative depression and delay in regaining consciousness was not seen except when patients had been given usual (but, following Pacatal, relatively large) amounts of Pentothal or ether. This depression was not seen when further experience with the drug showed that only minimal amounts of anaesthetic agents were necessary to maintain adequate depth of anaesthesia

Though conscious in response to questioning or painful stimuli, most patients usually slept peacefully if left undisturbed. This tranquil state lasted for about 4½ to 5 hours after administration and narcotics were rarely needed. When this tranquil state wore off, most patients rested quietly for about another six hours, particularly if usual doses of analgesics had been given to combat pain

Postoperative restlessness was unusual, particularly in children following minor operative procedures

The incidence of immediate postoperative emesis appeared to be greatly reduced, it occurred in 10.5 per cent of cases. Ten patients with a history of post-anaesthetic hyperemesis were given Pacatal during anaesthesia and three did not vomit after operation

No profound hypotension was seen, but a slight hypotension of 10–15 per cent of expected blood pressure levels was sometimes seen, when moderate amounts of Pentothal or ether had been given during anaesthesia

In the postoperative period, Pacatal was repeated 27 times when its main effect had apparently worn off. Emesis was controlled in 16 out of 18 patients and restlessness was improved in 6 out of 9 cases

There was no increased incidence of urinary retention after operation and no case of albuminuria or haematuria attributable to the use of Pacatal. Increased secretions of the respiratory tract or hyperpyrexia were not seen. There was no clinical evidence of liver damage or alteration in the blood picture.

OTHER USES

In Obstetrics

Pacatal was given in doses of 150 mg intravenously to 15 multigravida during the second stage of labour. No analgesic effects were seen and no potentiation of Demerol which had been given to 12 patients. Course of labour was very rapid (possibly even accelerated) and all delivered normally. No effects on the babies were seen. The patients were tranquil after delivery

Pacatal 100 mg was given intravenously before spinal anaesthesia to five patients. Hypotension in 3 cases responded rapidly to Methedrine. A fair sedative effect was obtained in all cases, but this seemed to be abolished when Methedrine was given

Pacatal was given 50 mg orally t.i.d. to 12 patients suffering from emesis gravidarum. Seven were cured, 3 helped and 2 not affected

Status Epilepticus

Pacatal (100–200 mg. 1M) was given to two patients in Status Epilepticus, having very frequent seizures uncontrolled by large doses of Dolantin, paraldehyde, and barbiturates. In both cases the number and severity of the attacks were greatly reduced but only a slight increase in somnolence occurred.

Shock

Although Pacatal is not a powerful vasodilator or anti-adrenergic agent, the work of Martin (26) prompted our use of Pacatal in one case of profound shock caused by severe head injury. The role of Pacatal combined with hypothermia was difficult to evaluate but the patient made a good immediate recovery.

E.E.G. AND E.K.G. INVESTIGATION

Pacatal was given intravenously to a healthy 176 lb (75 Kg) adult male and the E.E.G. and E.K.G. findings were as follows

The resting E.E.G. showed normal alpha activity at 11 c/s

Drug A (Pacatal 100 mg.) showed no noteworthy effect

Approximately three minutes after the administration of Drug B (a second dose of Pacatal 100 mg) the alpha activity was replaced by slow activity at 5 c/s and 7 c/s

The pattern was *not* that usually associated with drowsiness or sleep, it does not resemble the effects of barbiturates and is worthy of further investigation

The E.K.G. tracings showed no abnormalities.

DISCUSSION

The precepts stated by Melville (27) and by Gilbert and co-authors (28) provided valuable guidance in attempting to evaluate Pacatal

Our observations on the effects of Pacatal have been varied and difficult to assess. The main reason for this was that, compared with the usual definite effects of chlorpromazine, those of Pacatal were less obvious—almost subtle or unobtrusive. At first, we considered that Pacatal produced very little effect, but as the series enlarged we became more convinced of the usefulness of Pacatal.

In this clinical study it was inevitable that comparison would be made with the effects of chlorpromazine. Although the actions of both drugs are similar in many respects, Pacatal appears to have a potency roughly 1/10 to 1/15 that of chlorpromazine. Pacatal has a much milder action and more even effect.

In comparative doses Pacatal produces less drowsiness and detachment from surroundings, but at least equal tranquillizing effects. Fewer side effects were seen with Pacatal as hypotension was unusual and never profound. The peripheral sympathetolytic effects of chlorpromazine were never seen. Pallor has been observed in ambulatory patients and in anaesthetized patients when blood loss was excessive. In such cases absence of hypotension and tachycardia suggested that the peripheral vasoconstriction was adequate in maintaining normal cardiac output. If the carotid sinus reflex was depressed it was not apparently abolished.

It is impossible without determinations of blood levels to determine whether in fact potentiation of narcotics and anaesthetic agents does occur, or whether the augmented effects were caused by "combinations." This drug lacks specific action as no one pharmacological effect is outstanding. Although the action of Pacatal appears to be mainly central, it would be invaluable if further pharmacological studies could determine its site of action.

In the postoperative period, decreased restlessness, nausea, and vomiting were a definite advantage. Compared with chlorpromazine, postoperative depression was seen less regularly and when present was of less profound and shorter duration. The further 5 or 6 hours of restfulness were of benefit to patients.

Pacatal may have specific usefulness in "poor risk" patients, as its use may fulfil the concept of almost homeopathic doses in the administration of other agents (29), with minimal side effects.

It is possible that further investigation will confirm its pharmacological value in preventing arrhythmias during hypothermia and intracardiac operations.

In view of the low toxicity of Pacatal and its many desirable features we feel that this agent merits further and more extensive investigation to determine its place of usefulness in anaesthesia and related fields

SUMMARY

The history of the introduction of a new phenothiazine derivative into medicine has been reviewed and allusion made to the concept of ataraxic drugs.

The pharmacology of Pacatal in animals has been briefly reviewed and also the clinical findings of other investigators.

This report deals with observations made on the use of Pacatal for 352 patients undergoing surgery, 44 obstetrical patients, and other uses in 3 patients.

Doses of 100-200 mg (1 mg./lb) were found effective irrespective of the route administered

Favourable effects noted include. good preoperative sedation, tranquillization more noticeable than hypnosis, ease of control of anaesthetic procedure (between anaesthesia and analgesia), possibility of decreased amounts of anaesthetic agents, antisecretory effects enabling the use of atropine to be avoided in adults, normal response to vasopressors, tranquil postoperative course, decreased incidence of postoperative nausea and vomiting

The drug was relatively non-toxic to the cardiovascular and respiratory systems. Dangerous potentiation of narcotics was not seen.

Irritation at the site of injection can occur. The drug is rapidly eliminated and postoperative depression is unusual. However, if anaesthetic agents (particularly Pentothal or ether) are used in moderate amounts following Pacatal administration, postoperative depression may be prolonged for two to three hours

Further investigation of this agent is considered desirable.

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RÉSUMÉ

Tout en repassant l'histoire de l'introduction d'un nouveau dérivé phénothiazine, on a fait allusion au concept de médicaments "ataraxiques."

On a également revu rapidement la pharmacologie de "Pacatal" chez les animaux ainsi que les résultats des travaux cliniques réalisés par d'autres chercheurs.

Ce travail se base sur des observations faites avec "Pacatal" en chirurgie chez 352 patients, en obstétrique chez 44 patients et en d'autres circonstances chez 3 patients.

Sans tenir compte du mode d'administration, des doses de 100 à 200 mgms (1 mgm/lb) ont été jugées efficaces.

Parmi les effets favorables, on note: une bonne sédation pré-opératoire, un calme plus marqué que l'hypnose, un contrôle facile de l'induction anesthésique (entre anesthésie et analgésie), un besoin moindre d'agents anesthésiques, des effets antisécrétoires allant jusqu'à éviter l'emploi d'atropine chez l'adulte, une réponse normale aux vasopresseurs, une période post-opératoire tranquille, des nausées et des vomissements post-opératoires diminués.

On a trouvé que le médicament ne produisait relativement pas de dépression sur les systèmes respiratoires et cardio-vasculaires, il n'a pas produit non plus de potentialisation dangereuse des narcotiques.

A l'endroit de l'injection, une irritation peut apparaître. Le médicament est rapidement éliminé et il est rare d'observer une dépression postopératoire. Cependant, si certains agents anesthésiques (particulièrement le pentothal ou l'éther) sont employés en quantité modérée après une administration de Pacatal, la dépression post-opératoire peut être prolongée de 2 à 3 heures.

De plus amples recherches sur cet agent seraient désirables.

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