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SOME PHARMACOLOGICAL PROPERTIES OF THIOPROPERAZINE AND THEIR MODIFICATION BY ANTI-PARKINSONIAN DRUGS

BY

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The pharmacological properties of a phenothiazine derivative thioproperazine have been compared with those of chlorpromazine, and the modifications by some anti-Parkinsonian drugs of its actions on the central nervous system have been studied. Thioproperazine was less potent than chlorpromazine in lowering blood pressure and antagonizing adrenaline in the cat, in depressing respiratory rate in the rabbit, in producing hypothermia and analgesia and in reducing the minimum anaesthetic dose of hexobarbitone in mice, and in protecting rats from convulsions induced by tryptamine. It was roughly equipotent to chlorpromazine in reducing locomotor activity of mice. Thioproperazine was more potent than chlorpromazine in protecting grouped mice from the acute toxicity of dexamphetamine, in preventing the acute behavioural disturbances produced by dexamphetamine in the rat, in producing a state of experimental catatonia in the rat and in preventing the emetic action of apomorphine in the dog. Hyoscine, benztropine or promethazine greatly reduced the ability of thioproperazine to prevent behavioural changes due to dexamphetamine in the rat and also abolished symptoms of experimental catatonia produced by thioproperazine. In contrast, the antiapomorphine activity of thioproperazine in the dog was not reduced to any extent by hyoscine or benztropine.

Since the initial studies on the use of chlorpromazine in the management of some psychiatric states, many phenothiazine derivatives have been synthesized and examined both in animals and in man for their actions on the central nervous system (Friend, 1960 ; Domino, 1962 ; Schenker & Herbst, 1963). Chlorpromazine may in many respects be considered the parent of these drugs and has been studied much more extensively than any of its subsequent analogues. In view of the numerous and potent pharmacological and biochemical actions of chlorpromazine, it is difficult to reach any conclusion as to which of these properties is related to its clinically useful psychiatric properties. This paper compares the pharmacological properties of chlorpromazine [2-chloro-10-(3-dimethylaminopropyl)phenothiazine] with those of an analogue, thioproperazine {2-dimethylsulphamoyl-10-[3-(4-methyl-1-piperazin-1-yl)propyl]phenothiazine which, in some respects, appears to have more specific central actions. Thioproperazine has been used clinically, primarily in the treatment of mania (Leitch, Cullen & Robertson, 1962 ; Lingjaerde, 1963) and of schizophrenia (Delay, Deniker, Ropert, Barande & Eurieult, 1958 ; Denham & Carrick, 1961), both on the continent and in this country, and a symposium on the

psychiatric actions of thioproperazine (Symposium sur le Majeptil, 1962) has been published. These reports indicate that thioproperazine is effective in mania and schizophrenia at lower doses than chlorpromazine.

One of the clinical disadvantages of thioproperazine and some related phenothiazines (trifluoperazine, prochlorperazine, etc.) is that they readily produce neurological disturbances including muscular rigidity, akinesia and tremor. These symptoms have been studied in detail (Delay, Deniker, Ropert, Beek, Barande & Eurieult, 1959; Delay & Deniker, 1961) and resemble Parkinsonism of the post-encephalitic type. These clinical disturbances can be controlled by drugs with anti-Parkinsonian properties, such as, for example, benztropine, promethazine and hyoscine. The pharmacological interaction in laboratory animals between anti-Parkinsonian drugs and chlorpromazine or thioproperazine does not appear to have been studied in any detail, and in view of the clinical use of such associations we considered such a pharmacological examination important. We have, therefore, in addition to comparing the pharmacological properties of thioproperazine with chlorpromazine, studied the effects of anti-Parkinsonian drugs on some of the central actions of thioproperazine. Some of the pharmacological properties of thioproperazine were initially described by Courvoisier, Ducrot, Fournel & Julou (1958).

METHODS

Rat phrenic nerve-diaphragm preparation

The preparation described by Bülbring (1946) was used in a 100 ml. organ-bath. The diaphragm was stimulated alternately directly and indirectly through the phrenic nerve. Drugs, in a volume not exceeding 1 ml. were added to the organ-bath and allowed to act for 5 min. The concentrations (μg/ml.) of the drugs required to inhibit contractions of the preparation to both direct and indirect stimulation were determined.

Experiments in mice

Albino mice, 18 to 25 g in weight and of either sex, were used, except where otherwise specified. Groups of ten animals were used for each dose, and the drugs were administered subcutaneously.

Acute toxicity. The acute toxicities in mice of thioproperazine and chlorpromazine were determined following subcutaneous administration to mice kept at a room temperature of 18 to 20° C. Deaths were recorded over a period of 5 days.

Hypothermia. Rectal temperatures of mice were measured using a type F thermistor inserted about 1 cm into the rectum. The thermistor formed part of a bridge circuit and the temperature was read from a microammeter. Temperature readings were taken periodically before and after the administration of the drugs. The ambient temperature was 18 to 20° C. The maximal hypothermia which occurred 1 to 2 hr after administration of various doses of drugs was determined and from a dose/response curve the dose (effective dose) required to produce a drop in temperature of 5° C was estimated.

Locomotor activity. Locomotor activity was measured by the interruption of a beam of light using a method similar to that described by Dews (1953). The dose of compound (ED50) which, when administered 1 hr before the test, reduced locomotor activity by 50% was determined.

Analgesic activity. Analgesic activity was measured by the method of Reinhard & DeBeer as described by Burn, Finney & Goodwin (1950). The percentage of mice showing analgesia at intervals up to 6 hr after administration of graded doses of the test drug was measured.

From a dose/response curve the effective dose (ED50) was determined at the optimal time (1 to 2 hr) after injection.

Reduction of the minimal anaesthetic dose of hexobarbitone. The minimal anaesthetic dose of hexobarbitone in mice was determined by injecting intravenously hexobarbitone sodium (at the rate of 0.05 ml. of a 2 mg/ml. solution in 10 sec) until the righting reflex was abolished for a 10 sec period. This minimal dose was determined in control animals and in animals treated 1 hr previously with graded doses of the test compounds. The dose of compound (ED50) required to reduce the minimal anaesthetic dose of hexobarbitone by 50% was determined from a dose/response curve.

Protection from dexamphetamine toxicity. Male mice were kept in groups of ten at an environmental temperature of $26 \pm 1^{\circ}$ C for at least 1 hr before the experiment. Test drugs were administered subcutaneously 1 hr before the injection of dexamphetamine in a dose (20 to 40 mg/kg) sufficient to cause about 90% mortality in the controls. Deaths were recorded up to 18 hr after injection of dexamphetamine and the percentage protection afforded by the test drug was determined. From a plot of percentage protection against log dose, the dose (ED50) affording 50% protection was determined.

Experiments in rats

Effect of dexamphetamine on behaviour. Rats were injected intraperitoneally with the test compound and 4 hr later dexamphetamine (10 mg/kg) was administered intraperitoneally. The presence or absence of the characteristic symptoms of agitation, tremor, exophthalmos and head swaying, produced by dexamphetamine under these conditions, was assessed quantally by four observers who were not aware of the drug treatment the rats had received. The results of these observations were then averaged and expressed as a percentage of the maximal possible score. The effects of various graded doses were determined, a dose/response curve was plotted, and the dose of compound (ED50) which reduced the agitation score to 50% of the maximum was found. Four rats per dose for each experiment were used.

Experimental catatonia. The test drug was given intraperitoneally. After 4 hr, tests for the maintenance of abnormal posture were made according to the method described by Wirth, Gosswald, Horlein, Risse & Kreiskott (1958). Scores for the degree of experimental catatonia at various doses of thioproperazine or chlorpromazine were determined and the dose (ED50) required to produce 50% of the maximal score was determined. Groups of four rats at each dose were used in each experiment.

Protection from tryptamine-convulsions. Test drugs in graded doses were given to groups of young (30 to 40 g) rats (four rats per group). After 4 hr the animals were given intravenously 30 mg/kg of tryptamine. The number of animals showing the characteristic clonic convulsive movements of the forelimbs was recorded. The dose of test drug (ED50) which reduced the incidence of convulsion by 50% of that in control animals was determined from the dose/response curve.

Experiments in rabbits

Respiratory depression in the conscious rabbit. This was measured by using animals restrained in a stock, using three animals per dose. The respiratory rate was counted and the mean of three observations at intervals of 10 min was taken as the control rate. The test drugs were infused into a marginal ear vein. After 30 min, the respiratory rate was again counted and this was expressed as a percentage reduction in the control respiratory rate. The effects of graded doses were determined. No attempt was made to record depth of respiration.

Experiments in cats

Cats were anaesthetized with chloralose (60 to 80 mg/kg, intravenously). The blood pressure was recorded by a mercury manometer from a femoral or carotid artery and drugs

were administered through a polyethylene cannula inserted into a femoral vein. Respiration was recorded with a tambour and valve (Gaddum, 1941) connected to the trachea.

Experiments on spinal reflexes were carried out in cats anaesthetized with chloralose. The patellar reflex was elicited by means of a mechanical hammer as described by Schweitzer & Wright (1937). The flexor reflex was elicited by electrical stimulation of the central end of the cut tibial nerve, whilst recording twitches of the tibialis anterior muscle using a spring myograph. Bipolar platinum stimulating electrodes were placed on the tibial nerve about 2 cm distal to the point where the tibial and peroneal nerves separate. The stimuli consisted of rectangular pulses of 0.5 msec duration delivered at a rate of 6 shocks/min, the voltage of the pulses being adjusted to give responses that were about 90% of the maximal.

Neuromuscular transmission was studied by recording from a spring myograph twitches of the tibialis anterior muscle produced by electrical stimulation of the peripheral end of the cut sciatic nerve. The stimuli consisted of rectangular pulses of 0.5 msec duration delivered at a rate of 1 shock/sec. The voltage was adjusted to give maximal twitches.

Experiments in dogs

The ability of thioproperazine or chlorpromazine to protect dogs from the emetic action of apomorphine was determined in a group of six animals which were used twice weekly with alternately a 3 and 4 day interval between experiments. In the first experiment a challenge dose of 0.1 mg/kg of apomorphine was administered subcutaneously and the number of retches (20 to 40) occurring in the next hour was recorded. After 3 to 4 days the dogs were injected subcutaneously with the test compound and 1 hr later the challenge dose of apormorphine was again given and the number of retches recorded. After 3 to 4 days the challenge dose of apomorphine alone was again administered. The percentage reduction in the number of retches produced by the treatment was determined from the number of retches on the day of treatment compared with the control values in the experiment immediately before and after. From a dose/response curve the dose of compound (ED50) reducing the number of retches by 50% of the control was determined.

Drugs

Chlorpromazine, promethazine, methotrimeprazine, phenoxybenzamine, phentolamine, tryptamine, codeine, adrenaline, bulbocapnine and apomorphine were used as the hydrochlorides. Thioproperazine and prochlorperazine were used as the dimethanesulphonates, and 9260 R.P. {2-dimethylsulphamoyl-10-[3-(4-methanesulphonylpiperazin-1-yl)propyl]phenothiazine and benztropine as the methanesulphonates. Other drugs used were hyoscine hydrobromide, trifluoperazine dihydrochloride, dexamphetamine sulphate, acetylcholine chloride, nicotine bitartrate and hexobarbitone sodium. All doses are expressed in terms of the salts which were dissolved in distilled water or 0.9% saline for injection.

RESULTS

Effects on blood pressure and respiration of the anaesthetized cat. Thioproperazine was weaker than chlorpromazine in lowering the blood pressure in the cat anaesthetized with chloralose (Table 1). Doses of 1 to 4 mg/kg of thioproperazine produced only transient changes in blood pressure whilst a similar dose of chlorpromazine usually produced a fall of 10 to 20 mm Hg in blood pressure. With these doses neither compound produced any marked change in respiration of the anaesthetized animal. Thioproperazine was a considerably weaker antagonist than chlorpromazine of the pressor responses to adrenaline or noradrenaline on blood pressure. Thus, whereas chlorpromazine in doses of 1 mg/kg intravenously produced 80 or 100% reduction in the height of the pressor response to intravenous injections of adrenaline and 40 to 60% in that to noradrenaline, the same dose of

TABLE 1

COMPARISON OF THE EFFECTS OF THIOPROPERAZINE AND CHLORPROMAZINE ON THE ARTERIAL PRESSURE, RESPIRATION AND PRESSOR RESPONSE TO ADRENALINE IN THE CAT ANAESTHETIZED WITH CHLORALOSE

Thioproperazine and chlorpromazine were given by intravenous infusion over 10 to 20 min. Figures in brackets refer to the numbers of experiments. The adrenaline was given intravenously in a dose of 10 μg/kg

		Effect on		
Drug	Dose (mg/kg)	Mean fall in arterial pressure (mm Hg)	Rate and depth of respiration	Pressor response to adrenaline
Thioproperazine	1	5 (6)	No change	10–20% reduction (4)
	4	8 (5)	No change	50% reduction (3)
	16	13 (5)	No change	Abolition (3)
	20	19 (5)	Transient 5% increase in depth	Reversal returning to pressor response after 2 hr (5 and 2)
	60	28 (2)		
Chlorpromazine	1	14 (8)	No change	80–100% reduction (4)
	1·5	18 (3)	No change	Abolition (3)
	4	12 (7)	Slight increase in rate and depth	Reversal (3 and 3)
	16	23 (7)		

thioproperazine produced little effect on the response to either drug and doses between 16 and 20 mg/kg were required to abolish the response to adrenaline.

Effects on neuromuscular transmission and spinal reflexes. On the isolated rat phrenic nerve-diaphragm preparation, thioproperazine had approximately one-seventh the potency of chlorpromazine in blocking neuromuscular transmission and in inhibiting the effects of direct stimulation (Table 2).

TABLE 2

A COMPARISON OF CHLORPROMAZINE AND THIOPROPERAZINE IN INHIBITING CONTRACTIONS OF RAT ISOLATED PHRENIC NERVE DIAPHRAGM PREPARATIONS STIMULATED DIRECTLY AND INDIRECTLY

Figures in brackets refer to numbers of experiments. The drugs were left in the organ-bath for 5 min

	Concentration (μg/ml.) to block contractions due to stimulations of	
Drug	Phrenic nerve	Diaphragm muscle
Thioproperazine	118 (8)	>160 (8)
Chlorpromazine	15 (5)	30 (5)

In the cat anaesthetized with chloralose neither chlorpromazine (1 to 16 mg/kg) nor thioproperazine (1 to 16 mg/kg) given by slow intravenous injection over 5 to 10 min had any significant effect on neuromuscular transmission of the sciatic nerve tibialis anterior preparation or on the flexor or patellar reflexes.

Respiratory depression in the conscious rabbit. Results showing the respiratory depressant action of increasing doses of thioproperazine, chlorpromazine or codeine in conscious rabbits are set out in Fig. 1, where each point represents the mean respiratory depression 30 min after administration of the drug. Thioproperazine was considerably weaker than either codeine or chlorpromazine in decreasing the rate of respiration of the conscious rabbit.

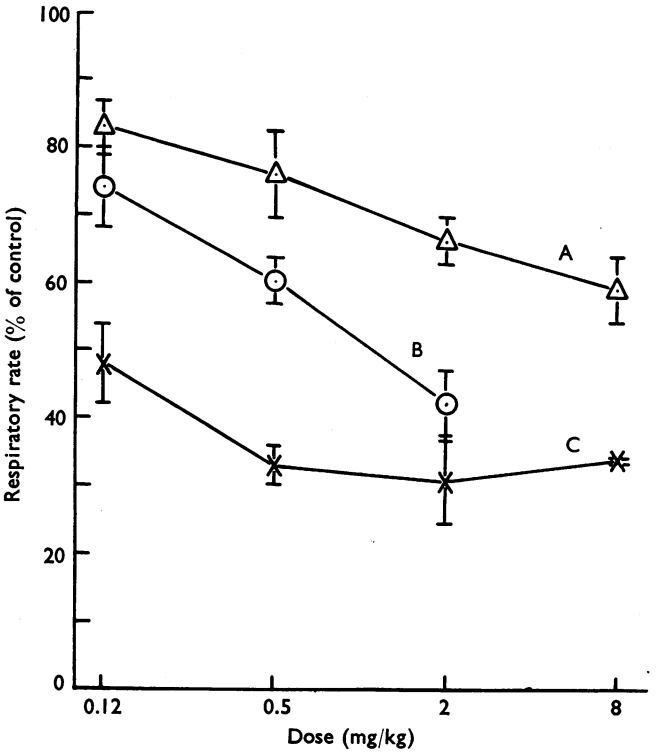


Fig. 1. The respiratory depressant action of thioproperazine compared with those of chlorpromazine and codeine in the conscious rabbit. The compounds were infused into a marginal ear vein to groups of three animals per dose. The respiratory rate 30 min after the drug administration was determined and expressed as a percentage of the control rate. The points give mean values and the vertical lines the standard deviations. A, thioproperazine ; B, codeine ; C, chlorpromazine. Ordinate : respiratory rate expressed as percentage of control rate ; abscissa : dose of compound (mg/kg).

Actions on the central nervous system. The effects of thioproperazine or chlorpromazine in various tests measuring central nervous activity are set out in Table 3. From the effective doses (see Methods) of the drugs in the individual tests the following points emerge. Firstly, in tests which assess the ability of the drug to reduce the minimal anaesthetic dose of hexobarbitone, to produce hypothermia, to produce analgesia, or to protect rats from the convulsant action of tryptamine, thioproperazine was one-sixtieth to one-twentieth as potent as chlorpromazine. Judged by their ability to reduce spontaneous locomotor activity in mice, the two drugs had similar potency. However, thioproperazine was considerably more potent than chlorpromazine in protecting groups of mice from the acute toxic effects of dexamphetamine, and in inhibiting the agitation and disorientation produced by a high dose of dexamphetamine in the rat. Dose/response curves of thioproperazine and chlorpromazine in protecting rats from the central actions of dexamphetamine are shown in Fig. 2. Phenoxybenzamine and phentolamine (1 to 20 mg/kg) were not effective in protecting rats against dexamphetamine in this test. These latter

TABLE 3

EFFECTIVE DOSES OF THIOPROPERAZINE AND CHLORPROMAZINE IN VARIOUS TESTS OF CENTRAL NERVOUS ACTIVITY

Values quoted are the mean effective doses (for definitions see Methods) with standard deviations. Figures in brackets refer to the numbers of experiments. S.c. = subcutaneous ; I.p. = intraperitoneal.

Test	Species	Route	Effective dose (mg/kg)	
			Thioproperazine	Chlorpromazine
Reduction of minimal anaesthetic dose of hexobarbitone	Mouse	S.c.	>80 (2)	2·5±1 (3)
Hypothermia	Mouse	S.c.	100±25 (2)	1·5±0·2 (3)
Analgesia	Mouse	S.c.	>1,000 (2)	15±5 (3)
Reduction in locomotor activity	Mouse	S.c.	6·8±2 (2)	3±1 (3)
Protection from dexamphetamine toxicity	Mouse	S.c.	0·5±0·4 (3)	1·7±0·5 (5)
Prevention of dexamphetamine-agitation	Rat	I.p.	0·5±0·1 (3)	10±2 (3)
Protection from tryptamine-convulsions	Rat	I.p.	>260 (7)	12±3 (4)
Experimental catatonia	Rat	I.p.	1·2±0·7 (6)	>20 (3)
Protection from apomorphine-emesis	Dog	S.c.	0·004±0·001 (2)	0·6±0·1 (2)

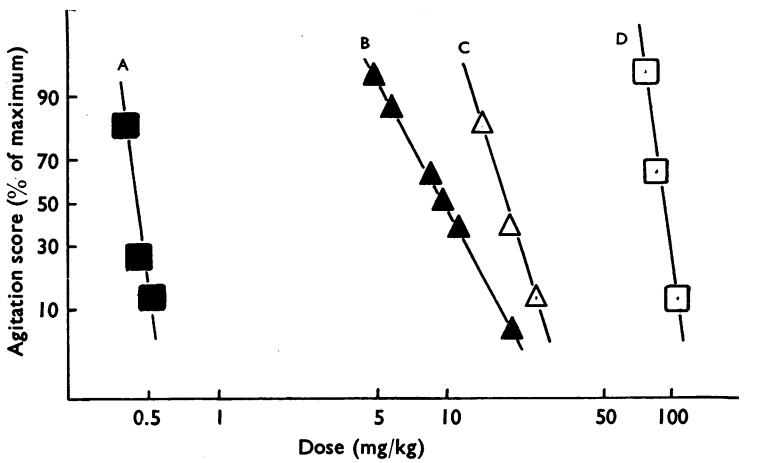


Fig. 2. Effect of hyoscine on the dose/response curves for thioproperazine and chlorpromazine in the antiamphetamine test in the rat. A, thioproperazine ; B, chlorpromazine ; C, chlorpromazine and hyoscine (1 mg/kg, intraperitoneally) 3 hr after chlorpromazine ; D, thioproperazine and hyoscine (1 mg/kg), intraperitoneally 3 hr after thioproperazine. The antiamphetamine test was carried out 4 hr after either A or B. Ordinate : agitation score expressed as percentage of maximum possible (probability scale) ; abscissa : intraperitoneal dose (mg/kg) of chlorpromazine or thioproperazine (log scale).

two adrenaline antagonists were tested since they protect mice from the acute toxic effects of dexamphetamine (Maxwell, 1959).

Another property present in thioproperazine to a much greater degree than in chlorpromazine is the ability to produce an experimental catatonia in rats not unlike that caused by bulbocapnine (De Jong, 1945). This condition was readily produced by injections of 5 mg/kg of thioproperazine (Fig. 3), and was characterized by

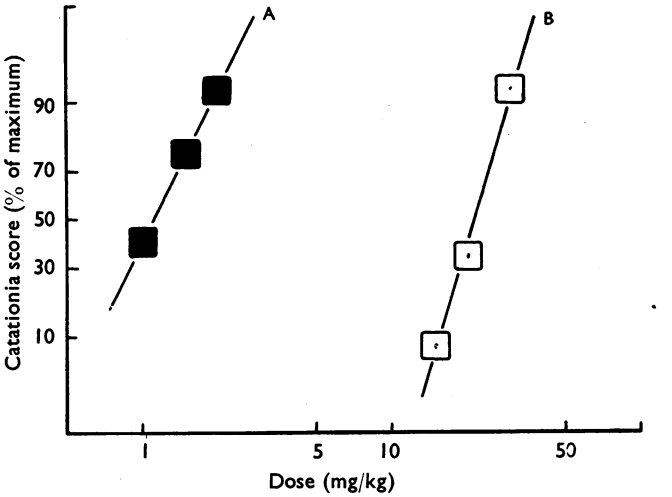


Fig. 3. Effect of hyoscine on the dose/response curves for thioproperazine in producing experimental catatonia in the rat. A, thioproperazine ; B, thioproperazine and hyoscine (1 mg/kg, intraperitoneally) given 3 hr after thioproperazine. The catatonia was assessed 4 hr after thioproperazine administration. Ordinate : catatonia score expressed as percentage of maximum possible score (probability scale) ; abscissa : intraperitoneal dose (mg/kg) of thioproperazine (log scale).

muscular rigidity and the ability of the animal to maintain an abnormal posture for considerable periods when gently placed in such a position. This effect could not be achieved with chlorpromazine in the doses (1 to 100 mg/kg) studied.

In the dog, thioproperazine (0.01 mg/kg) completely prevented the emetic action of a challenging dose of apomorphine. In contrast, bulbocapnine, which was effective in subcutaneous doses of 30 mg/kg in producing experimental catatonia in the rat, gave no protection in subcutaneous doses of 2 to 5 mg/kg against vomiting induced by apomorphine in the dog.

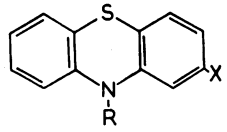
In an attempt to obtain some insight as to which pharmacological property of thioproperazine was related to its value in psychiatry, we compared (Table 4) the central nervous actions of a group of chemically related phenothiazine compounds and of bulbocapnine with their reported clinical potency. With the exception of 9260 R.P. which has had limited clinical use, all the phenothiazines chosen have had quite extensive use in clinical psychiatry, and their relative clinical potency (Robson & Stacey, 1962) has been taken for comparative purposes. Bulbocapnine was also included because of its ability to produce experimental catatonia.

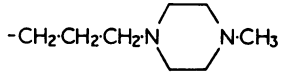
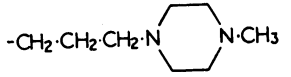
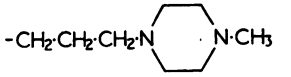
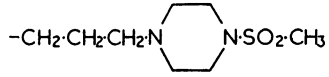
The central actions studied in this comparison were the protection from agitation due to dexamphetamine or convulsions due to tryptamine in the rat, the production of experimental catatonia in the rat, and the inhibition of vomiting induced by apomorphine in the dog. A simple test of sedation such as the reduction of the minimal anaesthetic dose of hexobarbitone was not used since thioproperazine has weak activity in this test (Table 3). 9260 R.P. showed weak activity in

TABLE 4

EFFECTIVE DOSES OF SOME PHENOTHIAZINE DERIVATIVES RELATED TO THIOPROPERAZINE AND OF BULBOCAPNINE IN SOME TESTS OF CENTRAL NERVOUS ACTION COMPARED WITH THEIR RELATIVE CLINICAL POTENCY

Figures quoted are the mean effective doses (for definition see Methods) with standard deviations. The numbers of experiments are indicated in brackets. The values for relative clinical potency are from Robson & Stacey (1962), except for that marked with an asterisk which is from Lambert *et al.* (1961). Injections into rats were intraperitoneal, and into dogs subcutaneous



Compound	Chemical formula of R	Chemical formula of X	Effective dose (mg/kg) to: Prevent dexamphetamine agitation in rat	Cause catatonia in rat	Prevent tryptamine-convulsions in rat	Prevent apomorphine-emesis in dog	Relative clinical potency
Thioproperazine		$-SO_2N(CH_3)_2$	0·5±0·1 (3)	1·2±0·7 (6)	>260 (7)	0·004±0·001 (2)	
Trifluoperazine		$-CF_3$	2 (1)	3 (1)	4±2 (4)	—	8—12
Prochlorperazine		—Cl	2·8±0·4	2·8±0·4	12±4 (3)	0·1 (1)	3—5
Chlorpromazine	$-CH_2\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$	—Cl	10±2 (4)	>20	12±3 (4)	0·6±0·1 (2)	1
Methotrimeprazine (laevo-isomer)	$-CH_2\cdot CH(CH_3)\cdot CH_2\cdot N(CH_3)_2$	$-O\cdot CH_3$	20 (1)	10 (1)	12±4 (3)	—	1
9260 R.P.		$-SO_2\cdot N(CH_3)_2$	21±0·3 (2)	32±8 (2)	>160 (1)	—	⩽1*
Bulbocapnine	—	—	180 (1)	18 (1)	—	>5 (1)	

our tests and its central actions appear to be limited to an inhibition of emesis due to apomorphine as reported by Lambert, Courvoisier & Julou (1961). Methotrimeprazine was more effective than 9260 R.P. in the tests in the rat and was similar to chlorpromazine in the majority of central actions studied here. Prochlorperazine was more potent than chlorpromazine in protecting rats from dexamphetamine, in producing experimental catatonia and in its antiapomorphine action. Trifluoperazine was some three- to five-times more potent than chlorpromazine in the tests in the rat. Thioproperazine was in turn more effective than trifluoperazine in protecting rats from agitation due to dexamphetamine and in producing experimental catatonia. However, it showed no detectable activity against convulsions due to tryptamine in contrast to the high activity of trifluoperazine. Bulbocapnine did not protect rats from dexamphetamine or dogs from apomorphine. Its only significant central action appeared to be the production of experimental catatonia and it was weaker than many of the phenothiazines in this context.

Effect of anti-Parkinsonian drugs on central actions of thioproperazine. In studying the effect of anti-Parkinsonian drugs on the central actions of thioproperazine we have limited our studies to four properties of thioproperazine, namely its antiamphetamine action in the mouse and rat, its cataleptic actions in the rat, and its antiapomorphine property in the dog. As examples of anti-Parkinsonian drugs we have taken benztropine, promethazine and hyoscine.

Results on the experimental catatonic and antiamphetamine properties are set out in Table 5. In the doses used, all three drugs cause the disappearance of the

TABLE 5

ANTAGONISM BY SOME ANTI-PARKINSONIAN DRUGS OF THE EXPERIMENTAL CATATONIA AND ANTIAMPHETAMINE ACTION OF THIOPROPERAZINE IN RATS

Each anti-Parkinsonian drug was given intraperitoneally 3 hr after graded intraperitoneal doses of thioproperazine and 1 hr before the assessment of experimental catatonia or of the antiamphetamine action. Figures refer to the mean effective doses (for definition see Methods) of thioproperazine, with standard deviations. The numbers of experiments are given in brackets

Test	Effective dose (mg/kg) of thioproperazine after			
	No other drug	Hyoscine (1 mg/kg)	Promethazine (12·5 mg/kg)	Benztropine (5 mg/kg)
Experimental catatonia	1·2±0·7 (6)	20 (1)	>10 (3)	>8 (3)
Protection from dexamphetamine-agitation	0·5±0·1 (3)	>16 (3) 90 (1)	>5 (2)	>4 (3)

symptoms of experimental catatonia, and the effect of hyoscine is illustrated in Fig. 3. Likewise the antiamphetamine activity of thioproperazine was reduced by at least a factor of ten by promethazine or benztropine, and over a hundredfold by hyoscine. Fig. 2 shows the dose/response curves for thioproperazine and chlorpromazine, by themselves and in rats injected intraperitoneally 1 hr previously with 1 mg/kg of hyoscine.

Experiments carried out to determine the effect of anti-Parkinsonian drugs on the activity of thioproperazine and chlorpromazine in protecting mice from the toxic effects of dexamphetamine yielded equivocal results. Thus, on the one hand,

promethazine has protective action of its own in this test (Maxwell, 1959) whilst hyoscine and benztropine appeared to increase the toxicity of dexamphetamine.

Results on the effects of hyoscine and benztropine on the antiapomorphine action of thioproperazine are set out in Table 6. Promethazine was not used in these experiments since it is known to be itself a weak antagonist of apomorphine.

TABLE 6

EFFECT OF SOME ANTI-PARKINSONIAN DRUGS ON THE ANTIAPOMORPHINE ACTION OF THIOPROPERAZINE IN THE DOG

Thioproperazine was given subcutaneously by itself or simultaneously with an anti-Parkinsonian drug 1 hr before apomorphine (0·1 mg/kg, subcutaneously). The number of retches in the hour following apomorphine was counted and compared with the response in the same dog treated 3 to 4 days previously and subsequently with apomorphine only. Figures in brackets refer to the numbers of experiments

Dose of thioproperazine (mg/kg)	Anti-Parkinson drug and dose (mg/kg)	% reduction in no. of retches						
		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Mean
0·01	—	100 (2)	100 (2)	100 (2)	100 (2)	—	—	100
0·01	Hyoscine (0·1)	100 (1)	100 (1)	100 (1)	100 (1)	—	—	100
0·01	Benztropine (0·1)	87 (2)	94 (2)	100 (2)	100 (2)	—	—	96
—	Hyoscine (0·1)	—	—	7 (1)	3 (1)	10 (1)	10 (1)	7·5
—	Benztropine (0·1)	21 (1)	15 (1)	16 (1)	17 (1)	—	—	17·25

The doses of anti-Parkinsonian drugs used here were lower than in the rat experiments since the dose of thioproperazine required was lower. The subcutaneous dose of thioproperazine (0.01 mg/kg) was slightly more than twice the effective dose (Table 3) and gave complete protection from the challenge dose of apomorphine.

Dogs treated with thioproperazine and hyoscine showed no response to apomorphine indicating that *if* the effective antiapomorphine activity of thioproperazine had been decreased this was by a factor of less than two. Hyoscine is not an inhibitor of emesis induced by apomorphine in the dog (Boyd & Cassel, 1957). A very slight effect was obtained with benztropine, but the change in the ED50 was again by a factor of less than two. Thus whereas, in the doses used, hyoscine, properazine or benztropine considerably reduced the ability of thioproperazine to produce experimental catatonia or to protect rats from agitation and disorientation due to dexamphetamine, these drugs had little significant effect on the antiapomorphine properties of thioproperazine in the dog.

Acute toxicities. The acute subcutaneous toxicities (LD50) of thioproperazine and chlorpromazine in mice were 800 mg/kg (range 680 to 920) and 420 mg/kg (340 to 500) respectively.

DISCUSSION

The weak sedative properties and high antiapomorphine activity of thioproperazine have previously been described by Courvoisier *et al.* (1958). These authors did not, however, describe its antiamphetamine and antitryptamine properties or investigate the effects of anti-Parkinsonian drugs.

Peripheral actions of thioproperazine

As determined by its effects on blood pressure, thioproperazine has a considerably weaker antiadrenaline action than has chlorpromazine. It also has weaker hypotensive and respiratory depressant properties.

On the isolated phrenic nerve-diaphragm preparation both chlorpromazine and thioproperazine were more effective in inhibiting the response to indirect than to direct stimulation. This agrees with the results of Su & Lee (1960) with chlorpromazine. Thioproperazine was, with both methods of stimulation, less potent than chlorpromazine. Slow intravenous infusion of up to 40 mg/kg of either chlorpromazine or thioproperazine was without significant effect on the sciatic nerve-tibialis anterior preparation of the chloralose cat. Jindahl & Desphande (1961) found that chlorpromazine, even when administered intra-arterially, was without effect on the contraction of the gastrocnemius muscle produced by stimulation of its motor nerve in the dog.

Central actions of thioproperazine

Chlorpromazine is known to have potent antiadrenaline properties and these may be exerted centrally. Thus Heibel, Bonvallet & Dell (1954) found that chlorpromazine suppressed activation of the electroencephalogram induced by adrenaline in the cat. Similar effects have been reported by Martin, Demaar & Unna (1958) and by Rothballer (1959). Heibel *et al.* (1954) suggested that the central depressant properties of chlorpromazine were due to an antagonism of endogenously liberated adrenaline in the brain stem. Tedeschi, Tedeschi & Fellows (1961) have compared the activity of a number of phenothiazine derivatives in antagonizing some central effects of 5-hydroxytryptamine and find some, although not complete, correlation between this property and what they term " tranquillizing activity."

The finding that thioproperazine has weak peripheral antiadrenaline properties and *in some respects* has more potent central actions than chlorpromazine, suggests that if antagonism of adrenaline at a central level is an important factor in the mode of action of these drugs then there is no correlation between the central and peripheral antiadrenaline actions.

In the doses and experimental preparation we have employed, neither thioproperazine nor chlorpromazine had any significant effect on either the patellar or flexor reflex of the cat. These results apparently disagree with those of De Salva & Oester (1960), who obtained some inhibition of these reflexes with chlorpromazine. That thioproperazine was without an effect on spinal reflexes in the anaesthetized cat is of note in view of the neurological effects (muscular rigidity and tremor) which the drug causes in conscious human subjects, and the experimental catatonia which is induced in the unanaesthetized rat.

McGeer, McGeer & McLennan (1961) have compared the effects of chlorpromazine with those of thioproperazine in inhibiting the actions of dopamine on the crayfish stretch receptor reflex. These workers found that, whilst chlorpromazine completely blocked the inhibitory effects of dopamine on the stretch receptor reflex, thioproperazine blocked 98% of the activity of dopamine, 70 to 80% of that of Factor I and 20% of that of γ-aminobutyric acid.

Thioproperazine appears to have negligible analgesic activity unlike the analgesic activity in mice of chlorpromazine and the chemically related methotrimeprazine which has been previously reported (Maxwell, Palmer & Ryall, 1961), and the last compound has useful analgesic properties in man (Lasagna & De Kornfeld, 1961).

That chlorpromazine protects mice kept in groups from the acute toxic effects of amphetamine was first reported independently by Lasagna & McCann (1957) and by Burn & Hobbs (1958). Since that time many workers (Hogn & Lasagna, 1960 ; Swinyard, Clark, Miyahara & Wolf, 1961 ; Fink & Larson, 1962) have studied the increased toxicity of amphetamine in mice kept in groups at a high ambient temperature. Askew (1962) found that compounds which antagonize the rise in body temperature of grouped mice given amphetamine also antagonize the drug's toxicity, and that protective effects of chlorpromazine might be related to an antagonism of the hyperpyrexic response to amphetamine. Maxwell (1959) found that a number of chemically distinct compounds possessing adrenaline-blocking action protected mice from the acute toxic effects of dexamphetamine and suggested that for chlorpromazine this action might be related to its peripheral adrenergic-blocking activity. That thioproperazine, with much weaker peripheral antiadrenaline properties than has chlorpromazine in the cat, is roughly equipotent to the latter drug in protecting mice from the acute toxic effects of dexamphetamine, suggests that although protection can be afforded by peripheral adrenergic blockade, such as produced for example by phenoxybenzamine, this is not the only mechanism which can afford protection. Probably thioproperazine protects against dexamphetamine toxicity in mice by a mechanism different from that induced by chlorpromazine. We have not studied the effect of thioproperazine on the hyperpyrexic response to amphetamine.

The difference between chlorpromazine and thioproperazine is more clearly brought out in the amphetamine-agitation test in the rat. In this procedure we found that peripheral adrenergic-blocking agents, such as phenoxybenzamine and phentolamine afforded no protection from the acute behavioural effects of intraperitoneal injections of dexamphetamine, although as previously mentioned they do protect against the acute toxicity of dexamphetamine in mice. Thioproperazine shows very high activity in protecting rats from the acute behavioural effects of dexamphetamine, being some twenty-times more potent than chlorpromazine. It is clear, therefore, that, in view of the weaker adrenergic-blocking properties of thioproperazine, activity in the rat antiamphetamine test is probably unrelated to peripheral (or central) antagonism of adrenaline whilst this may be an important factor in protecting aggregated mice from the acute toxic effects of dexamphetamine. The probable difference in the mechanisms by which chlorpromazine and thioproperazine protect rats against dexamphetamine is emphasized by Fig. 2, where it is shown that hyoscine greatly reduces the action of thioproperazine whilst not significantly affecting that of chlorpromazine.

The experimental catatonia produced by various related phenothiazine derivatives has been described by Courvoisier, Ducrot & Julou (1958) and by others (Beaulnes & Viens, 1961). The mechanism by which this experimental catatonia is produced has not however been studied.

The finding of the very high antiapomorphine activity of thioproperazine in the dog agrees with the results of Courvoisier *et al.* (1958). Although the mechanism by which thioproperazine prevents the emetic action of apomorpine has not been studied in detail, it is not unreasonable to suppose that the mechanism may be similar to that of chlorpromazine (Brand, Harris, Borrison & Goodman, 1954).

An attempt at correlating the central actions of thioproperazine and chemically related compounds with their psychiatric usefulness has been set out in Table 4. Any such attempt is made difficult by the lack of objective, comparative information on the potency of drugs in various psychiatric disorders. The results of Robson & Stacey (1962) have been used, although these authors did not quote a figure for the relative clinical potency of thioproperazine or 9260 R. P. Although we have avoided attempting to obtain a precise figure for thioproperazine, it would appear from the clinical papers on this drug (for example, Delay *et al.*, 1958 ; Leitch *et al.*, 1962 ; Denham & Carrick, 1961) that thioproperazine is effective in mania and schizophrenia at smaller doses than chlorpromazine and hence the relative clinical potency is considerably greater than one.

The possibility that the high antiapomorphine activity of these compounds might be the pharmacological action responsible for the psychiatric effects has been eliminated by the work of Lambert *et al.* (1961) with the phenothiazine compound 9260 R. P. This drug was reported to be a very potent antagonist of vomiting due to apomorphine but was found to be of no psychiatric value in conditions which responded well to thioproperazine. As distinct from thioproperazine, 9260 R.P. had weak activity in the tests in the rat. The activity in protecting rats from convulsions due to tryptamine is also not correlated with clinical value since thioproperazine showed no detectable activity in this test. The difference between thioproperazine and trifluoperazine in this tryptamine-antagonism test is, however, of note. Increasing potency in producing experimental catatonia correlates with increasing psychiatric potency amongst the phenothiazines. Unfortunately, we are not aware of a phenothiazine derivative which produces experimental catatonia but has no other central action. Bulbocapnine, however, produces experimental catatonia and is inactive in the other tests. We have found no reference claiming it to be of clinical psychiatric value.

The one remaining property to be discussed is the ability of drugs to prevent the acute behavioural disturbance produced by dexamphetamine in the rat, and this appears to fit the clinical results with both the phenothiazine series and bulbocapnine. Furthermore, as pointed out by Connell (1958), the amphetamines are capable, when administered in high doses, of producing severe psychiatric disturbances in man, and these disturbances are sometimes indistinguishable from acute schizophrenia. It is not unreasonable to suppose, therefore, that a drug which in low doses prevents the agitation and disorientation produced by dexamphetamine in an experimental animal, might be of value in the management of schizophrenia or mania in man.

Effect of anti-Parkinsonian drugs on the central actions of thioproperazine

In spite of the fact that clinically thioproperazine and some related phenothiazines are not infrequently used in association with anti-Parkinsonian drugs, the

pharmacology of such associations has not been studied in any detail. It is, therefore, interesting that with hyoscine and benztropine both the experimental catatonia and the antiamphetamine (agitation) properties of thioproperazine were antagonized whilst leaving intact the antiapomorphine action in the dog. It is also of note that a sedative phenothiazine derivative promethazine can inhibit both the antiamphetamine (agitation) properties and the experimental catatonia produced by a related phenothiazine compound. Morpurgo (1962) has reported that the catatonia produced by the phenothiazine derivative perphenazine is abolished by hyoscine and other anti-Parkinsonian drugs.

The possible psychiatric importance of the neurological Parkinson-like phenomena produced by thioproperazine and related drugs (trifluoperazine, prochlorperazine) has been reviewed in detail elsewhere (Bordeleau, 1961) without any firm conclusion being reached, and the possible interrelationship between Parkinsonism and schizophrenia has been discussed by Kline & Mettler (1961). The clinical use of anti-Parkinsonian drugs in association with psychiatric treatment with thioproperazine and related phenothiazines is quite widespread. It is not known whether the ancillary use of an anti-Parkinsonian drug reduces the clinically useful effects of thioproperazine in mania or schizophrenia. As mentioned above, we consider that the antiamphetamine properties of thioproperazine may be related to its clinical psychiatric effects. The finding that anti-Parkinsonian drugs such as benztropine, hyoscine or promethazine inhibit the antiamphetamine properties of, as well as the experimental catatonia produced by, thioproperazine, suggests that clinically the use of these ancillary drugs may decrease the psychiatric effectiveness of thioproperazine.

The mechanism of the central nervous action of thioproperazine is unknown. It appears that its central action is not due to antagonism of adrenergic effects at a central level. The fact that some but not all of the central actions of thioproperazine may be antagonized by anti-Parkinsonian drugs with central anticholinergic properties suggests that thioproperazine may have some effect on a cholinergic mechanism in the central nervous system. Another possible explanation arises from the work of Barbeau & Sourkes (1961) and of Ehringer & Hornykiewicz (1960) who have reported that low levels of dopamine in the basal ganglia are associated with Parkinsonism. An antagonism of the actions of dopamine in the central nervous system might, therefore, lead to the production of extrapyramidal symptoms of Parkinsonism. In agreement with this idea are the results of Everett & Wiggand (1962) showing that states of excitement in mice are associated with increased brain levels of dopamine. Obviously, however, much additional work would be required to elucidate the mechanism of action of this and related drugs.

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