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CENTRALLY ACTING MUSCLE RELAXANTS IN TETANUS

BY

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The anti-tetanus activity of a number of phenothiazine derivatives and other centrally acting muscle relaxants, such as mephenesin, dicyclopropyl ketoxime, 2-amino-6-methylbenzothiazole and meprobamate, has been determined in rabbits with experimental local tetanus. Structure–activity relationships were obtained for the phenothiazine derivatives and their anti-tetanus activity correlated with other central and peripheral properties. Both dicyclopropyl ketoxime and 2-amino-6-methylbenzothiazole were twice as active as mephenesin. Meprobamate does not appear to be primarily a muscle relaxant of the mephenesin type.

Tetanus may be suppressed by drugs from a variety of chemical groups having widely differing types of activity. Two drugs that have had considerable clinical use are the centrally acting muscle relaxants, mephenesin and chlorpromazine. They both reduce muscle spasm and control convulsions without causing loss of consciousness; although when tested against local tetanus in the rabbit they have distinctly different types of activity (Webster, unpublished).

In the present work further compounds, either similar in structure to chlorpromazine, that is, other phenothiazine derivatives, or similar in action to mephenesin, have been tested and their relative activities determined. Some preliminary results have been published previously (Laurence & Webster, 1958b).

Derivatives of phenothiazine (Table 1) are obtained either by modifying the aminopropyl side-chain (R_1) or by introducing various radicals into position 2 of the phenothiazine nucleus (R_2). The effect of these changes has been assessed by testing a range of 8 derivatives.

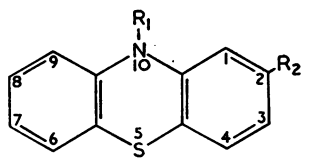
Promethazine, the basic member of the group, is the 2-dimethylaminopropyl derivative of phenothiazine. Replacement of its side-chain by the non-ramified 3-dimethylaminopropyl radical gives promazine. The effect on anti-tetanus activity of this change and of introducing a chlorine atom or acetyl group into position 2 of promazine has been determined in a quantitative assay of promethazine, promazine, chlorpromazine and acepromazine.

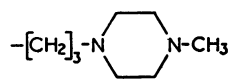
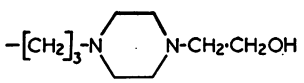
Further compounds tested include trimeprazine and methotrimeprazine, in which the 3-aminopropyl side-chain has been further modified by the addition of a methyl group to the second carbon atom, and perphenazine and prochlorperazine, in both of which a piperazine ring has been incorporated in the side-chain. Other derivatives were tested, but their potency has not been exactly determined.

* Stothert Research Fellow of the Royal Society.

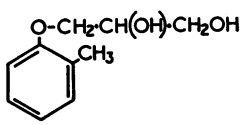
TABLE 1

THE STRUCTURAL FORMULAE OF SOME PHENOTHIAZINES TESTED FOR ANTI-TETANUS ACTIVITY

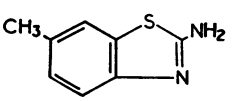


R_1	R_2			
	H	–Cl	–OCH_3	–$CO.CH_3$
–H	Phenothiazine			
$-CH_2.CH(CH_3).N(CH_3)_2$	Promethazine			
$-[CH_2]_3.N(CH_3)_2$	Promazine	Chlorpromazine		Acepromazine
$-CH_2.CH(CH_3).CH_2.N(CH_3)_2$	Trimeprazine		Methotrimeprazine	
		Prochlorperazine		
		Perphenazine		

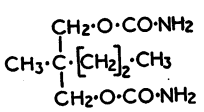
If the rapid and complete abolition of tetanus produced by mephenesin results from its depressant action on spinal interneurones, then other centrally acting muscle relaxants, which are similar in action to mephenesin, may also be effective against tetanus. Three such compounds, whose formulae are shown in Fig. 1, have been tested. They are meprobamate, 2-amino-6-methylbenzothiazole and dicyclopropyl ketoxime.



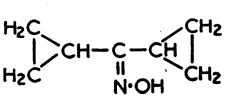
3-(o-Tolyloxy)propane-1,2-diol
Mephenesin



2-Amino-6-methylbenzothiazole
SKF 1045 A



2,2-Di(carbamoyloxymethyl)pentane
Meprobamate



Dicyclopropyl ketoxime
MR 710

Fig. 1. Structural formulae of some centrally acting muscle relaxants.

One of the main disadvantages of mephenesin is that it is short-acting due to the rapid oxidation of its hydroxyl group (Riley & Berger, 1949). Attempts have been made to produce longer-acting compounds by blocking this group. A series of

derivatives was prepared by Berger (1952) in which the hydroxyl group was transformed to a carbamoyloxy group, and of these 2,2-di(carbamoyloxymethyl)pentane (meprobamate) was found to possess central actions similar to mephenesin and to be more potent and longer-acting. The induction period and duration of paralysis produced by meprobamate in mice are both ten times as long as the corresponding periods for mephenesin. It is more active than mephenesin against leptazol and electroshock-induced convulsions, but only equally active against strychnine convulsions (Berger, 1954). Abolition of the flexor, crossed extensor and linguomandibular reflexes in the cat is obtained with 20 to 40 mg/kg compared with half this dose of mephenesin. This difference in potency on spinal reflexes has also been observed by Pfeiffer, Riopelle, Smith, Jenney & Williams (1957). Meprobamate has had wide use as a tranquillizing agent, and although it does not produce any marked change in the electroencephalogram it is known to synchronize activity recorded from the thalamus (Berger, Campbell, Hendley, Ludwig & Lynes, 1957; Hendley, Lynes & Berger, 1955). Anderson & Kjaer (1958) and Perlstein (1959) have used it to relieve muscle spasm in human tetanus.

The compound 2-amino-6-methylbenzothiazole is chemically related to benzimidazole, which produces muscular relaxation, antagonizes strychnine convulsions, abolishes multisynaptic reflexes without affecting monosynaptic transmission and reduces rigidity in decerebrate cats (Goodman, Gilman & Hart, 1943; Goodman & Hart, 1944) but is less active than mephenesin. A series of benzazole derivatives were compared by Domino, Unna & Kerwin (1952) for their ability to produce paralysis in mice, rabbits and dogs. Most of them produced a mixture of stimulating and depressant effects, but the substituted 2-aminobenzothiazoles were particularly potent paralysing agents and 2-amino-6-methylbenzothiazole especially free of stimulating effects. This compound was shown by Funderburk, King, Domino & Unna (1953), using myographic and ventral root recording, to abolish polysynaptic reflexes and also the facilitating and inhibitory effects of bulbar stimulation on spinal activity. It also reduced decerebrate rigidity, and spasticity caused by anoxia of the spinal cord. In all these actions it is twice as potent as mephenesin and longer-acting. Doses that depressed the spinal cord had no effect on the electroencephalogram. The effects on spinal activity were confirmed by King & Unna (1954).

Dicyclopropyl ketoxime is a new spinal depressant, more active than mephenesin, which has been used successfully in the control of tetanus spasms and convulsions (Richards, Blockus, Elam & Perlstein, 1958).

METHODS

Local tetanus was induced in rabbits by the injection of 625 mouse minimal lethal doses (MLD) of toxin into the gastrocnemius muscle of one hind limb of the rabbit and activated by a standard afferent stimulus (Laurence & Webster, 1958a). Resulting muscle activity was measured by quantitative electromyography and the level of tetanus expressed in terms of units of activity per minute (Laurence & Webster, 1958b). Percentage reductions were calculated for the 30 min following each injection. All drugs were injected intravenously and all were in aqueous solution apart from dicyclopropyl ketoxime and meprobamate, which were prepared in aqueous propylene glycol.

RESULTS

Phenothiazine derivatives

The following phenothiazines were selected for accurate assay on 7 rabbits, all of which received two doses of each compound:

Promethazine hydrochloride
10-(2-dimethylaminopropyl)phenothiazine hydrochloride.

Promazine hydrochloride
10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

Chlorpromazine hydrochloride
2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

Acepromazine maleate
2-acetyl-10-(3-dimethylaminopropyl)phenothiazine maleate.

The % reduction produced by each dose is given in Table 2 together with the dose producing a 50% reduction of activity calculated graphically from the mean results. The activity ratio of each compound relative to chlorpromazine, calculated

TABLE 2

REDUCTIONS IN TETANUS ACTIVITY RECORDED IN THE ASSAY OF THE ANTI-TETANUS ACTIVITY OF PROMETHAZINE, PROMAZINE, CHLORPROMAZINE AND ACEPROMAZINE

The 50% reduction doses were determined graphically from the regression line obtained from the plot of mean results. Deviations from parallelism were calculated in comparison with chlorpromazine. Reductions were calculated for the 30 min after each injection

	% reduction							
	Promethazine		Promazine		Chlorpromazine		Acepromazine	
Dose mg/kg:	0·5	1·0	0·25	0·50	0·125	0·25	0·0125	0·025
Rabbit								
1	34	65	22	72	17	50	44	72
2	37	64	17	17	28	51	0	14
3	18	78	12	29	45	35	23	61
4	61	89	46	59	26	69	28	78
5	50	81	41	61	34	76	56	64
6	58	71	21	72	53	73	56	75
7	44	86	63	90	36	70	60	58
Mean	43	76	31	57	34	60	38	60
s.d.	14·8	9·95	22·6	25·7	12·6	15·3	22·2	21·7
Dose causing 50% reduction (base mg/kg)	0·536		0·384		0·18		0·019	
Activity ratio	0·34		0·47		1·0		9·4	
Regression								
t	4·92		2·14		3·6		1·89	
P	0·001		0·1–0·05		0·1–0·001		0·1–0·05	
Deviation from parallel *t*	0·77		0·09		—		0·4	

from the dose causing 50% reduction, together with the "t" value for significance of regression and deviation from parallelism, is also given. Acepromazine was found to be 9.4 times as active as chlorpromazine. Promazine (0.46 times) and promethazine (0.34 times) were both less active.

The "t" value for regression is highly significant for promethazine and chlorpromazine but not significant for promazine and acepromazine. The results obtained with the latter two drugs must therefore be viewed with caution. A reversal of response was obtained with two doses of acepromazine in one animal.

The following phenothiazines were also tested:

Trimeprazine tartrate
10-(3-dimethylamino-2-methylpropyl)phenothiazine tartrate.

Methotrimeprazine
10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine.

Perphenazine
2-chloro-10-[3-{4-(2-hydroxyethyl)piperazin-1-yl} propyl]phenothiazine.

Percentage reductions in activity were recorded in a number of animals for varied doses of the above derivatives, injected without any systematic order. Each rabbit received at least one dose of chlorpromazine and one dose of another compound. The following simplified procedure was then adopted to determine anti-tetanus activity. The reductions in tetanus activity were averaged, each average being the mean of at least 4 observations. The final activity ratios were determined by assuming a regression for chlorpromazine similar to that found in the experiments summarized in Table 2, the justification for adopting this procedure being that the reductions in tetanus obtained with chorpromazine in the present series were similar to those in the earlier one. The activity ratios relative to chlorpromazine, obtained in this manner, were methotrimeprazine, 2.4; trimeprazine, 0.5; and perphenazine, 0.25.

Prochlorperazine methanesulphonate, 2-chloro-10-{3-(4-methylpiperazin-1-yl)-propyl}phenothiazine methanesulphonate, showed anti-tetanus activity only with doses in excess of 1 mg/kg and probably possesses 1/10th of the activity of chlorpromazine. A similar order of activity was obtained with pecazine [mepazine; 10-(1-methylpiperid-3-ylmethyl)phenothiazine].

In summary the following anti-tetanus activities were found. The bracketed values indicate approximate estimates.

Acepromazine	9.4	Promazine	0.46
Methotrimeprazine	(2.4)	Promethazine	0.34
Chlorpromazine	1.0	Perphenazine	(0.25)
Trimeprazine	(0.5)	Prochlorperazine	(0.1)

Compounds with mephenesin-like action

The effects of mephenesin, meprobamate, dicyclopropyl ketoxime and 2-amino-6-methylbenzothiazole were tested on a number of rabbits. Whenever possible more than one drug was given to each animal, but due to unaccountable fluctuations in the persistence of local tetanus during the experiment this was not always possible. Recorded reductions in activity are given in Table 3. Although these results do not lend themselves to statistical analysis, the best estimate of relative activity was

TABLE 3

PERCENTAGE REDUCTIONS IN TETANUS ACTIVITY PRODUCED BY SOME CENTRALLY ACTING MUSCLE RELAXANTS

Percentage reductions in tetanus activity were calculated for 20 min after each injection. The method of calculating relative activities is outlined in the text

	Mephenesin		2-Amino-6-methyl-benzothiazole		Dicyclopropyl ketoxime		Meprobamate	
Animal	Dose mg/kg	% reduction	Dose mg/kg	% reduction	Dose mg/kg	% reduction	Dose mg/kg	% reduction
1			20	61	20	75		
2	50	36	25	60	25	81		
3	50	69			25	84	30	42
4					25	42	30	13
5	50	92	25	92	25	69		
6			25	90				
7					25	76		
8	25	57					25	16
9	25	49					50	43
Activity ratio	1·0		2·6		2·3		0·43	

obtained by a method similar to that outlined in the preceding section except that the average regressions for mephenesin and meprobamate were used for the calculation of activity ratios.

Both dicyclopropyl ketoxime and 2-amino-6-methylbenzothiazole were over twice as active as mephenesin, but meprobamate showed less anti-tetanus activity at the dose used. The mean time courses of action of these drugs are plotted in Fig. 2.

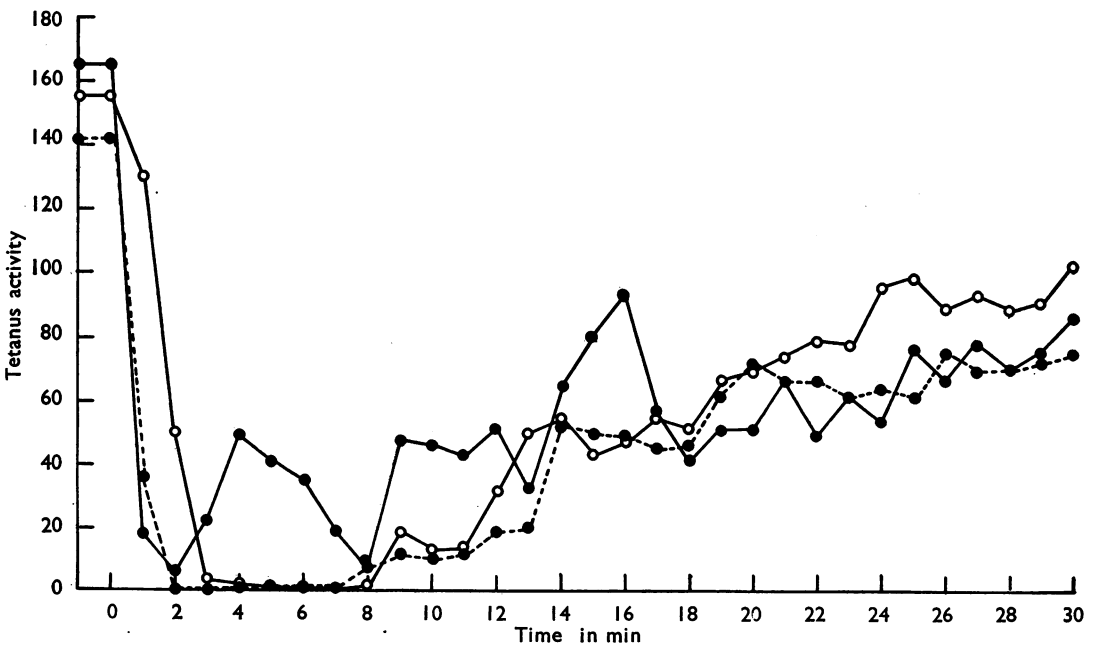


Fig. 2. Mean time course of the anti-tetanus activity of mephenesin (●---●), dicyclopropyl ketoxime (●——●) and 2-amino-6-methyl-benzothiazole (○——○). Mean results for 4 animals are shown. All injections were performed at 0 min. Tetanus activity is expressed as the count of units of integrated electromyogram activity.

Although all compounds were basically similar in action, dicyclopropyl ketoxime did not produce the same depth of depression as mephenesin, and in each animal receiving this compound sudden bursts of activity lasting 2 to 3 min occurred between periods of complete abolition.

DISCUSSION

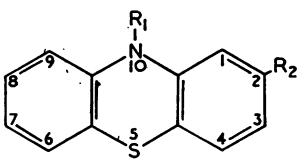
In these experiments phenothiazine derivatives with different side-chains and with various radicals attached to position 2 of the phenothiazine nucleus (Table 1) have been tested for anti-tetanus activity. The results obtained make it possible to draw certain conclusions regarding structure–activity relationships.

Representatives of five series of derivatives with different side-chains, promethazine, promazine, trimeprazine, prochlorperazine and perphenazine, have been investigated. The data are summarized in Table 4.

TABLE 4

THE EFFECT OF CHEMICAL STRUCTURE ON THE ANTI-TETANUS ACTIVITY OF SOME PHENOTHIAZINE DERIVATIVES RELATIVE TO CHLORPROMAZINE

The experimentally determined activity ratios are shown together in the square with each compound. The contribution of the side-chains to the activity ratios is given by the factors r_1 and r_2. The method of calculation of r_1 and r_2 is discussed in the text



R_1		R_2			
		—	-Cl	$-OCH_3$	$-CO.CH_3$
	r_1/r_2	0·46	1·0	2·2	9·4
$-CH_2.CH(CH_3).CH_2.N(CH_3)_2$	1·09	Trimeprazine 0·5		Metho-trimeprazine 2·4	
$-[CH_2]_3.N(CH_3)_2$	1·0	Promazine 0.46	Chlorpro-mazine 1·0		Acepro-mazine 9·4
$-CH_2.CH(CH_3).N(CH_3)_2$	0·716	Prometha-zine 0·33			
$-[CH_2]_3-N$ (piperazine) $N-CH_2.CH_2OH$	0·25		Perphenazine 0·25		
$-[CH_2]_3-N$ (piperazine) $N-CH_3$	0·1		Prochlor-perazine 0.1		

This table contains activity ratios relative to chlorpromazine, of the anti-tetanus activity of a number of phenothiazine derivatives differing in respect of side-chains R_1 and R_2. The contributions r_1 and r_2 of each side-chain to the activity ratio have been calculated in such a way that $r_1 r_2$ = activity ratio. For example, to calculate the contributions of the side-chains in methotrimeprazine:

r_1 (trimeprazine side-chain R_1): $TP/PZ = 0.5/0.46 = 1.09$

r_2 (methoxyl side-chain R_2): $\frac{MT}{TP} \Big/ \frac{CP}{PZ} = \frac{2.4}{0.5} \Big/ \frac{1}{0.46} = 2.2$

Hence r_1r_2 (1.09) (2.2)=2.4=experimental activity ratio. TP=trimeprazine, PZ=promazine, MT=methotrimeprazine, CP=chlorpromazine.

The most active compounds are those with a 3-dimethylaminopropyl or a 3-dimethylamino-2-methylpropyl side-chain. The introduction of a piperazine ring reduces anti-tetanus activity considerably. The order of activity of the different side-chains is given in Table 4. With regard to the side-chain R_2 the acetyl and methoxyl derivatives are the most active. The order of potency of the side-chains R_2 is $COCH_3 : OCH_3 : Cl : H$ in the ratio 9.4:2.2:1.0:0.46.

It would be interesting to test the validity of the assumptions made in calculating the contributions of the two side-chains to anti-tetanus activity by testing compounds whose activity can be predicted from Table 4 by "completing a square." Thus the activity of methoxypromazine would be expected to be 2.2 and that of chlorpromethazine 0.72.

TABLE 5

A COMPARISON OF THE ANTI-TETANUS AND OTHER CENTRAL ACTIONS OF SOME PHENOTHIAZINE DERIVATIVES

The activity of each compound is expressed in relation to chlorpromazine. Some values were estimated from experimental results given in the papers referred to and are therefore only approximate

Derivative	Anti-tetanus activity	Depression of motor activity	Conditioned response	Anaesthetic potentiation	Anti-emetic activity	Reference
Acepromazine	9·4	1·66	—	—	—	(1)
		2·0	—	—	—	(2)
	—			6·0	2·0	(3)
Methotrimeprazine	2·4	2·5	2·0	4·0	0·9	(4)
Trimeprazine	0·5	0·66	0·6	0·8	0·33	(5)
Promazine	0·47	0·5				(6)
		0·5	0·5	0·5	0·2	(7)
Promethazine	0·34	0·05	0·5			(8)
				0·25		(9)
					0·1	(10)
Perphenazine	0·25	10·0	10·0	1·0		(6)
					24·0	(11)
Prochlorperazine	0·1	0·4	1·0	0·5	4·0	(12)

References: (1) Delay & Deniker (1957). (2) Wirth, Gässwald, Hörlein, Risse & Kreiskott (1958). (3) Mercier, Schmitt, Navarro, Gavend & Gavend (1957). (4) Courvoisier, Ducrot, Fournel & Julou (1957b, 1957c). (5) Courvoisier, Ducrot, Fournel & Julou (1958). (6) Arrigoni-Martelli & Kramer (1959). (7) Wirth (1958). (8) Fellows & Cook (1957). (9) Kopera & Armitage (1954). (10) Courvoisier, Fournel, Ducrot, Kolsky & Koetschet (1953). (11) Rosenkilde & Govier (1957). (12) Courvoisier, Ducrot, Fournel & Julou (1957a).

In an attempt to correlate anti-tetanus activity with some other property of the phenothiazine derivatives the literature on the pharmacology of the eight derivatives tested was reviewed. Amongst other indices of central nervous system activity, summarized in Table 5, only that for potentiation of anaesthesia appears to be correlated with anti-tetanus activity. Acepromazine is 6 times as active as chlorpromazine in this respect, which agrees reasonably with anti-tetanus activity (9.4 times), but perphenazine and prochlorperazine are relatively more active in prolonging anaesthesia than against tetanus.

From observations on anti-adrenaline, hypothermic and antihistamine activity, summarized in Table 6, it appears that there is a good correlation between anti-

TABLE 6

A COMPARISON OF THE ANTI-TETANUS, ANTI-ADRENALINE, ANTIHISTAMINE AND HYPOTHERMIC ACTIVITY OF SOME PHENOTHIAZINE DERIVATIVES

Derivative	Anti-tetanus activity	Anti-adrenaline activity	Anti-histamine activity	Hypo-thermic activity	Ref.
Acepromazine	9·4	10·0			(13)
		10·0			(14)
				2·0	(3)
Metho-trimeprazine	2·4	1·2	150	2·0	(4)
Chlorpromazine	1·0	1·0	1·0	1·0	
Trimeprazine	0·5	0·25	120	0·6	(5)
Promazine	0·47	0·5	0·5	—	(7)
Promethazine	0·34	0·1		0·25	(9)
			100		(10)
Perphenazine	0·25	0·25	1·0	0·05	(6)
Prochlorperazine	0·1	0·17	0·5	0·4	(12)

References continuous with Table 5. (13) Schmitt *et al.* (1957). (14) Brunaud *et al.* (1957a). The activity of all compounds is expressed in relation to chlorpromazine.

adrenaline and anti-tetanus activity. This is the only test in which acepromazine is 10 times as active as chlorpromazine. The anti-adrenaline activity of most other compounds is within a factor of two of their anti-tetanus activity. Some reduction in anti-adrenaline activity occurs in compounds which are powerful antihistamines, such as promethazine, trimeprazine and methotrimeprazine, all of which are over 100 times as active as chlorpromazine in this respect. A close correlation between anti-adrenaline and barbiturate potentiation has been reported by Brunaud, Schmitt, Aurousseau & Navarro (1957a & b) for a series of phenothiazine derivatives.

Some of the central effects of chlorpromazine can probably be explained by its adrenolytic activity. Adrenaline is known to produce electroencephalogram arousal (Bonvallet, Dell & Hiebel, 1954) and to facilitate spinal cord activity by an action on the brain stem (Dell, Bonvallet & Hugelin, 1954). Chlorpromazine has been shown to antagonize electroencephalogram arousal, whether induced by adrenaline (Hiebel, Bonvallet & Dell, 1954 ; Dell, Bonvallet & Hugelin, 1956 ; Bradley & Hance, 1957) or by nociceptive stimulation (Longo, Von Berger & Bovet, 1954 ; Rinaldi & Himwich, 1955 ; Bradley & Hance, 1957 ; and Unna & Martin, 1957) and to inhibit the facilitating effect of brain stem stimulation on spinal activity (Dasgupta & Werner, 1955 ; Henatsch & Ingvar, 1956).

Acepromazine is known to block the arousal response in a dose 1/6 to 1/10 of that of chlorpromazine (Schmitt, Mercier, Aurousseau, Hallot & Comoy, 1957). In addition, although chlorpromazine offers no protection against strychnine and leptazol it counteracts the convulsions produced by amphetamine and cocaine (Meidinger, 1956), both of which have central actions similar to adrenaline.

The ineffectiveness of meprobamate against experimental tetanus is rather surprising and not easily explained in view of its supposed muscle-relaxing activity and its apparent clinical value in tetanus (Perlstein, 1959). The fact that most of the information on this compound has come from one laboratory prompted Pfeiffer *et al.* (1957) to repeat some of the early pharmacological investigations. The

results of their experiments showed that meprobamate in fact possessed few of the properties of mephenesin. They preferred to classify it as a barbiturate with some of the properties of trimethadione, which is known to have no anti-tetanus activity (unpublished data).

A consideration of the difference in the effectiveness of mephenesin and meprobamate against strychnine and leptazol convulsions may help to explain the weak anti-tetanus activity of meprobamate. Compounds with relatively specific anti-strychnine activity are usually effective anti-tetanus drugs, probably because of the similar central actions of strychnine and tetanus toxin (a possible exception are the phenothiazine derivatives). Drugs which are especially effective against leptazol, however, are usually relatively weak anti-tetanus agents, unless they are capable of producing a widespread depression of the central nervous system.

Meprobamate is 5 times as active as mephenesin against leptazol and electroshock-induced convulsions, but only equally effective against strychnine convulsions (Berger, 1954 ; Pfeiffer *et al.*, 1957). Qualitative differences between the effects of these two compounds on strychnine and leptazol convulsions have also been observed. Pfeiffer *et al.* (1957) found that leptazol produced clonic convulsions when given after mephenesin but tonic extensor convulsions after meprobamate. In addition, meprobamate failed to raise the threshold to timed intravenous infusions of strychnine above 30%, whereas mephenesin, in smaller dose, raised it to above 100%. In this respect meprobamate resembled trimethadione. If anti-strychnine activity can be taken as a reliable guide of anti-tetanus potency these results suggest that mephenesin might possibly be more effective against tetanus than meprobamate.

Since both tetanus toxin and strychnine are thought to act primarily at the spinal level the ability of drugs to depress spinal reflexes should be a reliable guide to anti-tetanus activity. Mephenesin is twice as active as meprobamate in this respect (Pfeiffer *et al.*, 1957), but only half as active as 2-amino-6-methylbenzothiazole (Funderburk *et al.*, 1953). This order of activity is comparable to their anti-tetanus potency.

Another difference between the central action of mephenesin and meprobamate has been reported by Perlstein (1956), who found that, unlike mephenesin, which is of little value in the treatment of epilepsy, meprobamate is very effective against petit mal. This is a condition which is believed to originate from a focal disturbance of subcortical centres where electroencephalogram observation (Hendley *et al.*, 1955) suggests that meprobamate may act. Perlstein (1956) found that meprobamate produced no relief of spasticity in patients with pyramidal disorders.

These observations suggest that meprobamate may not be primarily a muscle relaxant of the mephenesin type. For, although it has been used with some apparent success in the relief of muscle tone in clinical tetanus (Perlstein, 1959), only those spasms induced by somatic stimuli such as noise, light or a pin-prick were controlled, whereas spasms triggered by visceral or propioceptive stimuli and which could be controlled with chlorpromazine were not suppressed (Perlstein, Stein & Elam, 1960).

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