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The Pharmacology of Chlorpromazine and Promethazine

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THE story of chlorpromazine and promethazine begins, so far as I am concerned, about eight years ago, with the results of an investigation carried out by Dawes (1946) in the Oxford laboratory, to find substitutes for quinidine for use in auricular fibrillation. Many substances were found to share with quinidine the power to prolong the refractory period of cardiac muscle. Among them were local anæsthetics such as procaine and amethocaine, spasmolytics such as atropine and papaverine, and analgesics such as pethidine. In fact, it appeared at first that in the possession of a quinidine-like action there was a common meeting ground for a large number of substances which were otherwise dissimilar. Dawes showed, however, that more than one property was shared by these different substances, and that, for example, all of them had a local anæsthetic action also.

A few months later we were excited by the arrival of some of the new antihistamine substance Neo-antergan (mepyramine), and it occurred to me to wonder whether it would share these properties too. My colleagues Dews and Graham (1946) found that it did. As a substance prolonging the refractory period of cardiac muscle, it was twice as active as quinidine, and as a local anæsthetic it was 3·1 times as active as procaine. Thus the class of substances widened, and was extended still further by Hutcheon (1953) to include a group of four related substances, one of which was promethazine and another was Diparcol (diethazine) which is used in the treatment of Parkinson's disease.

Fall of body temperature.—The disclosure of so many common properties in substances used for so wide a range of therapeutic effects was of great interest from the pharmacological point of view, since it offered the prospect of introducing some order into the chaos of the actions of alkaloids. The textbooks of pharmacology during the last half-century give few clues to the relation of one substance to another; procaine is described as a local anæsthetic and atropine as a spasmolytic or as a substance which inhibits the action of cholinergic nerves. The relation of procaine to atropine is, however, rarely or never discussed. It therefore seemed desirable to see how much farther the parallelism in the properties of these substances would prevail. As a next step an investigation was made into their effect on body temperature. For in 1931 Glaubach and Pick showed that when procaine was injected into guinea-pigs, it had the peculiar action of causing body temperature to fall. This property seemed sufficiently remote from other properties of procaine that there was a good chance that it would not be shared by other substances.

Our results (Burn and Dutta, 1948*a*; Dutta, 1948) soon showed that the action of procaine was shared by pethidine, atropine, Benadryl (diphenhydramine) and quinidine. Observations were made in mice recording the rectal temperature by a thermocouple. Equal numbers of injected and control mice were kept side by side, and the difference in the mean temperature of the injected mice from the mean temperature of the control mice was calculated. Observations were also made in mice after adrenalectomy, and the difference in the temperature was then found to be greater than before, and of longer duration. The results with Benadryl (20 mg./kg.) were similar in all respects to those with pethidine, but when atropine and quinidine were used in similar dose to pethidine they caused very little fall of temperature unless the mice were adrenalectomized. The fall then was prolonged and with quinidine profound.

Thus the property of lowering body temperature which procaine possessed was also shared by quinidine, by an antihistamine, by atropine and by an analgesic substance. The similarity between these different agents was strengthened.

Abolition of constrictor action of adrenaline.—To test the similarity farther we chose another unusual property of one substance, to see if it was shared by the others. Bussell (1940) had shown that atropine exerted a vasodilator action in vessels in which a tone was maintained by adrenaline, and he had also shown that in the vessels of the perfused rabbit ear, atropine could abolish the vasoconstrictor action of adrenaline. We examined pethidine, procaine, Benadryl and quinidine to see if they acted like atropine (Burn and Dutta, 1948*b*). Each of these substances was found to abolish the vasoconstrictor action of adrenaline; atropine, Benadryl and pethidine were similar to one another in potency, quinidine being weaker and procaine very much weaker. Here again, was evidence of a resemblance of the properties of these different agents.

Ganglion-blocking action.—Experiments were also made (Dutta, 1949*a*) to see if these substances possessed a ganglion-blocking action. For this purpose the superior cervical ganglion of the cat was perfused by Kibjakow's well-known method, and stimuli were applied to the cervical sympathetic chain. A record of the contractions of the nictitating membrane was obtained to indicate the effectiveness of the transmission of impulses through the ganglia. Again, it was found that atropine, pethidine, procaine and quinidine were able to diminish the effect of preganglionic stimuli, though atropine which was active in an amount of 50 μg. was five to ten times more powerful than the others. In a later paper Dutta (1949*b*) described a similar action of the two antihistamine substances diphenhydramine (Benadryl) and antazoline (Antistin); their potency was about one-fifth that of atropine.

Similarity of properties.—The similarity of the properties of many local anæsthetics, quinidine-like substances, analgesics, spasmolytics and antihistamine substances was therefore borne out by all investigations. The results made it possible to predict with some approach to accuracy the general properties of other substances which possessed one of these actions. Thus we could say that any new antihistamine would have a quinidine-like action, would be a local anæsthetic, would lower body temperature and so on. Hutcheon (1953) examined four substances related to promethazine, and was able to compare their actions as local anæsthetics, as inhibitors of salivary secretion, as spasmolytics, and as quinidine-like substances.

When, therefore, chlorpromazine was introduced into clinical use by Laborit and Huguenard (1951) it was possible to forecast its general properties from the fact that it was a close chemical relation of promethazine, with the result that when the paper on its pharmacological action by Courvoisier *et al.* (1953) appeared, it contained few surprises.

These workers showed as might be expected that it abolished or reversed the action of adrenaline on the blood pressure and reduced its vasoconstrictor action. It possessed a quinidine-like action, but very little antihistamine action; it had a striking action in lowering body temperature, it was a local anæsthetic, and it had a central sedative effect. It had other effects like those of promethazine, being anti-emetic and increasing capillary resistance to the action of ovalbumin and other agents.

Because of the use which has been made of chlorpromazine in operations, and of the interest which it has aroused, we felt it worth while to examine it at Oxford, and to note for ourselves what effects it produced.

Effect on temperature.—We turned our attention first to its action on body temperature, and since it has been usually given together with pethidine and promethazine in anæsthetic procedures, my colleagues, Mr. A. K. Armitage and Dr. J. Kopera, compared the three substances. The results of Courvoisier and her colleagues indicated that in mice chlorpromazine was 25 times as effective as promethazine, which seemed to us a surprisingly high figure. Our results were obtained by recording the rectal temperature of mice with thermocouples and using in each experiment the same number of injected mice and of control mice. We determined the effect of a given amount of each substance by the difference in the mean temperature of the two groups. We found that chlorpromazine given in the dose of 1 mg./kg. exerted a greater and much more prolonged effect than 30 mg./kg. of either promethazine or pethidine. These two substances were similar in activity.

There has been much discussion and some confusion about the cause of this fall of temperature. One view is that suggested by Courvoisier *et al.* (1953) who said that "one can then liken the effects of chlorpromazine to an actual chemical adrenalectomy". This idea appeals to those who believe that activity of the adrenal cortex indicates the existence of stress, that stress is invariably bad for the organism, and that activity of the adrenal cortex should always be avoided. Thus Wells (1954) referring to the use of chlorpromazine "which puts the heat-regulating mechanism out of action" says "if it can be shown that in hibernation the stress response is minimal . . .".

Now we know that the adrenal gland is active at low temperature. Adrenal cortical extracts are tested biologically by their ability to prolong the life of young adrenalectomized rats exposed to a temperature of 2° C. But the adrenal glands are also active when body temperature is reduced by drugs. This was shown by Dutta and myself for atropine, quinidine, Benadryl, procaine and pethidine. The fall of temperature caused by these substances was greater—and often much greater—in adrenalectomized mice (compared with adrenalectomized controls) than in normal mice. This proved that the fall of temperature occurred in spite of the activity of the adrenal glands and not because that activity had been paralysed. It may well be that there is a maximal activity of the adrenals during drug hypothermia and that in this sense the body is subjected to maximal stress.

The other view of the cause of the fall of temperature is that it is due to a block of the neuro-vegetative system, which we call the autonomic system. This view has been expressed by Laborit and Huguenard (1951) and accepted by various workers in this country. Whatever is meant by such a block, it is clearly not ganglionic blockade, since a full dose of hexamethonium (5 mg./kg.) has little effect in lowering temperature in mice.

It is, of course, perfectly possible that interference or block of the sympathetic system may play a part in the fall of temperature, for the experiments of Sawyer and Schlossberg (1933) showed that cats which were sympathectomized had much greater difficulty in controlling their temperature

than normal cats. At 8°–9°C., sympathectomized cats shivered the whole time and nevertheless the rectal temperatures fell. Normal cats, on the other hand, shivered only occasionally and their temperatures rose.

There is, however, no evidence that chlorpromazine blocks the sympathetic system. It is true that it is an anti-adrenaline substance and that it can reduce or abolish the vasoconstrictor action of adrenaline. However, even its anti-adrenaline action is limited for Courvoisier *et al.* (1953) showed that chlorpromazine did not reduce the action of adrenaline in releasing glucose from the liver. Anti-adrenaline substances in any case have very little action on the sympathetic system, for this acts by liberating noradrenaline, which is not appreciably affected by chlorpromazine.

Effect on skeletal muscle.—Since the maintenance of body temperature is primarily the concern of skeletal muscles, we were anxious to see what effect chlorpromazine would have on them. In their paper Courvoisier and her colleagues recorded that chlorpromazine did not alter the toxicity of the curarizing agent gallamine given intravenously, but that in a dose of 10 mg./kg. it diminished the amount required to cause "head-drop" (that is, a paralysis of the neck muscles) to about 40% of the normal. Furthermore, in a dose of 20 mg./kg. it prolonged the duration of curarization from 3·25 to 4·5 hr.

We made observations on cats, first anæsthetized with chloralose and then decerebrated, in which we recorded the contractions of the gastrocnemius muscle by attaching the tendo Achillis to a tension lever; we stimulated the muscle both through the sciatic nerve and directly. We soon confirmed the observation that the injection of chlorpromazine in the amount of 1·3 mg./kg. prolonged the action of d-tubocurarine, but we also found that doses of 3 mg./kg. caused a gradual failure not only of contractions evoked by nerve stimulation, but also of those caused by direct stimulation, so that the muscle became inexcitable no matter how great a stimulus was applied. The results showed that chlorpromazine exerted a direct paralytic action on skeletal muscle, though the onset of this effect was delayed and sometimes preceded by an initial phase of augmentation. Dutta (1949*a*) described a similar effect due to pethidine when using the isolated rat diaphragm.

Similar effects to those of chlorpromazine were obtained with promethazine and with pethidine, though only when larger amounts were used. Chlorpromazine appeared to be two to three times as active as promethazine, and six times as active as pethidine, but it is not possible by experiments of this kind in cats to make a quantitative comparison of different substances. In a preliminary experiment on Dr. E. Bülbring's preparation of the rat diaphragm stimulated through the phrenic nerve, chlorpromazine was found to be 3·5 times more active than promethazine.

These results on skeletal muscle were striking in view of the amounts required. Dundee *et al.* (1953) used for their patients 50 mg. chlorpromazine, 100 mg. pethidine and 50 mg. promethazine, given intravenously. This was three to four hours after premedication with pethidine 100 mg. and promethazine (amount unspecified) by intramuscular injection. The results in the cat suggest that these amounts given to patients produce a paralysis of the skeletal muscles which might account for the fall of body temperature observed. Caution should, however, be exercised in assuming that all the skeletal muscles are paralysed to the same extent as the gastrocnemius. We did not observe that respiration was arrested by these substances and therefore the diaphragm was not paralysed.

However, we may conclude that an effect on skeletal muscles plays a part, and perhaps a large part, in causing the fall of temperature. In view of the general depressant action of chlorpromazine on the central nervous system it seems probable that there is also an effect on the heat-regulating centre, though there is no evidence that this effect is a "central autonomic block".

The toxic action of chlorpromazine.—In their long paper of 57 pages, Courvoisier and her colleagues devoted only half a page to the important subject of chronic toxicity. They administered chlorpromazine to dogs and said that a daily injection of 20 mg./kg. for a month did not cause any death. They did not say how many dogs were used. Histological examination revealed changes both in the kidneys and in the lungs. Changes were produced in the kidneys by amounts as low as 2 mg./kg. What was, however, very surprising was that there was no reference to the liver, for it is in the liver that toxic effects might be expected.

However, Moyer *et al.* (1954) describe observations made in 15 control subjects and 9 patients, which showed that when chlorpromazine was given orally in 25 mg. four times daily for a week there was no evidence of liver damage. There was no rise of serum bilirubin or change in thymol turbidity or bromsulphalein tests. Nor was there evidence of any change in renal function.

One of the simplest ways of determining chronic toxicity is by carrying out growth tests in young rats, and we have made comparative tests with the three substances. We found that as much as 100 mg./kg. pethidine daily had no effect on growth, while promethazine in a daily total of 90 mg./kg. in 2 doses caused retardation of growth. Chlorpromazine was rather more toxic and caused retardation of growth and an occasional death in a daily total of 20 mg./kg. in 2 doses. With both chlorpromazine and promethazine the retardation of growth or loss of weight was seen during the first three or four days, after which the rats grew at about the same rate as the controls although the injections of the two substances were continued. The results, however, indicated that chlorpromazine had more toxicity than was to be supposed from the work of Courvoisier and her colleagues. Our own results are not yet complete.

Other effects.—We tested chlorpromazine in other ways. We compared it with promethazine and pethidine for prolonging the time of sleep produced by pentobarbitone and found that it was three times more powerful than these two substances. However, we failed to find any potentiation of the action of morphine by chlorpromazine.

Again, we compared it with pethidine and promethazine for its local anæsthetic action, using intracutaneous injection in the guinea-pig, which measures the action on sensory nerve endings. Chlorpromazine was found 1·16 times stronger than promethazine, and 2·12 times stronger than pethidine.

The anti-adrenaline action of these substances was compared in three ways, and again chlorpromazine was more powerful than promethazine, and very much more powerful than pethidine. The comparison was made first by their reduction of the pressor effect of adrenaline in the spinal cat; second, by their reduction of the constrictor effect of adrenaline in the perfused vessels of the rabbit ear, and third, by their reduction of the simulant action of adrenaline on the isolated rabbit uterus.

The antihistamine action of these substances was tested on the guinea-pig bronchioles using the method of Konzett and Roessler (1940). We found that promethazine was 100 times more active than chlorpromazine. This fully confirms the finding of Courvoisier and her colleagues.

Discussion

The position of chlorpromazine can be looked at first from the point of view of its pharmacological properties. The pharmacological evidence concerning chlorpromazine which has been published hitherto was not surprising, and did not indicate that there was any therapeutic use for which it was particularly suited. The first property described by Courvoisier *et al.* which it possessed to an unusual extent was its anti-adrenaline action, which might make it useful in the treatment of Raynaud's disease. A factor contrary to such a use would be the accompanying drowsiness and mental depression which would disturb some patients. The other unusual property was its power to lower body temperature. This would not have seemed a property of any clinical value to most pharmacologists since a lowering of body temperature by a drug would be regarded as a harmful action.

It is true that recently the lowering of body temperature by physical means has been adopted as a procedure to facilitate operations on the heart or main blood vessels (Bigelow *et al.*, 1950). When a large part of the circulation must be interrupted, it is a sound physiological principle to reduce the tissue demand for oxygen by reducing the temperature. Having this in mind, Laborit seems to have reached the conclusion that it is equally justifiable to reduce body temperature by using a drug or rather a mixture of drugs. The reduction of body temperature by the action of a drug surely indicates that the tissues are being poisoned, for the body makes every effort to maintain a constant temperature in ordinary circumstances.

The use of these drugs, moreover, has one aspect to which little reference has been made, namely, that once they are given, the patient's condition is out of the anæsthetist's control. At one time substances like pentobarbitone and bromethol were used for producing full anæsthesia; they were indeed introduced for this purpose. It was then found that a proportion of patients were unusually sensitive and that the ordinary anæsthetic dose was fatal to them. These substances then reverted to the position of basal anæsthetics, and were given in lower dose to ensure that there were no more deaths. More rapidly destroyed barbiturates like hexobarbitone and thiopentone were introduced and are now regularly used, because the anæsthetist knows with much more certainty when the patient will come round. Short-acting substances are safer. The same is true of curarizing agents. The safest of these is succinylcholine which is so transient in its action that it is given in an intravenous drip. In both cases the preference for short-acting drugs is obviously sound.

But now the advocates of chlorpromazine have conveniently forgotten this experience and are using a substance which, when given, produces its full effect slowly, and of which the effect is unpredictably long. Surely it is not necessary to point out that there is a wide range of sensitiveness among different patients towards any drug, and that the use of a standard dosage of chlorpromazine will certainly have far greater effect in lowering temperature in some than in others. For these more sensitive patients there is no antidote, and all that the anæsthetist can do is to hope that they will not die. Whatever this position is, it is certainly not progress.

Conclusion

There are difficult and prolonged operations where the need to reduce post-operative shock is paramount, and where risks must be taken so far as the patient's later condition is concerned. There is evident agreement among anæsthetists who have used chlorpromazine that the signs of post-operative shock are very few. But even so the anæsthetist should, I think, bear in mind that little is yet known of the late effects of hypothermia induced by chlorpromazine. One may ask whether it is certain that there is no long-term effect on the patient's brain. Above all, nothing has been said about the effect of prolonged hypothermia on resistance to bacterial invasion. It is very difficult to believe that our past experience was all wrong, and that exposure to cold is a good thing. Are people who have been chilled to the point of a drop in body temperature really not in danger of serious infection, as we have always believed, and is that chilling less dangerous when it is achieved by

reducing metabolic processes with a drug? No doubt Time will supply the answer, and we may hope that we will get it without paying too high a price.

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Dr. D. A. B. Hopkin, Lambeth Hospital, London: The essential action of chlorpromazine lies in its action on the autonomic nervous system. Hypothermia is a secondary consideration. Laborit (1954) maintains that cooling benefits patients because it reduces cellular metabolism. Chlorpromazine permits cooling of semi-conscious patients before and after operation without bringing into action defence mechanisms against cold, which involve both the autonomic nervous system and the endocrine glands. Workers in this country (Smith and Fairer, 1953) and in France (Tardieu, 1954*a*) agree that all the advantages claimed for the use of chlorpromazine in anæsthesia can be obtained without resort to hypothermia.

Cathala and Pocidalo (1952) have shown that in animals chlorpromazine has a central action which besides including a degree of narcosis has a specific action in depressing the sympathetic centres of the mid-brain. Tardieu (1954*b*) maintains that this property is not possessed by any other sympatholytic drug.

Robertson (1954) has been able to demonstrate that chlorpromazine blocks sympathetic ganglia in low concentration. Further experiments showed that this differs from the block produced by methonium compounds. Clinical experience confirms this since marked vasodilatation and hypotension do not occur.

Jaulmes, Laborit, and Benitte (1952) have shown that both experimentally and clinically chlorpromazine confers protection against both traumatic and hæmorrhagic shock. The peripheral circulation appears to be stabilized. The small blood vessels and the capillaries appear to be impervious to either dilator or constrictor influences, and the circulatory changes which appear early in shock do not occur.

There is nothing new about sympatholytic drugs being of use in shock prevention. Such claims have been made for spinal analgesia, for methonium compounds, and for intravenous procaine. None of these have been an unqualified success because they lacked the central effect of chlorpromazine, and their action was not carried on sufficiently long into the post-operative period to allow the effects of trauma to die down.

The drugs with which Professor Burn classed promethazine and chlorpromazine all have a reputation for relieving bronchospasm, and prevention of post-operative pulmonary complications. Chlorpromazine is outstanding in this respect, and promethazine alone seems able to reduce the incidence of laryngospasm during anæsthesia.

There are therefore two good reasons for using them in anæsthesia: shock prevention, and reduction of post-operative pulmonary complications.

The experience of Dr. Bernard Kenton (Bethnal Green) and myself in over 500 patients fully confirms this. We have found the drugs of particular value in treatment of hæmorrhagic shock. They enable operation to be undertaken earlier, and massive blood transfusion is no longer necessary, and indeed can be dangerous. Two to three pints of blood are sufficient to restore full hæmoglobin value in severe hæmatemesis, when emergency gastrectomy is performed.

No toxic side-effects have been noticed. Occasionally post-operative tachycardia is observed. This settles within thirty-six hours. If delayed shock is seen it is probably due to too small a dose of chlorpromazine, since the maximum effect seems to wear off within five to six hours.

Our experience leads us to believe that these drugs have a real value in the prophylaxis and treatment of traumatic and operative shock, and can play an important part in prevention of post-operative morbidity, in particular that associated with pulmonary complications.

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