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CHLORPROMAZINE HYDROCHLORIDE IN ANAESTHESIA

A REVIEW OF 360 CASES

JOHN TAIT RUSSELL, M.B., B.CH. (RAND), D.A. (ENG.), D.A. (IRE.)

Assistant Anaesthetist, Johannesburg General Hospital

Anaesthetists all over the world are constantly seeking techniques which will protect patients from surgical assaults and yet ensure a rapid return of consciousness and minimal morbidity and mortality. Possibly what may yet prove to be one of the most useful aids since the introduction of the relaxants is the ever-growing knowledge of the phenothiazine derivatives. Of these, the most generally useful to date is chlorpromazine hydrochloride (dimethyl amino-propyl-N-chloro-phenothiazine hydrochloride)—Largactil. First brought to the attention of the medical profession in 1952 by Laborit and Huguenard[1] and Delay *et al.*,[2] this drug has received considerable attention in all parts of the world.

Pharmacology

Decourt[3] discusses the 'narcobiotic effect' which protects from the 'phenomena of Reilly'[4] or, as Selye[4] terms it, the 'reaction of alarm'. (Samson Wright,[5] commenting on a review[6] of this French work, prefers to suspend judgment until it has been confirmed.) This narcobiotic action is said to diminish the activity of all the cells of the body, increasing their resistance to stress. The clinical result of this will depend on the effects on the most specialized and active cells of the body, such as those of the reticular formations, particularly in the brain. This will affect the central control of heat regulation, the vomiting centre, and the general tone of encephalic activity. This function is not related to its anti-adrenaline action. Promethazine acts in a similar way, but is a potent antihistaminic with little or no anti-adrenaline action.

Chlorpromazine appears to have no ganglion-blocking action,[7–9] but depends, for its clinical effects on this action on the reticular formations and its anti-adrenaline action.

Natural sleep and the sleep produced by chlorpromazine was compared by Terzian[10] and found to be similar. This was confirmed by Hiebel *et al.*[11] and Dobkin *et al.*[12] by means of electro-encephalographic tracings.

Experimental work on animals

The following has been shown in experimental work on animals with chlorpromazine:

1. Sedative effects are proportional to the dose administered.
2. Convulsions due to strychnine, picrotoxin and metrazol are not affected by the drug.
3. Neither competitive block nor depolarizing block is produced at the neuromuscular plate.[12]
4. Small doses block sympathetic vasopressor reflexes; large doses block vagal reflexes.[13]
5. It protects against ventricular extrasystoles and fibrillation during chloroform anaesthesia in dogs and cats.[13]
6. It has a strong anti-emetic action in animals and humans, which is believed to be due to competition for the chemo-receptor emetic trigger-zone and depression of the reticular vomiting centre.[14]
7. It causes no significant alteration in the glomerular filtration-rate or renal blood-flow in dogs.[15]

CLINICAL SERIES

The present series of 360 cases comprise a cross-section of operations performed at the average general hospital, under general anaesthesia (Table I). All these anaesthetics were administered by the author, either alone or, in the thoracic operations, with Dr. C. H. van Hasselt. No shocked or exsanguinated patients were given chlorpromazine since it was felt that the peripheral vasodilatation caused by the drug was a complete contraindication in these cases.

Premedication Technique. On the evening before operation, at 8 p.m., the patients were given 100 mg. of chlorpromazine orally. If by 11 p.m. they were not asleep a small dose of a barbiturate (1½ gr. of quinalbarbitone) was administered. Patients were warned that getting out of bed might cause dizziness; 2 patients who ignored this warning actually fainted (due to the fact

that the blood pressure becomes orthostatic). In the earlier cases 150 mg. was given, as recommended by Dobkin *et al.*,[12] but because of the rather high incidence of giddiness, even on sitting up in bed, this dose was reduced to 100 mg. In children and small or debilitated patients this oral evening dose was omitted.

In adults over 10 stone, on the day of operation, 50 mg. of chlorpromazine was administered intramuscularly 2 hours before operation (in children and small adults the dose was 1 mg. per 3 lb. body weight). This injection did not cause any local reaction in any of our patients. Atropine, 1/100 gr., was given ½ hour before operation, because it was found that the drying effect of the chlorpromazine alone was not sufficient.

Anaesthetic Technique. Induction was usually effected with thiopentone sodium, except in the smallest children. Endotracheal intubation was performed where there was difficulty with the airway, or when relaxants were used and controlled respiration was required. Maintenance of anaesthesia was varied, either closed or semi-closed circuits being used. Nitrous oxide and oxygen was the routine anaesthetic, with minimal trichlorethylene, pethidine in fractional doses, minimal ether, or cyclopropane.

Types of Operation performed. The operations included in the series of 360 cases are shown in Table I:

TABLE I

Gynaecological		
Total abdominal hysterectomy	31	
Vaginal hysterectomy and repair	20	
Fothergill repair	22	
Salpingectomy and oophorectomy	8	Total 81
Plastic		
Skin grafts	23	
Plastic operations to face	12	
Plastic operations to breasts	3	
Cleft palate and hare lip	12	Total 50
General Surgery		
Gastrectomy	20	
Cholecystectomy	16	
Intestinal obstruction	7	
Perforated peptic ulcer	3	
Appendicectomy	27	
Herniorrhaphy	14	
Mastectomy	14	
Amputation of leg	4	
Subclavian aneurism (false)	1	
Dissection of cervical glands	10	
Ligation of vena cava *	1	Total 117
Ear, Nose and Throat		
Laryngectomy	4	
Mastoids	15	
Antrostomy	12	
Tonsillectomy	17	Total 48
Urological		
Nephrectomy	7	
Prostatectomy	10	
Urethropexy	2	Total 19
Thoracic		
Pneumonectomy	5	
Lobectomy	14	
Diaphragmatic herniorrhaphy	4	
Mitral valvotomy†	18	
Aortic valvotomy‡	1	
Patent ductus arteriosus	2	
Thoracotomy and lung biopsy	1	
Gastro-pharyngostomy	2	Total 47

Total of all operations 360

* Previous mitral valvotomy; very apprehensive.

† One case of acute pulmonary oedema on induction.
‡ A 25-minute cardiac arrest, with recovery.

CLINICAL EFFECTS

Pre-operative

The demeanour of patients was calm and they did not appear apprehensive (*la belle indifférence* mentioned by Dobkin[19] in a recent article). A common remark was, 'Doctor, I'm terrified!', this usually said with a happy smile! As a rule they slept quietly in the anteroom to the theatre, were easily aroused to answer questions, but went off to sleep again almost immediately.

There were exceptions to this. One was a child who had had a series of plastic operations. Undoubtedly she would have done better on rectal 'pentothal', for she yelled from the time she was brought to the theatre until induced. This did little to impress the surgeon with the value of chlorpromazine as a premedicant! However, this was the only child who did not manifest *la belle indifférence*.

The only other patient who did not derive pre-operative benefit was a 35-year old woman with congestive cardiac failure who had undergone a mitral valvotomy 2 years before and was now to have a ligation of her inferior vena cava, in an attempt to reduce the load on the right side of the heart. She was very frightened, but came through the operation extremely well.

The patient's skin was warm and dry, in some cases pale, but this was variable, the pallor developing during operation, after operation, or not at all. The temperature usually fell slightly, but the fall was seldom more than 1-2° F. Clinically, respiration appeared normal (Dobkin,[12] found a rise in oxygen consumption, but depressed respiration). Blood pressure tended to fall, but seldom by more than 20 mm. Hg systolic, and easily controlled by positioning. The pulse rate varied, but was usually raised to about 90 per minute.

Both the drop in blood pressure and the raised pulse-rate are due to a peripheral vasodilatation. This suggests that the use of chlorpromazine in shocked or exsanguinated patients is contra-indicated.

Course of Anaesthesia

Induction was uneventful as a general rule; relatively small doses of thiopentone were required, 0·25-0·5 g. being a usual amount even in robust patients. In fact it was found that, in order to get a speedy post-operative recovery of reflexes, smaller doses than usual were essential. This, however, did not apply to the relaxants in this series of cases.

Maintenance of anaesthesia was effected with a minimum of anaesthetic, less being required than with other premedicants.

One of the most striking features was the protection given to the patient from shock-producing procedures, such as pulling on the mesentery, and thoracotomy in which the rib-spreader was used. The blood pressure and pulse remained remarkably constant and, providing that blood replacement was adequate, the patient retained his or her condition remarkably well. Sometimes there was marked pallor, but pulse and blood pressure remained unaltered, the skin remaining dry and warm. Nevertheless, this pallor would sometimes cause comment from the surgeon.

Reaction to accumulation of carbon dioxide is minimal. The pulse will become full and bounding but there will be no sweating. A nice full pulse may mean, therefore, not that the patient is in excellent condition, but that the carbon dioxide has reached dangerous levels.

In operations on the head and neck a reasonable degree of hypotension could be attained by raising the head of the operating table. Pressures of 80-90 mm. Hg. were usual. The blood pressure rose immediately when the head of the table was dropped. This, it is felt, is a safer method of producing hypotension than most of the others in use at present; it gives sufficient aid to the surgeon for the usual run of operations, without extreme risk to the patient.

In the thoracic operations, we were satisfied that chlorpromazine was of real benefit to the patient. The cardiotomies gave us less cause for alarm than usual, although the number of cases in this series is too small for definite conclusions. Other workers have found the drug to be beneficial in this type of case[19,20] (Boulton[20] used the drug by mouth alone).

No difficulties were experienced in assessing the depth of anaesthesia, such as were found when we used the 'lytic cocktail' (see further remarks).

Post-operative Course

Patients recovered their reflexes and answered to their names either before they left the operating theatre or within 5-10 minutes of returning to the ward. This compares favourably with the other methods of pre-medication.

The amounts of post-operative analgesic drugs were not decreased to any extent, for the chlorpromazine is usually excreted within 6 hours. If post-operative analgesics were given in a reasonable time (2-3 hours after operation) the patients were comfortable and moved about easily in bed. Most patients sat up on the first post-operative day, which is important in preventing pulmonary and thrombotic complications.

There were no cases of venous thrombosis in the series (the general incidence of thrombosis at this hospital is low).

There was little amnesia for pre-operative events, but these were viewed with equanimity.

Post-operative nausea and vomiting were minimal. Patients would vomit once but, once the contents of the stomach had been evacuated, only 2 of this series of patients complained of nausea, and only one continued vomiting—for 1 day.

In this series there were no cases of liver damage which is one of the serious complications of chlorpromazine.[21,22,23]

Comparison with Alternative Techniques

The routine of premedication described in this paper was undertaken as an alternative to the intravenous use of the 'lytic cocktail' which was applied in a series of over 70 cases at this hospital in 1954. The 'lytic' mixture consisted of: Chlorpromazine 50 mg., Promethazine (Phenergan) 50mg., and Pethidine 100 mg. It was run into a vein in a dilute solution, the patient's condition being assessed every few minutes.

The advantages of the 'cocktail' technique were:

1. Prevention of traumatic shock.
2. Almost complete absence of post-operative nausea and vomiting.
3. Tremendous reduction in the amount of anaesthetic drugs.
4. Ease of endotracheal intubation due to depression of the respiratory reflexes (this does not really apply, for the short-acting relaxants, succinyl choline for example, facilitate intubation to a remarkable degree).

The disadvantages, which in our opinion outweigh the advantages, are:

1. Extremely slow return of the patient's protective reflexes (one patient was unconscious for more than 10 hours after the operation).
2. Marked drop in blood pressure, particularly in patients with hypertension (one patient's systolic blood-pressure dropped from 220 mm. Hg to 80 mm.).
3. Difficulty in assessing the patient's condition and the stage of anaesthesia. Patients apparently well anaesthetized would suddenly react violently to stimuli. Blood replacement had to be meticulous, for the patient's initial response to blood loss was minimal. (This applies to a lesser extent when the drug is used intramuscularly.)
4. Difficulty in deciding which drug was responsible for any untoward effects, there being no really effective antidote to chlorpromazine. Polypharmacy is not necessarily synonymous with balanced anaesthesia.[16]
5. Respiratory depression over a long period leading to carbon-dioxide accumulation with all its dangers, as recently pointed out by Pask.[17]
6. Frequent occurrence of venous thrombosis even when dilute solutions were used.

It is therefore surprising that in March 1955, a further series of cases was written up in which this 'cocktail' technique was used.[18]

The 'lytic cocktail' technique did suggest that a method might be evolved which would give the advantages of sedation, protection from traumatic shock, and marked reduction in post-operative nausea and vomiting. The use of chlorpromazine alone, given intramuscularly, was first suggested by Dobkin *et al.*[12]

DISCUSSION

The *advantages* of chlorpromazine used as a premedication were virtually those of the 'lytic cocktail' with less disadvantages. The advantages are as follows:

1. Protection of the patient from neurogenic shock.
2. Reduction in post-operative nausea and vomiting.
3. Reduction in anaesthetic agents required.
4. No long period of unconsciousness with its concomitant dangers of increased morbidity.
5. No marked depression of respiration.

6. The pre-operative equanimity exhibited by practically all patients, without deep narcosis.

7. Orthostatic blood pressure, giving a degree of easily obtainable but safe hypotension when required.

8. Minimal depression of the cough reflex.

9. No sweating, and thus less fluid loss during operation.

The *disadvantages* are as follows:

1. The extreme care that has to be taken to replace blood loss.

2. Orthostatic blood-pressure (this is also an advantage) for 4-6 hours. This leads to occasional faintness and sometimes even to collapse. Positioning of the patient in the head-down position is usually sufficient to raise the blood pressure within a few minutes.

At no time did we have to resort to vasopressor drugs, although there is some doubt whether, except for noradrenaline, these drugs have much effect in this way. Occasional patients did complain, even when lying flat, that they felt 'terrible'. These patients all had a drop in blood pressure above average.

3. When post-operative collapse occurred (it did happen in 2 cases—both gynaecological operations) it was difficult to decide whether the collapse was due to haemorrhage, to shock, or to the chlorpromazine. On both occasions the blood pressure rose with blood transfusion. These cases both help to show the importance of adequate blood-replacement.

4. There is no true antidote but, if the intramuscular dosage of 1 mg. per 2½ lb. body-weight is not exceeded, reactions are minimal.

It appears that chlorpromazine used as a premedicant drug is of real advantage to patients and may even be the factor which 'gets them through'. Post-operative morbidity is decreased, for the patient remains in better condition than would otherwise have been the case, and thus recovery is facilitated.

SUMMARY

The pharmacology of chlorpromazine is briefly discussed.

A series of 360 cases are reviewed in which chlorpromazine was used as a premedicant drug.

The advantages and disadvantages are enumerated, the former outweighing the latter.

The use of the 'lytic cocktail' is discussed, to be condemned as 'polypharmacy'.

The reasons for not using chlorpromazine in shocked patients are mentioned.

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