CHLORPROMAZINE AND ALLIED SUBSTANCES

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Chlorpromazine (largactil) was synthesized in 1950 by Charpentier at the Rhone-Poulenc Laboratories. It is a phenothiazine derivative closely related to promethazine (phenergan).

Formulae

Promethazine Hydrochloride
(Phenergan)

Promethazine (phenergan) has two methyl groups, which in these derivatives are associated with strong antihistaminic power, while chlorpromazine is a propylamine phenothiazine, which has more marked central nervous system effects but only one-hundredth of the antihistamine potency of promethazine.

The Department of Pharmacology at Oxford has pointed out (Burns, 1948; Burns and Dutta, 1948; Dews and Graham, 1946) that atropine, pethidine, procaine, quinidine and also the antihistamine drugs share many properties in common; spasmolytic, analgesic, 'quinidine-like,' hypothermic and antihistamine effects are all seen. These multiple effects were expected and later

Chlorpromazine Hydrochloride
(4560 R.P.)
(Largactil)

demonstrated in the case of chlorpromazine (Burns, 1954). Their very multiplicity makes the assessment of the action of chlorpromazine difficult when it is given alone; when given in conjunction with other drugs the confusion becomes greater and there have been times when it has seemed that this confusion has in some measure affected the critical powers of its administrator.

Chlorpromazine is well absorbed by mouth, its effect, maximal in about three hours, being maintained for several hours. Intramuscular injection produces sedation in some 30 minutes lasting four

or five hours, while intravenously the effects are seen within five to ten minutes. The drug is very soluble in water, forming an acid solution irritant to the tissues. It is therefore given by injection either well diluted intravenously or deeply into a muscle; repeated intramuscular administration may, however, give rise to pain with local induration, leucocytosis and fever. Only about 8 per cent of the total dose is excreted in the urine. The way in which the drug is broken down is not known but it is probable that the liver is concerned since the drug's effect is more marked in cases of liver disease.

In animals very large doses cause death which may occur rapidly with convulsions or be more delayed when muscular hypotonia is marked. In man, attempted suicide by taking 70 25 mgm. tablets (1,750 mgm.) was followed by complete recovery in three days. More serious effects have followed prolonged administration and are therefore not so likely to be seen by the anaesthetists as by psychiatrists or general physicians.

Phenothiazine, from which chlorpromazine is derived, contains a benzene ring which is well recognized as a possible cause of liver and bone marrow damage. Minor liver changes are not unusual if chlorpromazine is given for several weeks as in psychiatric work. In an early series (Anton Stevens, 1954) jaundice occurred several times but always cleared up on stopping the drug, but recently reports of more persistent jaundice lasting up to five months have been published. In several carefully studied cases the jaundice has been of obstructive type (Van Ommen and Brown, 1954), and it was impossible to differentiate between chlorpromazine jaundice and obstructive jaundice from other causes, by liver function tests; on histological examination there was no evidence of liver cell damage, but bile thrombi were noted in the ducts. A transient eosinophilia (up to 40 per cent. of white cells) and the history of drug administration were helpful points in diagnosis and should be kept in mind to avoid unnecessary surgical interventions. These findings resemble those reported in cases receiving arsphenamine and methyltestosterone therapy. A few deaths from liver failure have been reported and I have recently heard of a doctor who has died after self administration of chlorpromazine to relieve the vomiting of digitalis. Not only was chlorpromazine contra-indicated because of the passive congestion of his liver due to heart failure, but he had, in addition, a history of infective hepatitis within the last four years. Decourt (1953) has stated that chlorpromazine in concentration of 1:400,000 is a general depressor of cellular activity. A quite usual dose in medicine and psychiatry is 75 mgm. daily representing one

part in a million concentration in the body tissue of an adult. After oral administration all the absorbed drug must travel via the portal circulation to the liver where most probably the local concentration is over 1:400,000, and continued administration is likely to be followed by toxic effects in a proportion of cases. While the incidence of liver damage is not high the risk is sufficiently great to make the administration of chlorpromazine for more than very short periods a step requiring serious consideration. A few cases of agranulocytosis have been reported and one has caused death but others have responded to the withdrawal of the drug and penicillin administration. Finally the makers warn us of the possibilities of contact dermatitis and perhaps we would be wise to avoid prolonged contact, by washing after handling the drug.

Sedative Effects

Drowsiness is a side effect of several of the antihistamine drugs especially diphenhydramine (benadryl) and promethazine (phenegan). With chlorpromazine it occurs even more strongly. The sedation in these cases differs from that seen after barbiturates. In the latter, conditioned reflex responses in rats persist until drowsiness is obvious while in the case of chlorpromazine and some other antihistamines, the rats cease to respond at a dosage which did not cause drowsiness. The sedation of chlorpromazine is marked by a listless apathy. The patient is usually calm and may not appear to sleep. The closed eyes and even snoring are largely due to muscular hypotonia. The patient will answer questions intelligently if asked firmly, but larger doses will usually cause actual sleep. This sleep effect differs from that of the barbiturates. Lehman and Hanrahan (1954) point out that chlorpromazine seems to act selectively on the *subcortical* centres of the brain which normally maintain wakefulness and psychomotor 'drive.' It is suggested that this area is in the 'reticular structure' of the mid brain, about which so much is being written today (Magoun, 1950). This hypothesis, while of no great practical importance, perhaps fits in with electroencephalographic findings, which in the case of chlorpromazine resemble those of sleep rather than those of the barbiturates, which are thought to act not only on the mid brain but also on the cortex.

Large doses of chlorpromazine and also antihistamines in animals cause convulsions. It is of interest that antihistamines have been thought to precipitate epileptic attacks and that coramine given to a patient who had had a full dose of chlorpromazine was followed by prolonged convulsions. These findings contrast with the known sedative effect of barbiturates in convulsive states.

which are thought to be cortical in origin. This relative freedom from cortical effects of chlorpromazine may explain the clearness of the mind which persists while the apathy and lack of 'drive' are noticeable. This can be demonstrated experimentally in man and in some measure in animals. I have seen no excitement stage as is seen sometimes with barbiturates. Psychiatrists find that while at first large doses quieten many excited patients inducing sleep, this sleep effect diminishes and after a few days patients can sit about while taking doses which made them almost comatose earlier on. In the favourable cases excitement and confusion may remain controlled in ambulant patients as long as the drug is continued, but when it is stopped many cases relapse (Stevens, 1953).

There seems to be a disinterestedness and a detachment in these patients, some of whom may still experience their hallucinations but are no longer disturbed by them. The term 'a chemical leucotomy' has been used and it will be remembered that the operation of leucotomy has been performed for pain in incurable disease. The patients are then said to experience their pain but it no longer worries them. Similarly chlorpromazine has no analgesic effects of its own—but good results have been reported in such cases as post-herpetic neuralgias and the effects have been described as an indifference to, rather than an absence of, pain (Sigwald and Bouttier, 1953).

When chlorpromazine-treated animals are given hypnotic or anaesthetic drugs such as barbiturates or ether, sleep time is prolonged. This so-called 'potentiation' also occurs in man. A similar effect with the analgesia of morphine has been claimed but could not be demonstrated by Kopera and Armitage (1954) in mice. The results of taking alcohol are modified, the excitement phase being eliminated, the subject passing directly into the stage of collapse.

Effects on Body Temperature

Man's first protection against cold is by constriction of the blood vessels of the skin. When this defence is overcome and the temperature of the blood drops $\frac{1}{2}^{\circ}\text{C}$. a second delayed mechanism, shivering, comes into action. In dogs mild shivering increases oxygen consumption twice and severe shivering three times; by this means the heat production of the body may be raised 300 per cent. These two defensive reactions, vasoconstriction and shivering may be prevented by drugs; most anaesthetic agents produce a certain degree of vasodilation of the skin vessels and deep anaesthesia or curarization will completely abolish shivering. Chlorpromazine is an effective vasodilator and reduces but does not always entirely abolish shivering. Both general anaesthesia and

chlorpromazine will each allow increased heat loss if the body is exposed. In view of the known effect of chlorpromazine in reducing the tone of the blood vessels and muscles it seems unnecessary to postulate a central effect on the thermoregulatory centre. The drug may thus be conveniently employed to facilitate cooling and by this means to reduce the oxygen consumption of the body. Apart from cooling, however, no such reduction of oxygen consumption has been found after administration of chlorpromazine *in vivo* (Dobkin *et al.*, 1954; Shackman *et al.*, 1954).

Anti-Emetic Properties

It often appears that the effects of a drug are increased in proportion to the strength of the administrator's convictions, and any recent remedy is likely to be effective in a good proportion of cases. Persistent hiccup, for example, has stopped dramatically three minutes after an intramuscular injection of chlorpromazine. Similarly the value of drugs in post-operative vomiting is difficult to assess. There is considerable evidence that chlorpromazine reduces the frequency of this complication, but there is still room for really well controlled experiments in the clinical field. Recent experimental work has shown that vomiting results from stimulation of the centre by a reflex arc arising from 'chemoreceptor trigger zone' situated on the surface of the medulla in the floor of the fourth ventricle. This trigger zone is activated by so-called central acting drugs such as apomorphine, morphine, etc., and by those stimuli from the vestibular apparatus which are responsible for motion sickness. Chlorpromazine is thought to act by competitive blocking of the receptors at this trigger zone when given in moderate doses. Much larger doses are said to have a direct depressant effect on the actual vomiting centre and will diminish the response to direct gastric irritation by copper sulphate or to stimulation of the vagus by veriloid.

Cardiovascular Effects

The effects of chlorpromazine on the cardiovascular system are mainly the result of its action in lowering the peripheral resistance by vasodilatation. The heart becomes more rapid presumably in an attempt to maintain the blood pressure. There is usually an increase in the cardiac output but in the vast majority of cases the blood pressure falls and becomes orthostatic.

The blood flow in the hand has been shown, by Foster (1954) and his co-workers, to be increased 284 per cent. after intravenous chlorpromazine. The intra-arterial injection of adrenalin produces constriction of the hand vessels, chlorpromazine given intra-arterially prevents this as does intra-

venous administration. The effect of noradrenalin is not blocked to anything like the same degree as that of adrenalin (Kopera and Armitage, 1954), and in those cases in which hypotension following the administration of chlorpromazine is too great or too prolonged, it would seem better to treat it by noradrenalin rather than by adrenalin. When noradrenalin is given to a patient, slowing of the pulse is usual presumably due to vagal reflexes excited by the raised pressure; after chlorpromazine the rise in pressure is less marked but is not accompanied by slowing of the pulse. There is evidence then that chlorpromazine is a powerful adrenalin blocking agent, it may be called a sympathetic blocking agent; it is in some measure a parasympathetic blocking agent and it has effects on the mid brain. Some would therefore go further and say that it is an autonomic blocking agent. But we should, I think, be careful to distinguish it in our minds from such drugs as hexamethonium, which are true ganglion blocking agents.

In haemorrhagic shock, vaso-constriction of sympathogenic origin, if persistent, may be a factor in making the shock irreversible: the vasoconstriction in the tissues being so extreme as to cause anoxic tissue damage so severe that even if the blood volume were completely restored recovery would, in any case, be impossible. It has been suggested that preventing this vasoconstriction lessens the incidence of irreversible shock. Chlorpromazine has been shown to have a shock sparing effect in experimental animals subjected to haemorrhage and trauma. But similar effects are seen with a wide variety of agents including atropine, barbiturates and some, but not all, anti-adrenaline drugs, and it seems that 'protection is not a function of increased blood flow in the tissues created by autonomic blockade' (Hershey *et al.*). In the case of chlorpromazine there is usually a fall in blood pressure which in itself is a factor in reducing blood loss. In man controlled experiment is difficult and it has yet to be proved that, provided blood is adequately transfused, chlorpromazine gives any better protection against operative shock than does good conventional modern anaesthesia. Many feel encouraged, however, by the condition of bad risk cases given chlorpromazine for very major operations.

Laborit and Huguenard were the first to use chlorpromazine when they added it to their so-called 'artificial hibernation' in 1951. This they defined as 'a pharmacodynamic technique which, by using autonomicolytic drugs aims at establishing a "controlled inhibition" of the autonomic system, a neuroplegia of homeostasis and, as a consequence, an attenuation of the regulatory reactions; it amounts to an economical method of

living with hypometabolism, muscular relaxation and a state of twilight sleep which resembles narcosis' (Huguenard, 1953). The substance and manner of expression of the assumptions and theories upon which these workers base their method have not proved acceptable to most anaesthetists in this country, who feel, moreover, that the method is unduly complicated and often carried further than is reasonable.

The author has used a much simplified modification of his technique for over 200 cases undergoing thoracic surgery. Premedication with promethazine (phenegan), 50 mgm. given by mouth four hours before operation, and pethidine, 100 mgm. given intramuscularly one hour before arrival in the theatre, has given reasonably satisfactory sedation. A mixture of promethazine, 50 mgm. chlorpromazine, 50 mgm., and pethidine, 100 mgm. in 250 cc. of 5 per cent. dextrose in water, is given intravenously in the anaesthetic room. After some ten minutes the patient becomes apathetic and drowsy; should the rapid and forceful heart action cause any distress the patient may be made comfortable by a 'sleep dose' of 100 to 150 mgm. of thiopentone. A fall in blood pressure to about 80 mm. of mercury is common in healthy adults and the dose of 'mixture' is therefore reduced in the frail or elderly. A further 100 to 150 mgm. thiopentone and a suitable dose of relaxant allow intubation with or without bronchial aspiration and blocking to be carried out carefully. Anaesthesia is maintained with nitrous oxide and oxygen with relaxant added as needed. While respiration is rather less depressed than with some other sequences the bronchial reflexes are quiet. This reduction in irritability has seemed of particular value in difficult cases with secretions and bronchospasm. After operation, in successful cases, the patients are pale, lying quietly with eyes closed, apparently untroubled by pain but capable of responding to requests to move or cough, shutting their eyes again when the physiotherapist leaves. The pressure tends to remain low while the drugs are active, and pain when it comes on some after an operation may be resented by a patient who has been, until then, comfortable. Relative comfort may be restored by pethidine or occasionally by a further dose of chlorpromazine given intramuscularly.

The incidence of vomiting after thoracic surgery when using a barbiturate, relaxant and nitrous oxide sequence is low and is still further reduced when chlorpromazine is used. It is not, however, abolished completely. Of our cases three with persistent hypotension were treated by intravenous infusion of nor-adrenalin and three developed transient auricular fibrillation. These six complications all followed resection for carcinoma of

the lung, when such sequelae may occur irrespective of the anaesthesia. The method seems to have been responsible for several cases of urinary retention occurring in men, several of whom required catheterization.

Many of the nursing and resident medical staff have come to prefer this technique for thoracic work. It is significant that when the routine use of this method was stopped after a trial period the surgeon at one hospital asked if it could be continued one week longer as he was operating on a surgical colleague; and that when the sister of one of the thoracic surgical wards herself underwent lobectomy, and later thoracoplasty, she chose chlorpromazine for herself.

An Assessment

The drug has undoubted value as an anti-emetic and has a place in the management of painful conditions and in psychiatry, but its continued administration carries the risk of damage to the liver and bone marrow. In anaesthesia the author's experience is largely limited to its use in surgery of the lung. Here the combination of drugs used allows repeated endobronchial instrumentation, provides satisfactory operating conditions and seems to lessen the discomforts of the post-operative period. With adequate after care significant complications have not been increased.

While conventional methods in skilled hands allow a more rapid return to normality and make assessment of the patient's condition easier, there is no doubt that several of the effects of chlorpromazine can conveniently fit into the pattern of anaesthetic requirements for major surgery. While grateful for this it would seem preferable to be able to control the extent of those various effects independently by manipulating the dosage of several different and shorter acting drugs. A sawn off shot gun may be effective but it is neither a weapon of precision nor is its use appropriate on all occasions.

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