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PHARMACOLOGY OF M & B 18,706, A DRUG WHICH SELECTIVELY REDUCES DECEREBRATE RIGIDITY

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1 (±)-10-(3-Dimethylamino-2-methylpropyl)-2-valeroylphenothiazine hydrochloride (M & B 18,706) has been compared with dimethothiazine, chlorpromazine, diazepam and baclofen for potency in reducing decerebrate rigidity in the cat and rat and for activity in causing ataxia or sedation.

2 When given intravenously M & B 18,706 had seven times the potency of dimethothiazine and one-half the potency of chlorpromazine in reducing the rigidity of the intercollicular decerebrate cat. When administered orally M & B 18,706 and chlorpromazine were equi-potent in reducing rigidity but M & B 18,706 was less effective than chlorpromazine in producing ataxia in this species.

3 In the rat, M & B 18,706 had one-quarter the potency of chlorpromazine for reducing decerebrate rigidity but had from 1/20th to 1/200th its potency in tests for sedative or tranquillizing activity.

4 M & B 18,706, like dimethothiazine and chlorpromazine, had little effect on the rigidity of ischaemic decerebrate cats and failed to inhibit polysynaptic spinal reflexes.

5 M & B 18,706 had intravenous potency comparable to chlorpromazine in reducing the pressor action of noradrenaline in the spinal cat.

Introduction

A drug which reduced intercollicular decerebrate rigidity by inhibiting fusimotor activity at a supraspinal level at a dose substantially less than that producing sedation or other untoward effects in experimental animals, might be of value in the management of patients with pyramidal spasticity. This hypothesis arose from a consideration of three pieces of information. First, the studies by Rushworth (1964a, b) on the pathophysiology of spasticity suggested that the muscles of the classical decerebrate cat present features which are similar to those of human spasticity. Thus the exaggerated stretch reflexes characteristic of clinical spasticity, like those of the intercollicular decerebrate cat, may require for their maintenance the integrity of the fusimotor system. Some types of human spasticity might depend on the release of fusimotor neurones from descending inhibition. The second piece of information came from the work of Henatsch & Ingvar (1956) who showed that chlorpromazine reduced the rate of discharge of fusimotor neurones in ventral root filaments of the decerebrate cat and the third was the clinical study by Matthews (1965) of chlorproethazine (the diethylamino analogue of chlorpromazine) in the treatment of spasticity.

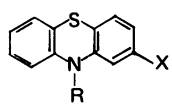
A series of phenothiazine derivatives related to chlorpromazine was studied and this indicated that it is possible in animals to separate potency in reducing intercollicular decerebrate rigidity from that produced by ischaemia (Maxwell & Read, 1972) and from activity in tests of ataxia and sedation (Keary & Maxwell, 1967). Dimethothiazine was selected from these and has proved to be of some value in the relief of spasticity in man (Matthews, Rushworth & Wakefield, 1972; Griffiths & Bowie, 1973). However, these studies have indicated the desirability of finding a drug which is more potent than dimethothiazine, but which maintains a wide separation between the dose effective in reducing experimental rigidity and that affecting spinal interneurones or having an effect in tests of sedative or neuroleptic activity.

Many phenothiazine derivatives and other compounds were tested (Amin, Jones & Maxwell, 1971), and (±)-10-(3-dimethylamino-2-methylpropyl)-2-valeroylphenothiazine hydrochloride (M & B 18,706, see below) was selected as a compound meriting detailed study. The present paper describes some of the pharmacological actions of M & B 18,706 in comparison with those

of dimethothiazine and chlorpromazine. In addition, data comparing M & B 18,706 with diazepam and baclofen are included since these compounds are said to be of value in the management of some types of clinical spasticity (Cook & Nathan, 1967; Hudgson & Weightman, 1971).

A preliminary account of this work has been given elsewhere (Maxwell, Read, Rhodes & Sumpter, 1972).

Drugs were administered by slow intravenous infusion at the rate of 0.1 to 1 mg kg^{-1} min^{-1} into a cannulated external jugular vein. The concentration of the solution used was chosen so that the dose required to abolish rigidity was administered over 1-3 minutes. Doses refer to the cumulative dose administered. The reduction of the control, integrated, EMG response after various cumulative doses of the drug was measured, and from a



Compound	R	X
M & B 18,706	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	$-CO.CH_2CH_2CH_2.CH_3$
Chlorpromazine	$-CH_2CH_2CH_2N(CH_3)_2$	$-Cl$
Dimethothiazine	$-CH_2CH(CH_3)N(CH_3)_2$	$-SO_2N(CH_3)_2$
Baclofen	$H_2N.CH_2.CH(C_6H_4Cl).CH_2.COOH$	

Methods

Experiments in the cat

Cats of either sex and weighing between 1.7 and 3 kg were used.

Effects on intercollicular decerebrate rigidity. The animal was lightly anaesthetized with ether or halothane, the carotid arteries clamped and the mid-brain sectioned between the colliculi (Keary & Maxwell, 1967). The anaesthetic was discontinued, and the clamps removed from the carotids 5 min after decerebration. Assessments of decerebrate rigidity did not begin until at least 1 h after decerebration.

The method used to quantify the degree of decerebrate rigidity was to measure the EMG response to slow stretch of quadriceps and has been described by Keary & Maxwell (1967) and Maxwell & Rhodes (1970). The EMG was integrated and displayed together with the raw EMG on a pen recorder. The integrator consisted of a simple half-wave rectifying circuit with an overall time-constant of 3.3 seconds.

dose-response line the effective dose required to reduce the response to 50% of the pre-drug level was determined.

Alternatively, drugs were administered orally 60 min before decerebration and the dose required to prevent decerebrate rigidity in 50% of animals was estimated from a dose-response curve.

Effects on ischaemic decerebrate rigidity. Ischaemically decerebrate cats were prepared by a method based on that described by Pollock & Davis (1930) and described by Maxwell & Read (1972). The basilar artery of ether-anaesthetized cats was ligated between the inferior and superior cerebellar arteries. Ether was then discontinued and the EMG activity of the quadriceps muscle was recorded as described for the intercollicular decerebrate preparation. Rigidity usually appeared 5-10 min after ligation of the basilar artery; drug studies did not begin until 1 h later.

Drugs were given by slow intravenous infusion. At the end of the experiment, the region of the cerebellum rendered ischaemic was determined by the intravenous injection of Evans Blue solution.

Experiments where less than 50% of the cerebellum was ischaemic were discarded.

Effects on spinal reflexes in the chloralose-anaesthetized cat Experiments on spinal reflexes were carried out in cats lightly anaesthetized with chloralose (60 mg/kg intravenously). The patellar reflex was elicited by means of a mechanical hammer as described by Schweitzer & Wright (1937). A flexor reflex was elicited by electrical stimulation of the central end of the cut tibial nerve whilst recording twitches of the tibialis anterior muscle. 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 stimulus consisted of a train of pulses, width 0.5 ms, repeated at intervals of 10 ms for a 100 ms period. The nerve was thus stimulated every 10 seconds.

Drugs were infused intravenously. In some experiments blood pressure was recorded from the carotid artery.

Production of ataxia Cats were dosed orally with the drugs in gelatine capsules. One hour later ataxia was assessed subjectively by observation of the cats in walking, climbing and jumping. The degree of ataxia was scored on a four point scale: 0 = normal, 1 = slight ataxia, 2 = moderate ataxia, 3 = severe ataxia. The dose required to produce a 'moderate' degree of ataxia was determined.

Sympathetic α-adrenoceptor blocking activity. Cats were anaesthetized with halothane and spinalized at the level of the first cervical vertebra. The brain was destroyed, respiration was maintained with a pump and anaesthesia was discontinued.

Blood pressure was recorded from a carotid artery. Noradrenaline was injected automatically at 3.5-7 min intervals into an external jugular vein. Two doses of noradrenaline were chosen, one being twice or four times the other, such that both gave pressor responses on the linear part of the dose-response line; when the responses were constant the test drug was injected intravenously. Antagonism to the noradrenaline-induced response was expressed in terms of the reduction in the apparent pressor potency of noradrenaline following injection of the test drug. A 50% reduction served to define the effective dose.

Experiments in the rat

Reduction of intercollicular decerebrate rigidity Rats of either sex weighing 400-500 g were anaesthetized with halothane, the carotid arteries were clamped and the brain was sectioned between the colliculi. The trachea was then cannulated and the clamps removed from the carotid arteries.

Rats were assessed subjectively by gentle manipulation of a leg for presence or absence of rigidity, and the intravenous dose of drug required to abolish the rigidity in each animal determined. The test compound was also administered orally 60 min before decerebration, the EMG was recorded from quadriceps and the presence of an EMG response taken as the indication of rigidity. The dose which abolished rigidity in 50% of the animals was determined.

Reduction of locomotor activity in the open field test The method described by Christmas & Maxwell (1970) with inexperienced rats was used. One hour after oral administration of the test drug or of solvent, the rats were placed singly in the open field and the number of spaces entered in 3 min noted. Each rat was used only once.

Mean scores for groups of five rats were expressed as a percentage of the control score and the dose required to produce a 50% reduction in ambulation was determined.

The rotating rod test Groups of five rats were dosed orally with drug or with solvent. One hour later they were placed on a revolving metal cylinder, rotating at about 5 rev/min and allowed to run until they fell off. The time each rat spent on the rod was recorded, and the effective dose was defined as the dose required to reduce the mean group score by 50% of the control score.

Antagonism of dexamphetamine-induced behaviour Test drugs or solvent were administered orally to groups of two rats 1 h before the subcutaneous injection of 4 mg/kg dexamphetamine sulphate. Thirty minutes later agitation was rated on a blind basis by a number of independent observers using a three-point scale: 0 = normal, 1 = slight stimulation, 2 = maximal stimulation. Groups of rats receiving no drugs, or dexamphetamine only, were included.

The dose required to reduce the score to 50% of that scored by the animals receiving dexamphetamine only was calculated.

Antagonism of apomorphine-induced behaviour This was investigated as described above for dexamphetamine, except that a subcutaneous dose of 2 mg/kg apomorphine was administered instead.

Experiments in the dog

Reduction of decerebrate rigidity The experiments were carried out as described for the cat.

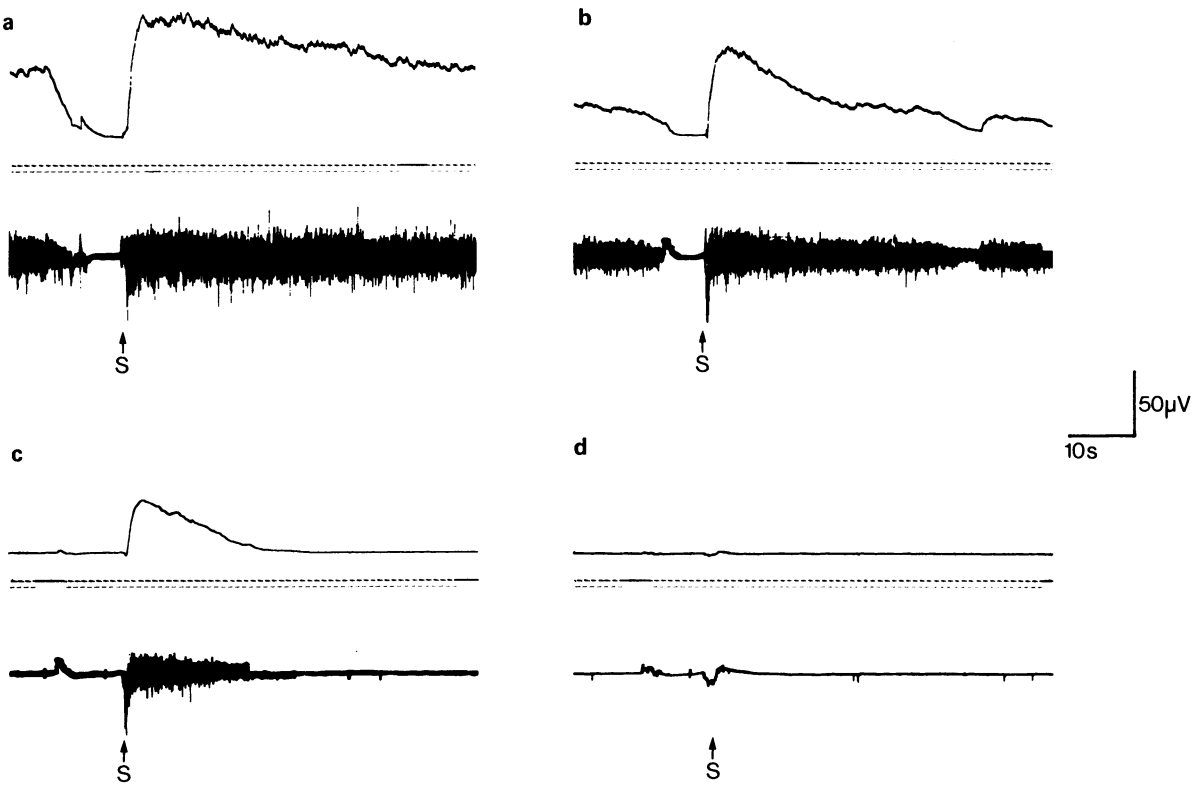


Fig. 1 The effect of intravenous M&B 18,706 on the rigidity of an intercollicular decerebrate cat. In each panel the lower tracing is the EMG from quadriceps muscle and the upper tracing is the integrated EMG (arbitrary scale). At S the lower leg was raised, removing tension on quadriceps, and then lowered, so that quadriceps was stretched by the weight of the lower leg. (a) control EMG response; (b) EMG response after 0.1 mg/kg M&B 18,706; (c) after 0.2 mg/kg M&B 18,706; (d) after 0.4 mg/kg M&B 18,706.

Cardiovascular effects Dogs were operated on to form carotid loops. After healing of the wound the dogs were trained to lie quietly while the blood pressure was recorded directly from the exteriorized carotid artery (Maxwell & McLusky, 1964). Drugs were administered by intravenous infusion into a cannulated saphenous vein.

Drugs

Drugs used were: M & B 18,706 (the hydrochloride); chlorpromazine hydrochloride; dimethothiazine mesylate; diazepam (Roche); baclofen (CIBA); dexamphetamine sulphate; apomorphine hydrochloride; (−)-noradrenaline bitartrate. Solutions of phenothiazine derivatives in isotonic saline were prepared immediately before use, care being taken to keep them out of sunlight.

Results

Experiments in the cat

Effects on intercollicular decerebrate rigidity The intravenous infusion of M & B 18,706 or other drugs studied produced a gradual reduction in the EMG response to slow stretch of quadriceps (Figure 1).

The intravenous dose of M & B 18,706 required to reduce by 50% the EMG response to stretch was 0.27 mg/kg (Figure 2). On this basis the intravenous potency of M & B 18,706 was approximately seven times that of dimethothiazine and 0.3 times that of chlorpromazine (Figure 2).

Although M & B 18,706 was less potent than chlorpromazine when administered intravenously, the two drugs appeared to be equipotent after oral

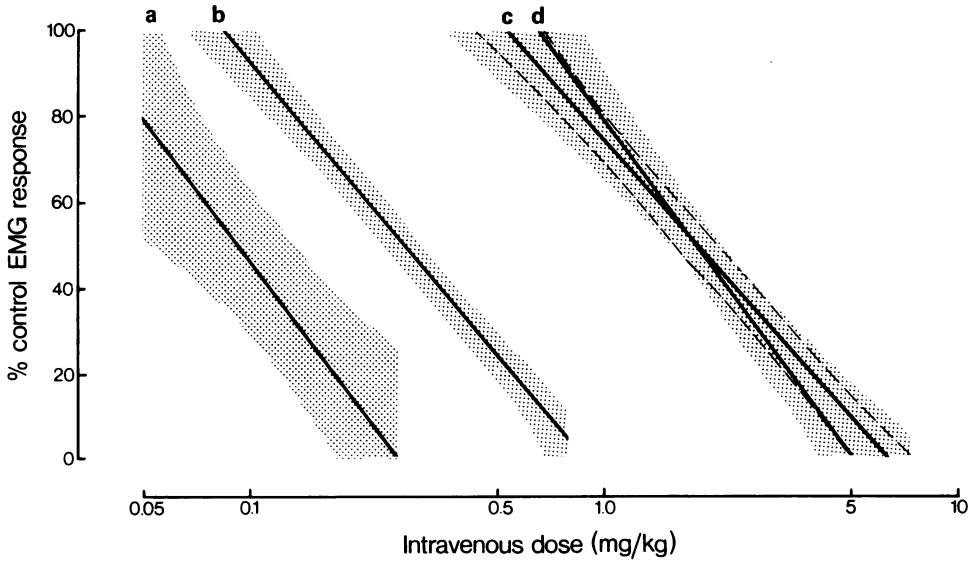


Fig. 2 Regression lines computed for chlorpromazine (four experiments) M&B 18,706 (16 experiments), dimethothiazine (six experiments) and baclofen (five experiments) in reducing rigidity in the intercollicular decerebrate cat. The shaded areas enclose the 95% confidence limits of the regression line. (a) Chlorpromazine; (b) M&B 18,706; (c) baclofen; (d) dimethothiazine.

administration (Table 1). M & B 18,706 was approximately six times as potent as dimethothiazine when administered orally.

No accurate determination of the relative duration of action of these drugs was made, but in six cats in which M & B 18,706 was infused intravenously until decerebrate rigidity was abolished and the infusion then terminated, rigidity, measured at 15 min intervals, had returned to the original level in approximately 3 hours. In similar experiments in four cats treated with dimethothiazine, rigidity returned after 2.5 hours. It appears, therefore, that M & B 18,706 and dimethothiazine have comparable durations of action following intravenous administration in the intercollicular decerebrate cat.

Effects on ischaemic decerebrate rigidity In contrast to the effects observed in the intercollicular preparations, removal of tension on quadriceps by raising the lower leg resulted in inhibition of EMG response (see Maxwell & Read, 1972) in only about 25% of ischaemic preparations (Figure 3).

The intravenous infusion of doses of M & B 18,706 up to 5 mg/kg had no significant effect on the EMG response produced by a slow stretch of quadriceps although this is approximately 10 times the dose required to abolish this response in intercollicular preparations (compare Figures 1 and 3). Higher doses of from 10-50 mg/kg did produce some reduction in the EMG response from quadriceps (Fig. 3) but in five ischaemically

Table 1 The activity of M & B 18,706, dimethothiazine, chlorpromazine, diazepam or baclofen in reducing intercollicular decerebrate rigidity and in producing ataxia in the cat.

	Reduction of intercollicular decerebrate rigidity		*Production of ataxia*
	Intravenous	*Oral*	*Oral*
M & B 18,706	0.27 (21)	0.5 (18)	c 25 (5)
Dimethothiazine	1.85 (6)	3.2 (14)	–
Chlorpromazine	0.1 (4)	0.7 (8)	c 10 (5)
Diazepam	0.2 (2)	2.7 (6)	c 2 (6)
Baclofen	1.8 (5)	3 (8)	c 2 (3)

Figures refer to the effective dose in mg/kg, with the number of experiments in parentheses.

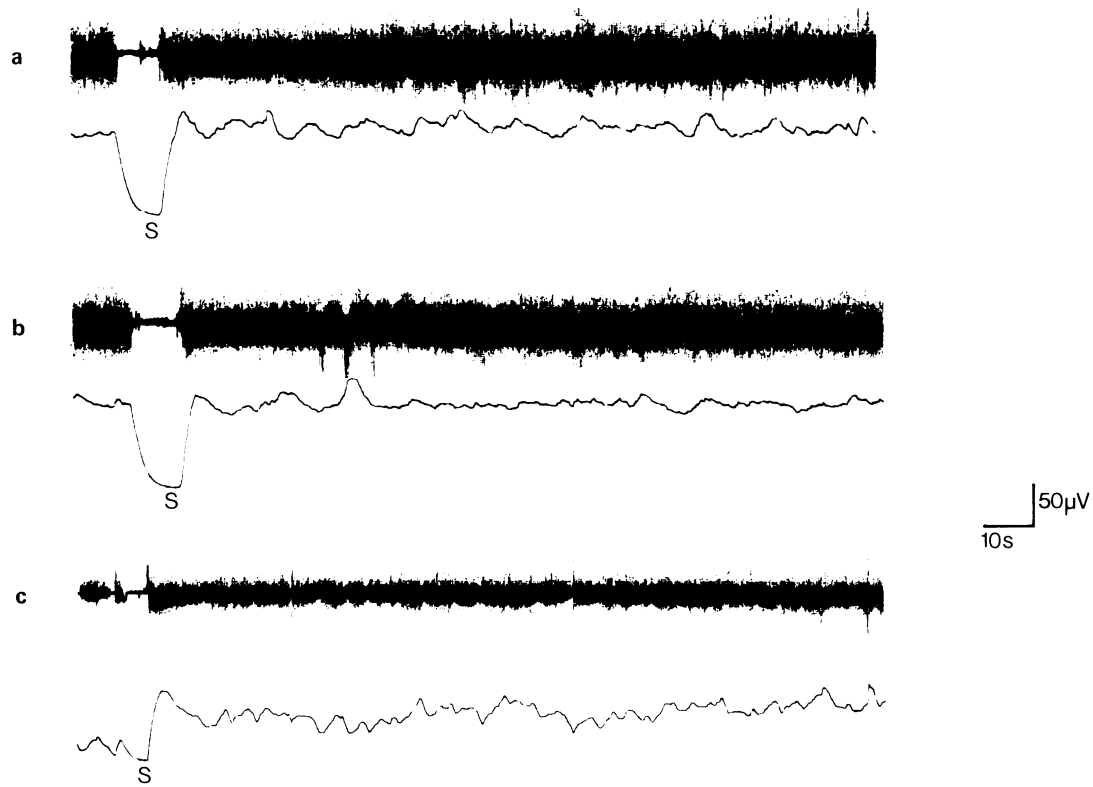


Fig. 3 The effect of intravenous M&B 18,706 on the rigidity of an ischaemically decerebrated cat. In each panel the upper tracing is the EMG from quadriceps, and the lower tracing is the integrated EMG (arbitrary scale). At S the lower leg was raised and then lowered as in Figure 1. (a) Control recording; (b) EMG after 5 mg/kg M&B 18,706; (c) after 10 mg/kg M&B 18,706. (Compare Figure 1).

decerebrate preparations, intravenous doses of up to 50 mg/kg did not completely abolish the EMG response to stretch. It is not clear why removal of the tension on quadriceps abolished the EMG response in some ischaemic preparations. There did not appear to be any difference between the effective doses of M & B 18,706 or other phenothiazines required to reduce rigidity in ischaemic preparations in which raising the lower leg abolished the EMG response, and those in which it did not.

Effects on spinal reflexes in the chloralose-anaesthetized cat Only M & B 18,706 and baclofen were studied in the present series of experiments since data on dimethothiazine and chlorpromazine obtained with the same method have been reported (Keary & Maxwell, 1967). Intravenous administration of 0.5-4 mg/kg M & B 18,706, doses which abolished the EMG in the intercollicular decerebrate cat, caused only slight reductions in the flexor and patellar reflexes in six chloralose-anaesthetized cats. In two further experiments the flexor reflex was abolished in this dose range, while in one cat the flexor reflex was abolished by 30 mg/kg M & B 18,706. In two experiments baclofen produced 50% depression of the flexor reflex at 0.6 mg/kg i.v., and of the patellar reflex at 2.6 mg/kg intravenously.

Production of ataxia The purpose of these experiments was to record any gross differences between the effects of the drugs when administered to conscious cats. No attempt was made to record subtle differences in behaviour produced by the drug, emphasis being placed on the production of ataxia. Diazepam and baclofen caused ataxia in cats with oral doses of 2 mg/kg, comparable to the oral dose required to reduce intercollicular decerebrate rigidity. A similar degree of ataxia was produced by M & B 18,706 or chlorpromazine in much higher doses of the order of 10 or 25 mg/kg

orally respectively (Table 1). These are some 15-50 times higher than the doses reducing intercollicular decerebrate rigidity. The degree of drowsiness produced by 10 mg/kg of chlorpromazine orally seemed to be greater than that produced by 2 mg/kg diazepam.

Sympathetic α-receptor blocking activity. The potency of M & B 18,706 was compared with that of dimethothiazine and chlorpromazine in inhibiting the pressor action of noradrenaline in the spinal cat. M & B 18,706 and chlorpromazine had comparable α-adrenoceptor blocking activity, the effective intravenous doses in this test being 0.2 and 0.25 mg/kg respectively. The corresponding dose of dimethothiazine was 13 mg/kg.

Experiments in the rat

Reduction of intercollicular decerebrate rigidity Decerebrate rigidity and its reduction were assessed subjectively in the rat. The values quoted in Table 2 are estimates of the effective intravenous and oral doses in the species. It is not valid therefore, to compare the effective doses of any one compound in the rat with those obtained by objective means in the cat. Within these limitations, the relative potencies of M & B 18,706, dimethothiazine and chlorpromazine in the rat following intravenous administration were comparable with those seen in the cat. The oral doses of M & B 18,706 or chlorpromazine required to abolish intercollicular decerebrate rigidity (17 and 4 mg/kg respectively; Table 2) were considerably greater than the intravenous effective doses (1.4 and 0.9 mg/kg respectively; Table 2). M & B 18,706 had one quarter the oral potency of chlorpromazine in this preparation.

Reduction of locomotor activity in the open field test Chlorpromazine was the most potent of the four drugs tested in reducing the locomotor activity of rats placed in the open field situation. The effective dose of chlorpromazine in this test (5.2 mg/kg; Table 2) was comparable with the effective oral dose in reducing intercollicular decerebrate rigidity. In contrast, the effective oral dose of M & B 18,706 in reducing locomotor activity was some six times higher than the corresponding dose required to reduce decerebrate rigidity. Little reduction in locomotor activity was produced by 400 mg/kg (the highest dose tested) of dimethothiazine.

Rotating rod test In this test, which possibly gives an indication of motor incoordination or ataxia, chlorpromazine was the most potent of the

Table 2 The activity of M & B 18,706, dimethothiazine, chlorpromazine or diazepam in reducing decerebrate rigidity and in tests of central depressant activity in the rat.

	Reduction of intercollicular decerebrate rigidity		*Reduction of ambulation in the open field situation*	*Rotating rod test*	*Antagonism of dexamphetamine-induced agitation*	*Antagonism of apomorphine-induced agitation*
	Intravenous	*Oral*	*Oral*	*Oral*	*Oral*	*Oral*
M & B 18,706	1.4 (5)	17 (23)	108	>200	245	>450
Dimethothiazine	2.5 (5)	–	>400	–	>450	>400
Chlorpromazine	0.9 (5)	4 (16)	5.2	2.7	6	17
Diazepam	1.2 (5)	–	139	21	–	–

Figures refer to the effective dose in mg/kg, with the number of animals used in the experiment on decerebrate rigidity in parentheses. Figures in other tests are means of at least two experiments with 15-20 rats per experiment.

drugs tested (Table 2), the effective dose being slightly less than the dose required to abolish decerebrate rigidity. M & B 18,706 was ineffective in this test at the highest dose (200 mg/kg orally) tested.

Antagonism of dexamphetamine- or apomorphine-induced agitation In contrast to the effectiveness of chlorpromazine in reducing the agitation produced by either dexamphetamine or apomorphine in the rat (effective doses of 6 or 17 mg/kg respectively; Table 2), very high doses of M & B 18,706 were required to antagonize the effects of dexamphetamine and it was ineffective against apomorphine-induced agitation at the highest (450 mg/kg) dose tested. Similarly, dimethothiazine was ineffective at the high doses examined.

Production of experimental catatonia Neither M & B 18,706 nor dimethothiazine produced symptoms of experimental catatonia in the high oral doses (up to 450 mg/kg) tested.

Experiments in the dog

The purpose of these experiments was to assess the cardiovascular actions of M & B 18,706 in the conscious animal, and to relate this to an estimate of the effective dose needed to abolish intercollicular decerebrate rigidity in this species.

Reduction of intercollicular decerebrate rigidity Only three experiments were carried out. In two experiments in which the effective intravenous dose of M & B 18,706 for reducing the EMG response to stretch of quadriceps was determined, the mean effective dose was 0.12 mg/kg. In one experiment the effective dose of dimethothiazine was found to be 1.1 mg/kg.

Actions on the cardiovascular system These experiments were carried out in conscious trained normotensive dogs with resting mean blood pressures of 122-134 mmHg and heart rates of 111-132 beats/minute. The intravenous infusion of 4 mg/kg of dimethothiazine over a period of 15 min produced a gradual fall in both arterial pressure and heart rate (Figure 4). After cessation of the infusion the arterial pressure and heart rate began to return to normal. In comparable experiments the intravenous infusion of 0.5 mg/kg of M & B 18,706 over a period of 10 min was accompanied by a gradual fall in arterial pressure of from 10-15% with only a slight change in heart rate. The doses of M & B 18,706 and dimethothiazine used in these experiments are four to five times the doses required to reduce intercollicular

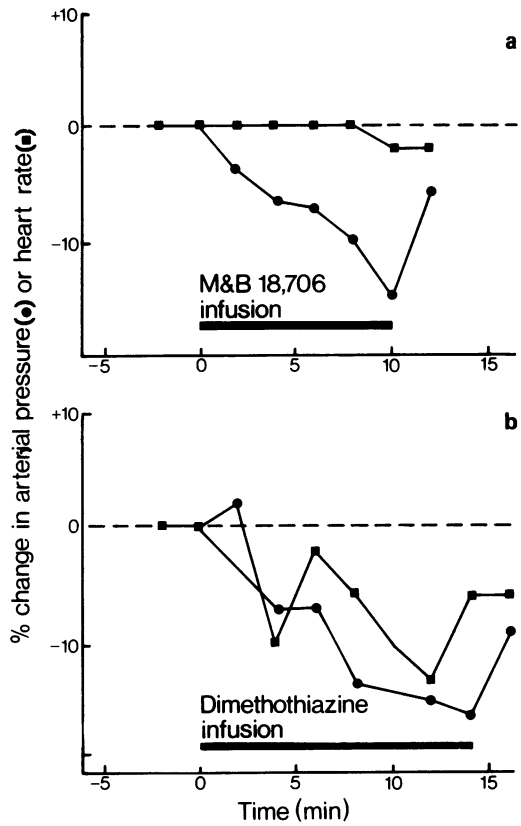


Fig. 4 The effect of slow intravenous infusion of (a) 0.5 mg/kg M&B 18,706 or (b) 4.0 mg/kg dimethothiazine on the arterial pressure (•) and heart rate (■) of conscious normotensive dogs. Each point is the mean of two experiments.

decerebrate rigidity in this species. Neither dimethothiazine nor M & B 18,706 caused any change in the ECG other than that due to the change in cardiac frequency.

Discussion

Chlorpromazine possesses many and diverse actions on the central nervous system. In addition to properties making it useful in the treatment of schizophrenia, it has a tendency to produce Parkinsonian-like extra-pyramidal effects in man and experimental catatonia in animals. Furthermore chlorpromazine is known to reduce rigidity of the intercollicular decerebrate cat, probably by depressing fusimotor activity by an action at a supra-spinal level (Henatsch & Ingvar, 1956). It would not be surprising if these actions involved

modulation of the actions of more than one neuro-transmitter in the central nervous system.

The work described in this paper is part of studies to find a compound which selectively reduces decerebrate rigidity by an action which depresses fusimotor activity but which has negligible sedative or other undesirable properties. Previous studies (Keary & Maxwell, 1967) indicated that dimethothiazine possessed some selectivity in abolishing the rigidity of the intercollicular decerebrate cat, and that this preparation has some predictive value for ability to reduce clinical spasticity (Matthews *et al.*, 1972; Griffiths & Bowie, 1973). Studies on muscle spindle afferent discharge in the decerebrate cat (Maxwell & Rhodes, 1970) and on the tonic vibration reflex in man (Crawley, Kennedy & Swash, 1973) are consistent with the view that dimethothiazine reduces fusimotor activity. A more potent compound with similar or greater selectivity was desirable, and M & B 18,706 was selected as a compound worthy of detailed investigation.

In the intercollicular decerebrate cat, M & B 18,706 had an oral potency comparable with that of chlorpromazine and some six times greater than that of dimethothiazine. No attempt was made to assess the sedative or psychoactive properties of M & B 18,706 in the cat, although the ability to produce symptoms of ataxia was determined. Whereas diazepam and baclofen produced symptoms of ataxia with a dose similar to that required to reduce decerebrate rigidity, M & B 18,706 did so only with doses approximately 50 times greater.

The majority of the tests used to measure the sedative or psychotropic properties of M & B 18,706 were carried out in the rat. Although we found it difficult to measure decerebrate rigidity reliably in this species, the relative activity of M & B 18,706 and chlorpromazine in this test was determined for comparison with potency in tests of sedative and other C.N.S. activity. Somewhat surprisingly we found M & B 18,706 was approximately one fourth as potent as chlorpromazine in reducing decerebrate rigidity in the rat following oral administration, whereas in the cat the two compounds have similar potency. As judged by ability to reduce locomotor activity in the open field situation and by its action in the rotating rod test, M & B 18,706 had weak central depressant or sedative properties, being from one twentieth to one hundredth as active as chlorpromazine. In the rotating rod test M & B 18,706 had less than one tenth the potency of diazepam.

It has been suggested that the ability of phenothiazine derivatives to reduce the behavioural symptoms produced by dexamphetamine or apomorphine in the rat may be correlated with their activity in the management of schizophrenia (Janssen, 1965; Irwin, 1966). M & B 18,706 had weak to negligible activity, approximately one fortieth that of chlorpromazine in antagonizing the effect of dexamphetamine or apomorphine. It is thus unlikely that the drug will be of value in the management of schizophrenia. M & B 18,706 did not produce symptoms of experimental catatonia in the rat, it is therefore unlikely to produce Parkinsonian-like extrapyramidal effects in man (Janssen, 1965; Irwin, 1966). Thus in the rat M & B 18,706 appears to have a selective action in reducing decerebrate rigidity.

M & B 18,706 is considerably more potent in reducing the rigidity of cats decerebrated at the intercollicular level than that of cats decerebrated by the ischaemic method. This is in agreement with data obtained with chlorpromazine (Henatsch & Ingvar, 1956) and some other phenothiazines (Maxwell & Read, 1972). This is to be expected if M & B 18,706, like chlorpromazine, and dimethothiazine, reduces decerebrate rigidity by abolishing the tonic discharge of fusimotor fibres innervating the muscle spindle. Neuropharmacological studies to be reported in detail later indicate that M & B 18,706 reduces the discharge frequency of afferent fibres from primary and secondary endings from muscle spindles in the soleus muscle of the intercollicular decerebrate cat, this action probably being due to a reduction in fusimotor tone (Maxwell & Sumpter, 1972).

Although the primary purpose of the experiments described here was to study in detail the actions of M & B 18,706 in the context of its possible use in the treatment of clinical spasticity, some of the results obtained are interesting in relation to the functional role of catecholamines in the central nervous system.

Drugs such as chlorpromazine or haloperidol which have proved useful in the treatment of schizophrenia and which are active in tests of neuroleptic activity increase the turnover of cerebral dopamine in doses which have no effect on other monoaminergic neurones (Andén, Corrodi & Fuxe, 1969; Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970; O'Keeffe, Sharman & Vogt, 1970). This is probably due to an inhibitory action of these drugs on dopaminergic neurones. M & B 18,706, which is chemically related to chlorpromazine, has low potency in tests for neuroleptic activity but high potency in inhibiting peripheral α-adrenoceptors; it is thus unlikely to affect dopaminergic receptors or to be of value in the treatment of schizophrenia. The compound may, however, inhibit cerebral noradrenergic receptors.

It is not clear what pharmacological action one

might expect from a drug which selectively inhibits noradrenergic receptors within the central nervous system since the possible functional role of noradrenergic neurones in the CNS is unclear (Vogt, 1973). Descending adrenergic pathways have been described (Dahlström & Fuxe, 1965; Fuxe, Hökfelt & Ungerstedt, 1969), and Ellaway & Pascoe (1968) have suggested that noradrenaline may be an excitatory transmitter involved in the control of fusimotor activity. An adrenergic control of tendon jerk reflexes in man has also been suggested (Phillips, Richens & Shand, 1973).

In addition, a preliminary report (Maxwell & Sumpter, 1972) indicates that there may be some correlation between the potency of some phenothiazines in reducing intercollicular decerebrate rigidity and blocking peripheral α-adrenoceptors. M & B 18,706 may, therefore, reduce fusimotor activity and decerebrate rigidity by inhibiting receptors for noradrenaline in the CNS whilst having little or no depressant action on receptors for dopamine. Whether it is of any therapeutic value in the treatment of spasticity remains to be seen.

References

AMIN, S.C., JONES, D.H. & MAXWELL, D.R. (1971). New phenothiazine derivatives. *British Patent Specification* 1,258,005. London: The Patent Office.

ANDÉN, N.-E., BUTCHER, S.G., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.*, **11**, 303-314.

ANDÉN, N.-E., CORRODI, H. & FUXE, K. (1969). Turnover studies using synthesis inhibition. In: *Metabolism of Amines in the Brain*, Ed., G. Hooper, pp. 38-47. London: MacMillan.

CHRISTMAS, A.J. & MAXWELL, D.R. (1970). A comparison of the effects of some benzodiazepines and other drugs on aggressive and exploratory behaviour in mice and rats. *Neuropharmacology*, **9**, 17-29.

COOK, J.B. & NATHAN, P.W. (1967). On the site of action of diazepam in spasticity in man. *J. Neurol. Sci.*, **5**, 33-37.

CRAWLEY, F.E.H., KENNEDY, P. & SWASH, M. (1973). Effect of dimethothiazine on tonic vibration reflex in man. *Br. J. Pharmac.*, **47**, 613-614P.

DAHLSTRÖM, A. & FUXE, K. (1965). Experimentally-induced changes in the intraneuronal amine levels of bulbospinal neuron systems. *Acta physiol. scand.*, **64**, suppl. 247.

ELLAWAY, P.H. & PASCOE, J.E. (1968). Noradrenaline as a transmitter in the spinal cord. *J. Physiol. (Lond.)*, **197**, 8-10P.

FUXE, K., HÖKFELT, T. & UNGERSTEDT, U. (1969). Distribution of monoamines in the mammalian C.N.S. by histochemical studies. In: *Metabolism of Brain Amines in the Brain*, Ed. G. Hooper, pp. 10-22. London: MacMillan.

GRIFFITHS, M.I. & BOWIE, E.M. (1973). The use of dimethothiazine in the treatment of childhood cerebral palsy. *Devl. Med. Child Neur.*, **15**, 25-32.

HENATSCH, H.-D. & INGVAR, D.H. (1956). Chlorpromazin und Spastizität eine experimentelle elektrophysiologische Untersuchung. *Arch. Psychiat. Nervkrankh.*, **195**, 77-93.

HUDGSON, P. & WEIGHTMAN, D. (1971). Baclofen in the treatment of spasticity. *Br. med. J.*, **4**, 15-17.

IRWIN, S. (1966). Considerations for the pre-clinical evaluation of new psychiatric drugs: A case study with phenothiazine-like tranquillizers. *Psychopharmacologia (Berl.)*, **9**, 259-287.

JANSSEN, P.A.J. (1965). Is it possible to predict the clinical effects of neuroleptic drugs (Major Tranquillizers) from animal data? *Arzneimittle-Forsch.*, **15**, 104-117.

KEARY, E.M. & MAXWELL, D.R. (1967). A comparison of the effects of chlorpromazine and some related phenothiazines in reducing the rigidity of the decerebrate cat and in some other central actions. *Br. J. Pharmac. Chemother.*, **30**, 400-416.

MATTHEWS, W.B. (1965). The action of chlorproethazine in spasticity. *Brain*, **88**, 1057-1064.

MATTHEWS, W.B., RUSHWORTH, G. & WAKEFIELD, G.S. (1972). Dimethothiazine in spasticity: a further attempt at pharmacological control. *Acta Neur. scand.*, **48**, 635-644.

MAXWELL, D.R. & McLUSKY, J.M. (1964). Hypotensive action of hydrochlorothiazide and clorexolone in the conscious normotensive dog. *Nature (Lond.)*, **202**, 300-301.

MAXWELL, D.R. & READ, M.A. (1972). The effects of some drugs on the rigidity of the cat due to ischaemic or intercollicular decerebration. *Neuropharmacology*, **11**, 849-855.

MAXWELL, D.R., READ, M.A., RHODES, K.F. & SUMPTER, E.A. (1972). Pharmacology of M & B 18,706–a selective fusimotor depressant. *Fifth International Congress of Pharmacology*–Abstracts of volunteer papers, p. 152, Bethesda.

MAXWELL, D.R. & RHODES, K.F. (1970). The effects of dimethothiazine on muscle spindle activity in the decerebrate cat. *Br. J. Pharmac.*, **39**, 520-532.

MAXWELL, D.R. & SUMPTER, E.A. (1972). Noradrenergic receptors and the control of fusimotor activity. *J. Physiol. (Lond.)*, **222**,, 173-175P.

O'KEEFFE, R., SHARMAN, D.F. & VOGT, M. (1970). Effect of drugs used in psychoses on cerebral dopamine metabolism. *Br. J. Pharmac.*, **38**, 287-304.

PHILLIPS, S.J., RICHENS, A. & SHAND, D.G. (1973). Adrenergic control of tendon jerk reflexes in man. *Br. J. Pharmac.*, **47**, 595-605.

POLLOCK, L.J. & DAVIS, L. (1930). The reflex activities of a decerebrate animal. *J. Comp. Neurol.*, **50**, 377-411.

RUSHWORTH, G. (1964a). Some aspects of the pathophysiology of spasticity and rigidity. *Clin. Pharmac. Ther.*, **5**, 828-836.

RUSHWORTH, G. (1964b). The nature and management of spasticity. *Proc. R. Soc. Med.*, **57**, 715-725.

SCHWEITZER, A. & WRIGHT, S. (1937). Effects on the knee jerk of stimulation of the central end of the vagus and of various changes in the circulation and respiration. *J. Physiol. (Lond.)*, **88**, 459-475.

VOGT, M. (1973). Functional aspects of the role of catecholamines in the central nervous system. In: *Catecholamines*, Ed. L.L. Iversen. *Br. med. Bull.*, **29**, 168-172.

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