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CHLORPROMAZINE: A LABORATORY AND CLINICAL INVESTIGATION * † ‡

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IN 1952, reports concerning the clinical use of chlorpromazine, a phenothiazine derivative, began to appear in the French literature (1, 2). The descriptions of its use were difficult to evaluate inasmuch as the drug was one of several employed simultaneously in the "lytic cocktail." The pharmacological data of Courvoisier (3) elucidated the status of the drug to some extent, but again the situation became confused as further clinical reports ascribed a wide range of activity to this compound. As we began to use the drug § clinically, it became evident that more laboratory work was necessary to assess properly the variations of clinical activity.

LABORATORY STUDIES

The purposes of our animal studies were as follows:

1. To determine the physiological effects of increasing doses of chlorpromazine in different animal species.
2. To investigate the effects of prolonged administration of the drug, incorporating liver and renal function tests along with gross and microscopic studies of organs.
3. To evaluate the adrenolytic or sympatholytic effects of chlorpromazine.

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§ Chlorpromazine was supplied as Thorazine® by Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

4. To show the "protective" effect exerted by this drug on the heart against drugs which produce abnormalities of conduction.
5. To determine the effect of increasing drug dosage on direct stimulation of the intact vagus nerve.
6. To investigate the action of increasing doses of the drug on ganglionic transmission.
7. To evaluate the protection afforded by the drug against induced vomiting.
8. To study the influence of chlorpromazine on oxygen consumption in the dog.

Method of Study. A total of 9 rabbits, 17 dogs and 8 cats were utilized in the acute experiments. Preparation of the rabbits was carried out under local anesthesia, while the dogs were given pento-

TABLE 1

CHLORPROMAZINE (MG. PER KILO I.V.)

	Well Tolerated	Hypotension	Electrocardiographic Changes	Lethal
Rabbits (8)	2.0	4–12	12–20	45–60
Dogs (6)	5.0	30–60	Not observed	Not observed
Cats (5)	4.0	10–15	Terminally	21–40

To show species variation in tolerance to chlorpromazine.
N.B. Tolerance from one animal to another also variable.

barbital, 25 mg. per kilogram, intravenously and the cats a similar dosage intraperitoneally. Subsequent injections of the barbiturate were not necessary. The femoral artery and vein were cannulated with large-bore polyethylene catheters and a pneumograph was fixed on the animal's chest. An endotracheal tube was placed in the trachea to avoid upper respiratory obstruction and to allow effective immediate artificial respiration when required. A six-channel Grass electroencephalographic machine recorded measurements. With the help of Statham pressure transducers and demodulators, it was possible to record simultaneously the blood pressure, pulse rate, venous pressure, respiratory rate and pattern and Lead II of the electrocardiogram.

Chlorpromazine Effect on Vital Functions. Progressively increasing doses of chlorpromazine were injected intravenously into 8 rabbits, 6 dogs and 5 cats. Table 1 indicates the range of doses administered. "Well tolerated" doses were those which produced little or no effect on blood pressure, respirations or pulse rate. These amounts were con-

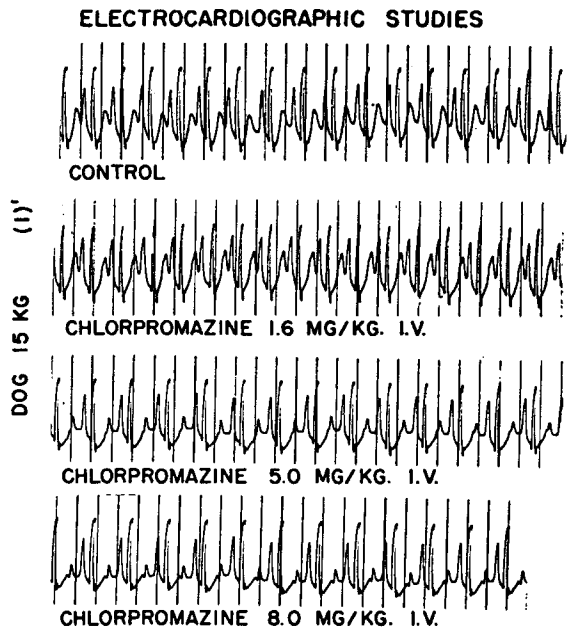

FIG. 1 (a).

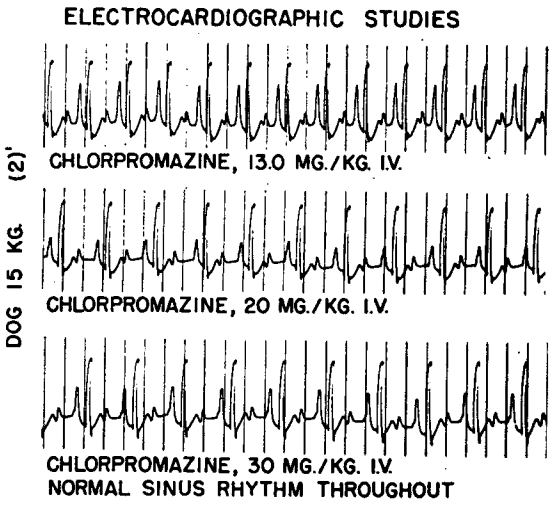

FIG. 1 (b).

FIG. 1. (a and b). Dog (15 g.), showing normal cardiac conduction after chlorpromazine, 1.6 to 30 mg. per kg. intravenously.

sidered to be in the "therapeutic range." Moderate to severe hypotension was noted with higher doses, although the onset of this alteration varied considerably from animal to animal, as well as from species to species.

Electrocardiographic arrhythmias began in rabbits in the dosage range from 12 to 20 mg. per kilogram. Such changes were not seen in the dog (fig. 1) and only terminally in the rabbit (fig. 2).

Apparently the dog is more resistant to large doses of this drug than is the rabbit. Death in these two last named species appeared to be primarily cardiac in origin. Preterminally the pulse rate became slow, delayed conduction arrhythmias occurred, there was widening of the QRS interval, and death occurred in asystole (fig. 2). Similar findings have been noted by other observers (3, 4).

Chronic Toxicity. Ten adult rabbits weighing between 2.5 and 4.5 kg. were maintained on chlorpromazine for periods of three months.

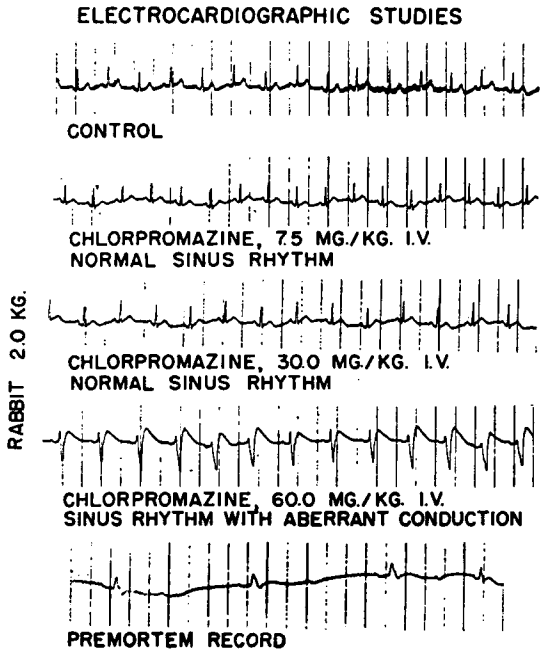

FIG. 2. Rabbit (2.0 kg.), showing aberrant conduction and premortem asystole after chlorpromazine, total dose 60 mg. per kg. intravenously.

Five animals received 25 mg. orally every other day, while the other 5 were given a dose of 4 mg. per kg. intramuscularly on alternate days. One animal died of unknown causes during the experimental period. Three other animals died as a result of technical errors while the function tests were being performed. No gross abnormalities of kidney or liver function were noted in this series except for the occurrence of glycosuria in three animals (3, 5).

The 9 rabbits which survived the period of testing were autopsied. Gross and microscopic studies were made of the heart, lungs, liver,

kidney and central nervous system. Apart from occasional evidence of inflammatory reaction, believed to result from endemic intercurrent infection, the organs examined were free of gross or microscopic lesions.

For a period of eight weeks, 10 rats received chlorpromazine, 1.5 mg. per kg. intramuscularly, three times weekly; 10 rats received 7.0 mg. orally at the same intervals, while 10 other rats served as controls. Fifty per cent of the animals injected intramuscularly died, while only 10 per cent of those receiving the drug orally and 20 per cent of the controls succumbed. All animals which received the drug lost weight consistently, while in the control group all but 2 gained weight

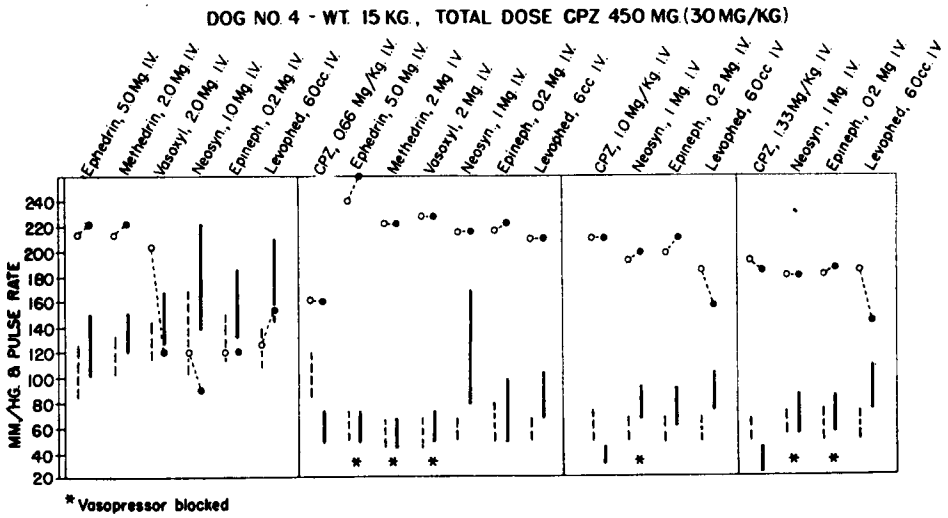

FIG. 3. Showing the hypotensive effect and sympatholytic action of chlorpromazine in the dog. Interrupted lines represent "control" blood pressures, continuous lines the effect of chlorpromazine and vasopressor drugs.

progressively (6). The increased mortality in the rats injected intramuscularly is of interest but is not believed to be significant.

The 22 rats which survived the experiment were autopsied. Gross and microscopic observations were made of the following tissues: heart, lung, liver, kidneys, adrenals, central nervous system, pancreas, spleen, striated muscle, esophagus, stomach, salivary gland, trachea, autonomic ganglia, bone marrow, thyroid and lymph nodes. Except for occasional areas of inflammatory reaction resulting from endemic infections, all the organs examined were free of gross or microscopic lesions. There was no evidence of old or recent cellular injury to parenchymatous tissues. The nervous systems were free of degenerative changes, and the hematopoietic tissues were normally active.

Sympatholytic Effect of Chlorpromazine. In 5 dogs and 5 cats

an effort was made to determine what effect increasing doses of chlorpromazine would have on the action of commonly employed vasopressor drugs. Doses of sympathotonic drugs were chosen which would increase the blood pressure consistently under normal circumstances. The following were the drugs and doses injected intravenously:

1. Ephedrine, 0.8 mg. per kg.
2. Desoxyephedrine (Methedrin®), 0.3 mg. per kg.
3. Methoxamine (Vasoxyl®), 0.3 mg. per. kg.
4. Neosynephrine®, 0.15 mg. per kg.
5. Epinephrine, 0.015 mg. per kg.
6. Levo-arterenol (Levophed®), 2.0 micrograms per kg.

It was noted in the controls that all vasopressors except ephedrine and desoxyephedrine were capable of inciting, not only an increase in blood pressure, but also numerous electrocardiographic changes (figs. 4, 5). These electrocardiographic disturbances, as well as alterations in blood pressure and pulse rate, could be blocked or modified by chlorpromazine intravenously. The results obtained are illustrated in figures 3, 4, and 5, and may be listed as follows for each species:

In the dog:

1. Ephedrine, Desoxyephedrine, Methoxamine — Complete vasopressor block with chlorpromazine, 0.25 to 1 mg. per kg.
2. Neosynephrine
   a. Electrocardiographic changes blocked with chlorpromazine, 0.25 to 1 mg. per kg.
   b. Pressor effects blocked with doses varying from 8.3 to 33.4 mg. per kg.
3. Epinephrine
   a. Electrocardiographic arrhythmias prevented by chlorpromazine, 3.0 to 4 mg. per kg.
   b. Vasopressor effects reversed with 5 mg. per kg. (1 animal).
   Vasopressor effects prevented with 20 mg. per kg. (1 animal).
   Vasopressor effects modified but not blocked in other animals with doses of 33 to 60 mg. per kg.
4. Levo-arterenol
   a. Electrocardiographic changes prevented with chlorpromazine, 30 mg. per kg.
   b. Vasopressor effects modified but not blocked with doses of 30 to 60 mg. per kg.

In the cat:

1. Ephedrine and desoxyephedrine	Vasopressor effects prevented with chlorpromazine, 1 to 6 mg. per kg.
2. Methoxamine	a. Electrocardiographic changes prevented with chlorpromazine, 1 to 6 mg. per kg. b. Vasopressor effects blocked with doses varying from 1 to 16 mg. per kg.
3. Neosynephrine	a. Electrocardiographic arrhythmias prevented by chlorpromazine, 1 to 6 mg. per kg. b. Vasopressor effect blocked by 11 to 18 mg. per kg.
4. Epinephrine	a. Electrocardiographic arrhythmias prevented by chlorpromazine, 1 to 6 mg. per kg. b. Vasopressor effect blocked by 5 mg. per kg. (1 animal). Vasopressor effect modified but not blocked by doses of 12 to 27 mg. per kg.
5. Levo-arterenol	a. Electrocardiographic changes prevented by chlorpromazine, 10 mg. per kg. b. Vasopressor effects modified but not blocked with doses from 12 to 27 mg. per kg.

These results indicate that, in the dog and cat, the action of the less potent sympathotonic drugs is prevented completely by relatively small doses of chlorpromazine, whereas the action of the potent vasopressors is modified but not inhibited completely even by large doses. Electrocardiographic arrhythmias induced by these vasopressors are prevented as a rule by small amounts of chlorpromazine. It is conceivable that such drugs as chlorpromazine might be a means of determining pharmacologically the potency of new vasopressor drugs. Certainly this experiment confirms the adrenergic blocking properties of chlorpromazine (4, 7, 8, 9).

Effect of Chlorpromazine on Induced Cardiac Arrhythmias. After preparation described previously, 5 dogs were anesthetized with nitrous oxide (75 per cent), oxygen (25 per cent), and trichloroethylene. The gases were allowed to bubble through the trichloroethylene to obtain an inhaled concentration of approximately 2.5 per cent (10). After fifteen minutes epinephrine, 0.015 mg. per kg., was injected intravenously. When the cardiac arrhythmias had subsided, the animal was allowed to rest for thirty minutes and then the procedure was repeated after various doses of chlorpromazine had been injected intravenously.

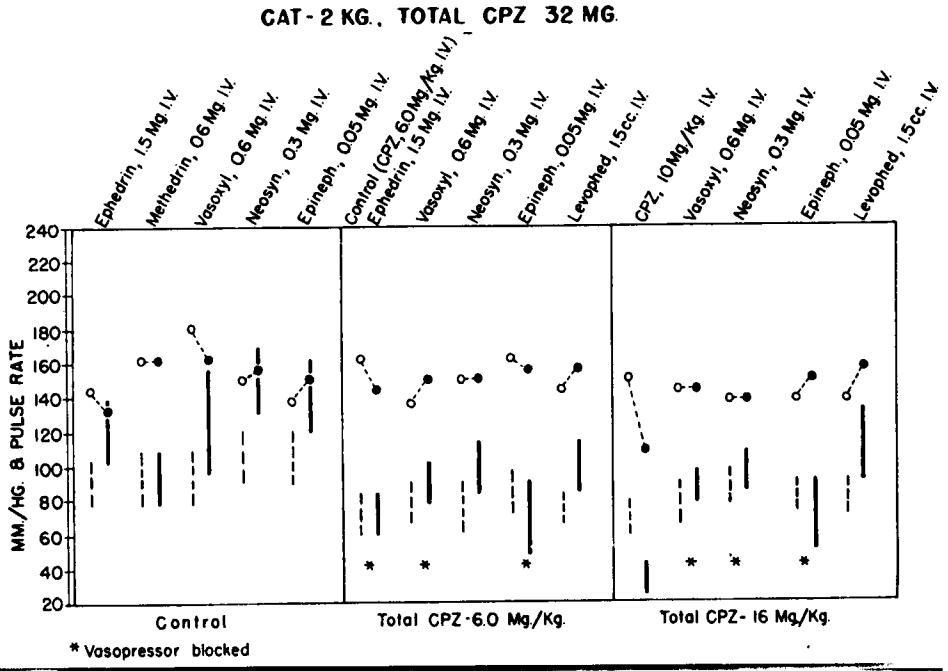

FIG. 4. Showing the hypotensive effect and sympatholytic action of chlorpromazine in the cat. Interrupted lines represent "control" blood pressures, continuous lines the effect of chlorpromazine and vasopressor drugs.

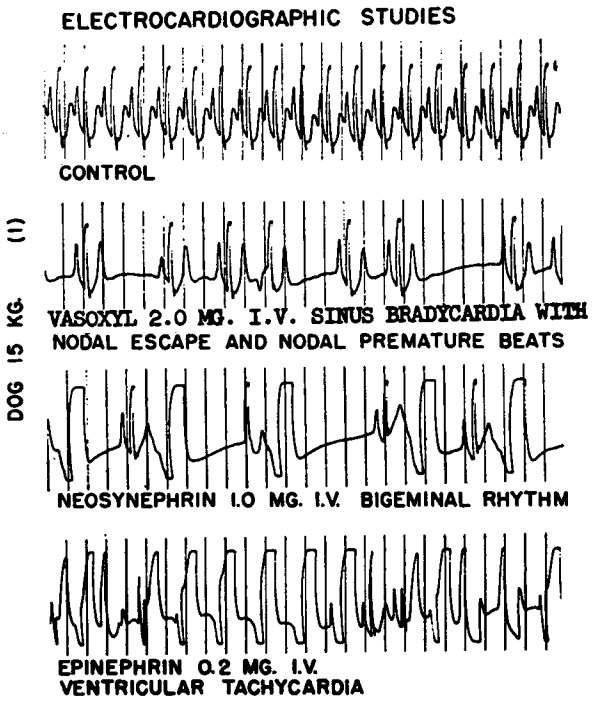

FIG. 5 (a).

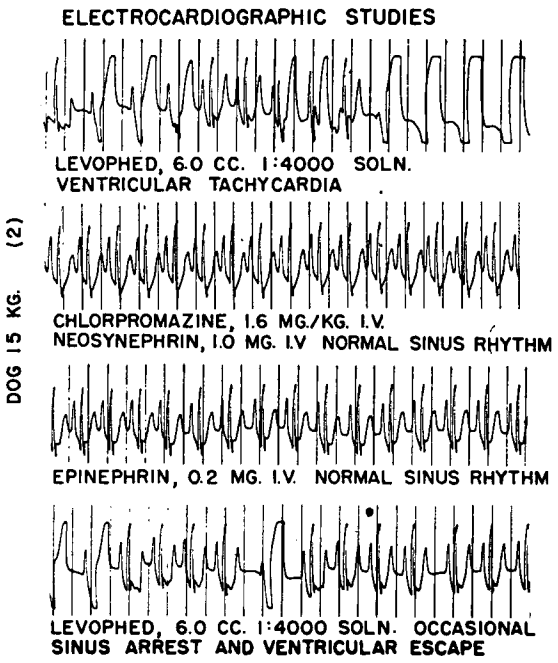

FIG. 5 (b).

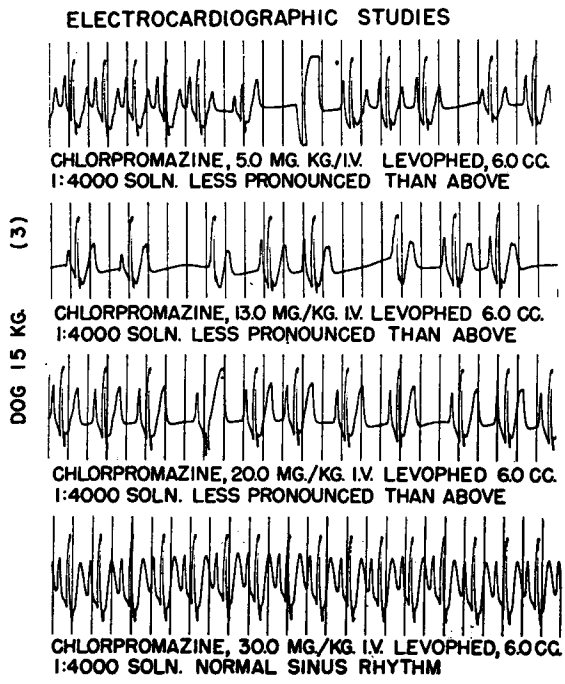

FIG. 5. (a, b, c). Showing the protective action of chlorpromazine in the dog against cardiac arrhythmias instigated by sympathomimetic amines.

In this group of experiments 1 dog developed ventricular fibrillation and died during the "control" administration of trichloroethylene. A second animal died in the same manner with the "control" injection of epinephrine. In the other 3 dogs the severe trichloroethylene-epinephrine arrhythmias were prevented or modified by chlorpromazine in dosages of 2.5, 3.0 and 4.6 mg. per kg. (fig. 6).

In one animal this protective action was found to last for 7 hours after the last injection of chlorpromazine. These findings again emphasize the adrenergic blocking properties of the drug (4, 7).

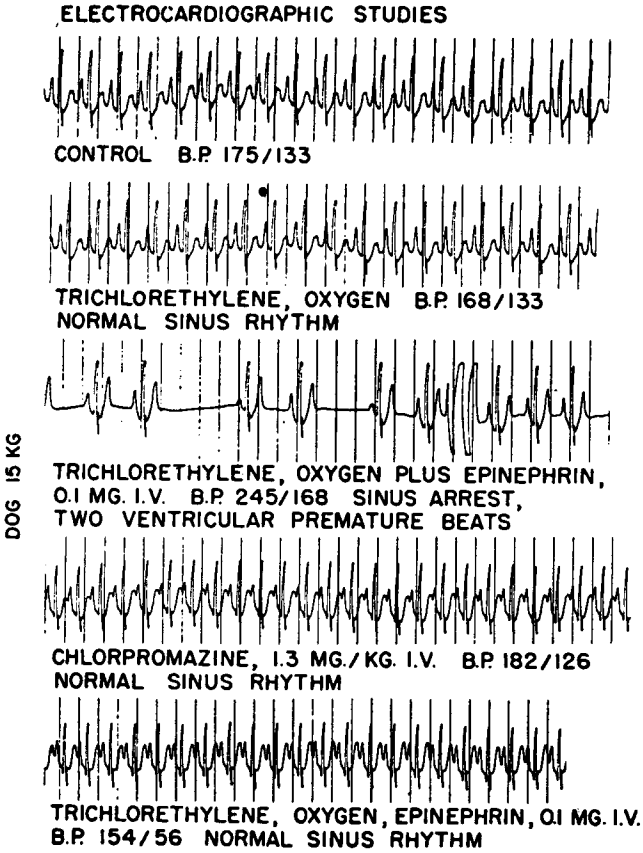

FIG. 6. Showing protection afforded by chlorpromazine in the dog against trichlorethylene-epinephrine arrhythmias.

Chlorpromazine and Direct Stimulation of Vagus Nerve. In 3 cats the vagus nerve was dissected out in the neck and preparation made for direct electrical stimulation. "Control" stimulation elicited hypotension and bradycardia in the animal (fig. 7). Employing a constant electrical stimulus, it was found that the hypotensive effect was prevented when doses of chlorpromazine of 18, 6 and 2.5 mg. per kg. had been administered intravenously. Bradycardia was not prevented

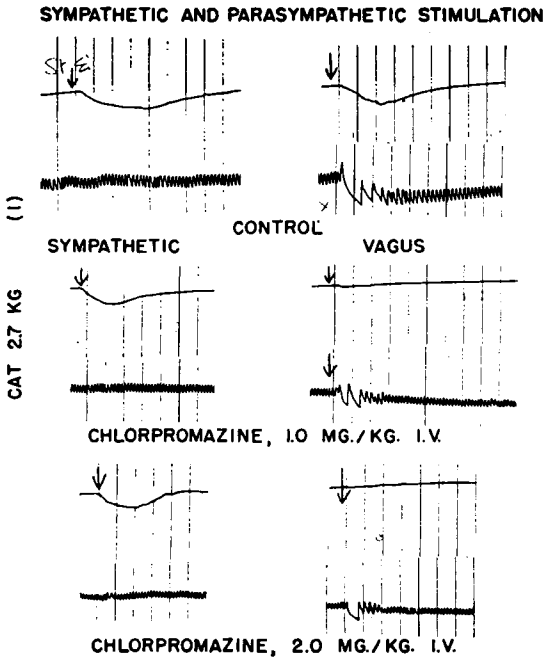

FIG. 7 (a).

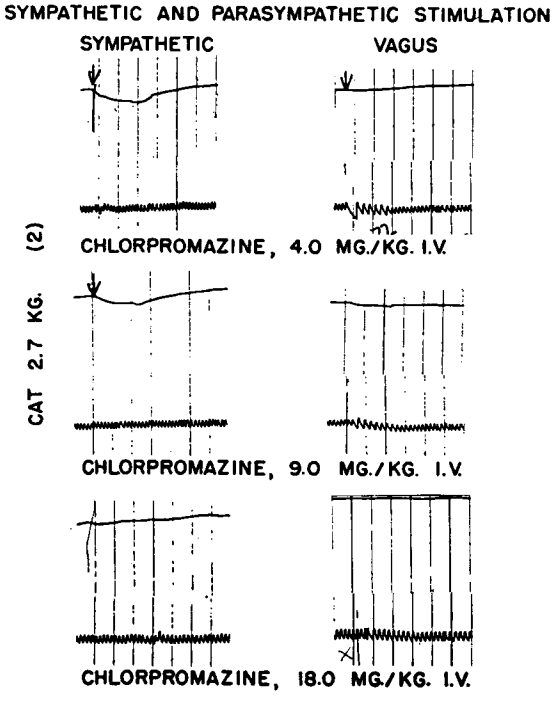

FIG. 7. (a, b). Showing (*a*) response of the nictitating membrane of the cat to preganglionic electrical stimulation, and (*b*) the fall in blood pressure and bradycardia associated with direct electrical stimulation of the vagus nerve. Note the failure of chlorpromazine to alter responses until high doses were administered.

after maximum doses of 18 and 6 mg. These latter amounts of chlorpromazine are considerably in excess of the "therapeutic" range. Similar minimal effects on vagus nerve transmission have been noted previously (3).

Effect of Chlorpromazine on Ganglionic Transmission. The cervical sympathetic chain was dissected out in 3 cats and prepared for direct electrical stimulation. The nictitating membrane of the animal's eye was attached to the rubber membrane of a drum by means of fine black silk. The drum itself was connected by copper tubing to a Statham transducer, so that variations of pressure within the drum, caused by movements of the nictitating membrane, could be recorded on the Grass machine.

"Control" stimulation of preganglionic sympathetic fibers elicited, through transfer across the superior cervical ganglion, a contraction of the nictitating membrane (fig. 7). Such ganglionic transmission was

TABLE 2

CHLORPROMAZINE AND OXYGEN CONSUMPTION

Dog	Weight	O_2 Con. (cc.'s per min.) Before CPZ	First Dose CPZ (mgm./kg.)	O_2 Con. (cc.'s per min.) After CPZ	Difference	Total Dose CPZ (mgm./kg.)	O_2 Con. (cc.'s per min.) After Total CPZ	Difference
1	11.3	65.3	2.5	65.3	0%	10	57.1	−13%
2	16.8	121	3	130	+ 8%	13	150	+20%
3	10	57.1	2.5	42.3	−26%	7.5	34.6	−40%
4	11.3	90	2.5	69.6	−23%	10	61.5	−42%
5	16.8	190	4.5	175	− 8%	13	1.5	−40%
6	10	115	2	71.4	−38%	4	73	−37%
7	8.6	75	2	79	+ 5%	7	69	− 8%

The oxygen consumption (in cc. per min.) of seven dogs with increasing doses of chlorpromazine.

not altered by chlorpromazine in dosages of 4.0 and 2.5 mg. per kg. When the total amount of chlorpromazine administered reached 9 and 18 mg. per kg., ganglionic transmission was attenuated but still present. It is apparent from this experiment that moderate dosages of chlorpromazine have little effect on ganglionic transmission in the sympathetic nervous system. These findings are not in keeping with those reported by Decourt (11).

Oxygen Consumption and Chlorpromazine. Seven dogs were anesthetized with pentobarbital, 25 mg. per kg. intravenously, and then intubated with a cuffed endotracheal tube in order to prevent leaking of gas about the tube. After waiting sixty minutes for the initial effect of the barbiturate to dissipate, each animal was connected to the Benedict-Roth spirometer and the oxygen consumption measured intermittently for fifteen minute periods. When the oxygen consumption had stabilized, as indicated by three similar successive determinations,

chlorpromazine was injected intravenously in progressively increasing amounts. After each chlorpromazine administration, oxygen consumption was measured for at least three 15 minute periods. The findings are shown in table 2.

Observations during this experiment indicated that, following chlorpromazine injection, the respiratory rate of the animals slowed to some extent, with a variable increase in tidal volume. In 3 animals the change in oxygen consumption, following even large doses of chlorpromazine, was equivocal, whereas in the other 4 dogs there was a definite tendency for the oxygen consumption to decrease with chlorpromazine administration. These results are not sufficiently numerous or unidirectional to be of over-all significance. It is noted that, in man, there is evidence to suggest that chlorpromazine in "therapeutic" amounts does not interfere with oxygen consumption (12).

Anti-Emetic Action of Chlorpromazine. Experimental vomiting was produced in 12 dogs, ranging in weight from 10 to 15 kg., by the

TABLE 3

EXPERIMENTAL VOMITING IN DOGS PRODUCED BY APOMORPHINE, 1.0 MG. PER KG.

	Controls	Chlorpromazine (1.0 mg. per kg.)
Dogs	12	12
Total times vomiting	71	24
Reduction in vomiting		66.2%

Effect of chlorpromazine, 1 mg. per kilogram, on vomiting induced by apomorphine 1.0 mg. (subcutaneously injected) in dogs.

subcutaneous injection of apomorphine, 1 mg. Notations were made of the total number of times these animals vomited. Three days later the experiment was repeated on the same animals under similar conditions, this time the animals being given chlorpromazine, 1 mg. per kg., intramuscularly, prior to the apomorphine. To control the test further, apomorphine alone was repeated in another three days. The results, including an average of the two controls, are shown in table 3. When the dogs were protected by chlorpromazine, they vomited 66.2 per cent fewer times than in the control periods. This reduction is of statistical significance ($p > 0.05$) (13) and is in keeping with other observations (14).

CLINICAL INVESTIGATIONS

The effects of chlorpromazine, given either intramuscularly or intravenously in dosages varying between 25 and 50 mg., have been studied in 185 patients (table 4). The drug was given in the preanesthetic period or during the course of operation. Intramuscular injection of the drug, in a concentration of 25 mg. per cc., caused in

most patients a painful, burning sensation which lasted from three to five minutes. No residual painful areas were reported. Intravenous administration was at the rate of 5 mg. per minute over a period of five minutes. A few patients complained of pain over the cannulated vein during the injection. No residual effects were noted.

Observations made in these 185 cases were as follows:

Effect on Sensorium. In 65 cases chlorpromazine was administered in association with local, regional, or spinal analgesia. All of these patients had previously received a narcotic, usually meperidine. In the majority of patients, chlorpromazine appeared to relieve tension, cause relaxation, and to "disconnect" the patient from the relative importance he had previously attached to the situation. Some patients would sleep through the entire procedure whereas others would open their eyes occasionally and appear oriented as to time and place. Deep unconsciousness was not observed. The action of chlorpromazine appeared to be less productive of stupor than did intravenous pentobarbital or meperidine. Considerable variation in degree of response to the drug existed. The exact effect on any one patient was not predictable.

TABLE 4

CHLORPROMAZINE—CLINICAL EVALUATION

Patients	CPZ	No response to Vasopressors	Hypotension (40 mm. +)
57	25 (I.M.)	6 (10%)	9 (15%)
64	35 (I.M.)	8 (12%)	10 (15%)
34	50 (I.M.)	3 (9%)	1 (3%)
30	25 (I.V.)	2 (6%)	4 (13%)

Summary of hypotensive and sympatholytic complication in 185 patients administered chlorpromazine.

Effect on Vital Functions. The administration of chlorpromazine in the doses mentioned had no noticeable effect on respiratory rate or volume. Likewise the pulse rate showed no marked fluctuations in either direction which could be attributed to the drug. In 24, or 13 per cent of the patients, a decrease in blood pressure of 40 mm. of mercury systolic or more occurred within fifteen minutes of the time chlorpromazine was administered. Several of these patients remained relatively hypotensive for as long as six hours after injection of the drug. None showed clinical evidence of the shock syndrome. The extremities were warm and dry and the pulse rate remained within normal limits.

Response to Injection of Sympathomimetic Drugs. In 20, or 10.8 per cent, of the patients studied the injection of vasopressor drugs, when hypotension was present following chlorpromazine administra-

tion, failed to re-establish normotensive levels. The drugs whose action appeared to be blocked included desoxyephedrine, methoxamine and epinephrine.

The patient whose anesthetic record is shown in figure 8 underwent excision of a hemangioma of the leg under general anesthesia. The normal, expected effect of desoxyephedrine is shown at point (1). At (2), the administration of chlorpromazine, 25 mg. intravenously, reduced the blood pressure to near its previous level. At (7) injection of desoxyephedrine produced no elevation in blood pressure. How-

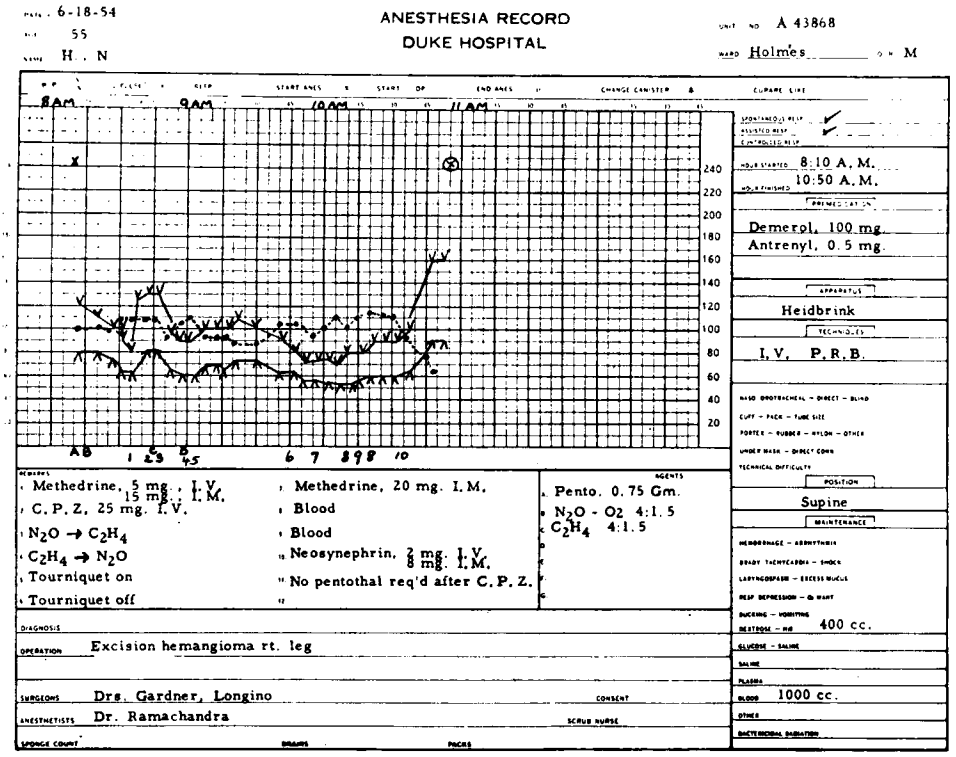

FIG. 8. Anesthetic record of a 55 year old patient under general anesthesia. Note at (1) the effect of desoxyephedrine; at (2) intravenous injection of chlorpromazine; at (7) desoxyephedrine not effective in raising blood pressure following chlorpromazine, and at (10) good reaction of patient to neosynephrine.

ever, thirty minutes later, at (10), neosynephrine, 10 mg., produced the anticipated elevation in pressure as well as bradycardia. Apparently the dose of chlorpromazine was not sufficient to block the action of this more potent vasopressor. A similar blocking or modifying action attributed to chlorpromazine has been shown recently in humans towards epinephrine and levo-arterenol (8).

Potentiation of Anesthetic Drugs. General anesthesia was given to 120 of the patients studied. In a certain number of these, the

distinct clinical impression was formed that the injection of chlorpromazine reduced the amounts of anesthetic drugs which were required. For example, the patient in figure 8 required Pentothal® sodium, 750 mg., during the first thirty minutes of the procedure. At this point chlorpromazine was given and, for the remaining two hours of surgery, no more Pentothal was indicated. Maintenance for this period of time on nitrous oxide or ethylene alone is not the usual course of events in this hospital. More objective evidence of the potentiating action of chlorpromazine has been published recently (15).

Contrary to the above impressions, there were a number of patients in whom it was believed that chlorpromazine did not contribute in any demonstrable manner to the state of anesthesia. This belief perhaps again emphasizes the unpredictable effect of the drug on any one patient.

Anti-Emetic Action. In this more or less acute study, the effects of chlorpromazine on the incidence of postoperative vomiting were not followed. This property of the drug has been described previously (16, 17). However, 6 patients who became nauseated and retched during spinal analgesia were comfortable within five minutes after the administration of chlorpromazine intravenously. These patients became drowsy and relaxed. One other patient became nauseated after the injection of chlorpromazine.

Effect on Reflex Activity. In the patients to whom chlorpromazine was administered prior to general anesthesia, clinical impression leaves one with the belief that reflex respiratory reactions, such as coughing, breath-holding and laryngospasm, particularly during the induction phase, were reduced in intensity. This is exemplified in nitrous oxide, oxygen, ether inductions. Even neophyte anesthesiologists can, with the aid of chlorpromazine, accomplish such inductions without the patient missing a breath!

Adjunct to Induced Hypotension. In the rather specialized field of neurosurgery and induced hypotension it has been found difficult in a certain few patients to produce the degree of hypotension required by ganglionic blocking drugs alone. However, the subsequent administration of chlorpromazine, 25 mg. intravenously, produced a stable satisfactory hypotension. In 5 such cases chlorpromazine has been useful in this way, and in one Regitin, an adrenolytic compound, has been of value.

It is suggested that induced hypotension may be inadequate in some instances because of some adrenalin-like substance acting directly on the arterioles. The constricting action of such a compound may be overcome by such drugs as chlorpromazine.

DISCUSSION

Several factors of interest emerge from this laboratory and clinical study: First is the apparent unpredictability of "therapeutic" doses of

chlorpromazine, both in the animal and the human. Since one of the principal actions of this drug appears to be on the sympathetic nervous system, perhaps this variation in action is due less to the properties of the drug than to the degree of sympathetic tone which may exist in the patient at the time of administration.

It is evident that chlorpromazine is capable of producing a hypotension, the degree of which is to some extent dependent on the amount administered. It is also clear that this drug will prevent or modify both the cardiac and peripheral actions of even the most potent sympathomimetic amines. In all probability the effect on vascular dynamics is due principally to the peripheral arteriolar vasodilating action of the drug, although a recent report suggests the possibility of a central action also (8). This vasodilating action competes successfully with the vasoconstricting potentialities of several of the less potent vasopressor drugs. It is interesting that chlorpromazine has least effect on the action of levo-arterenol, which is believed to be the physiological hormone of sympathetic transmission.

The protective action of chlorpromazine against the cardiac arrhythmias induced by the sympathomimetic amines is difficult to explain. It may be that the arrhythmias are secondary to the hypertension associated normally with the injection of a vasopressor; or the chlorpromazine may depress directly the irritability of myocardial tissues.

Recognition of the fact that chlorpromazine not only can produce hypotension, but will oppose its restitution to normal by modifying the action of vasopressor drugs, leads to a word of caution regarding its indiscriminate use. This drug should be administered parenterally only under close medical supervision and to those patients in whom a marked fall in blood pressure would not be a critical omen. If an emergency should arise, levo-arterenol or neosynephrine would prove of most benefit in restoring blood pressure.

The protective action accorded the heart by chlorpromazine during exposure to hydrocarbon-epinephrine combinations is of some importance clinically. Since cyclopropane, trichloroethylene and chloroform produce some of their conduction disturbances as a result of increasing vagal tone, it is unlikely that chlorpromazine, having little effect on vagal transmission, would interrupt this sequence of events. However, these hydrocarbons, particularly in the presence of epinephrine, increase myocardial irritability to the point at times of interrupting cardiac function completely. Apparently by nullifying the expected epinephrine effect, chlorpromazine can prevent or modify these dangerous arrhythmias. The clinical possibilities of chlorpromazine in this regard are obvious.

The work reported herein does not indicate the specific sites of action of chlorpromazine. From its effect on the sensorium, one can certainly affirm a central site of action which is probably not pri-

marily cortical. The investigations of the autonomic nervous system show a blocking of sympathetic impulses with small doses of chlorpromazine, but no blocking of parasympathetic impulses until high doses are used. The site where sympathetic impulses are blocked has been shown to be not at the ganglionic junction. The exact place of action, at present unknown, is most likely to be peripheral but it may be in part central (8).

SUMMARY

Chlorpromazine was studied in the laboratory and clinically.

1. Progressively increasing doses of chlorpromazine were given to dogs, rabbits and cats, in order to determine what were "well-tolerated" amounts and when the "toxic" or physiologically abnormal range was entered.

2. Ten rabbits and 30 rats were given chlorpromazine regularly for 3 months to determine the chronic toxicity of the drug. The animals were autopsied after the performance of liver and kidney function tests and gross and microscopic studies were made of the tissues.

3. In 5 dogs and 5 cats the action of chlorpromazine was determined when the animals received sympathomimetic amines. Various degrees of sympatholytic effects were noted.

4. The protective action of chlorpromazine against trichloroethylene-epinephrine arrhythmias was demonstrated in 5 dogs.

5. Only after relatively large doses of chlorpromazine was the cardiac effect of direct vagal nerve stimulation attenuated.

6. In 3 cats it was shown that relatively large doses of chlorpromazine had little effect on ganglionic transmission in the sympathetic nervous system.

7. Oxygen consumption in 7 dogs receiving chlorpromazine showed an overall tendency to decrease, but this change was not considered sufficiently constant to be significant.

8. Experimental vomiting produced by apomorphine in 12 dogs was reduced 66.2 per cent by the prior administration of chlorpromazine.

9. In the human, chlorpromazine, intravenously or intramuscularly, appeared to relieve tension, cause relaxation and to "disconnect" the patient.

10. In 13 per cent of the patients studied, the fall in blood pressure was more than 40 mm. of mercury systolic within 15 minutes of chlorpromazine administration.

11. Of the 185 patients studied, 20 failed to respond as expected to the administration of vasopressor drugs after the injection of chlorpromazine.

12. Clinical impression suggests that in some cases chlorpromazine may potentiate the action of anesthetic drugs.

13. The anti-emetic action of chlorpromazine was confirmed in a few cases.

14. The possibility of chlorpromazine reducing reflex activity, especially during induction, was noted.

15. The use of chlorpromazine as an adjunct to ganglionic blocking drugs was suggested.

16. The unpredictability of action of clinical doses of chlorpromazine was emphasized.

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