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TACHYPHYLAXIS TO THE ANTI-TETANUS ACTIVITY OF SOME PHENOTHIAZINE COMPOUNDS

BY

D. R. LAURENCE AND R. A. WEBSTER

From the Department of Pharmacology, University College, London

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Although chlorpromazine and acepromazine were the most potent suppressants of local tetanus induced in rabbits by intramuscular injection of the toxin of *Cl. tetani*, repeated injections lost their effect (tachyphylaxis) and sometimes even increased muscle activity, as did single large injections of either of the two drugs. As neither tachyphylaxis nor stimulation occurred in spinal animals, these effects might arise from an action in the brain-stem reticular formation on which chlorpromazine has been shown to have both inhibitory and excitatory effects. The possible cause of the tachyphylaxis is discussed. Evidence is advanced to support the view that tachyphylaxis can occur when chlorpromazine is used in the treatment of tetanus in man. Methotrimeprazine was more potent than chlorpromazine, but less prone to induce tachyphylaxis. These qualities rendered it more desirable for clinical use than the other two compounds.

The phenothiazine derivatives are known to abolish muscle spasm of tetanus both in animals (Laurence & Webster, 1958b) and in man (Adams, Wright, Berman & Laurence, 1959). Quantitative assessments of the activity of a number of these compounds in animals have shown acepromazine and chlorpromazine to be the most potent, acepromazine being ten times as active as chlorpromazine.

When repeated doses of both drugs were given to rabbits with local tetanus over periods of up to eight hours, it was found that a dose, initially effective, might become ineffective or even increase muscle activity. This reduced response to repeated doses, or tachyphylaxis, is the principal subject of this report.

METHODS

Local tetanus was induced in one hind limb of rabbits by the injection of 1,250 mouse minimum lethal doses (M.L.D.) of tetanus toxin into the gastrocnemius muscle.

The intensity of muscle spasm was measured by integrated electromyography which allows the level of tetanus to be expressed in units of activity per minute (Laurence & Webster, 1958a).

Tetanus was maintained at a constant level by employing either an auditory and vibratory stimulus (Laurence & Webster, 1958a), or, in the case of spinal animals, an electrical stimulus. Body temperature of the animals was maintained by electrical radiant heaters throughout the experiment.

Drugs were given intravenously. In the cross-over method of testing at least 24 hr elapsed between each experiment on the same animal. Counts of activity were made during ten

consecutive control periods each of 1 min before each experiment, and then minute counts of muscle activity were recorded for 20 min after the first injection. Subsequently, in prolonged experiments, aggregate counts for 10 min periods were alternated with minute counts for 5 min.

RESULTS

Tachyphylaxis to, and stimulation by, chlorpromazine and acepromazine. An attempt was made to suppress tetanus almost continuously for approximately 8 hr with repeated doses of 1 mg/kg of either acepromazine or chlorpromazine. Injections were made whenever activity returned to 75% of the untreated control value. It was not always easy to apply this criterion, for activity often returned to, and remained for some while at, just below 75% of the control value. On these occasions a further injection was made if activity remained at the same level for 30 min.

On other occasions, when an injection was followed by increased muscle activity, as sometimes happened, another injection was not made immediately but only after the stimulation had lasted for a few minutes and was unequivocal.

The effect of repeated doses of chlorpromazine on the integrated electromyogram is shown in Fig. 1. It can be seen that activity increased above the control after the third, continued to increase after the fourth, and was barely affected by the fifth dose. The result of a similar experiment with acepromazine is shown in Fig. 2. A relatively high dose was used which soon ceased to have any material suppressant effect.

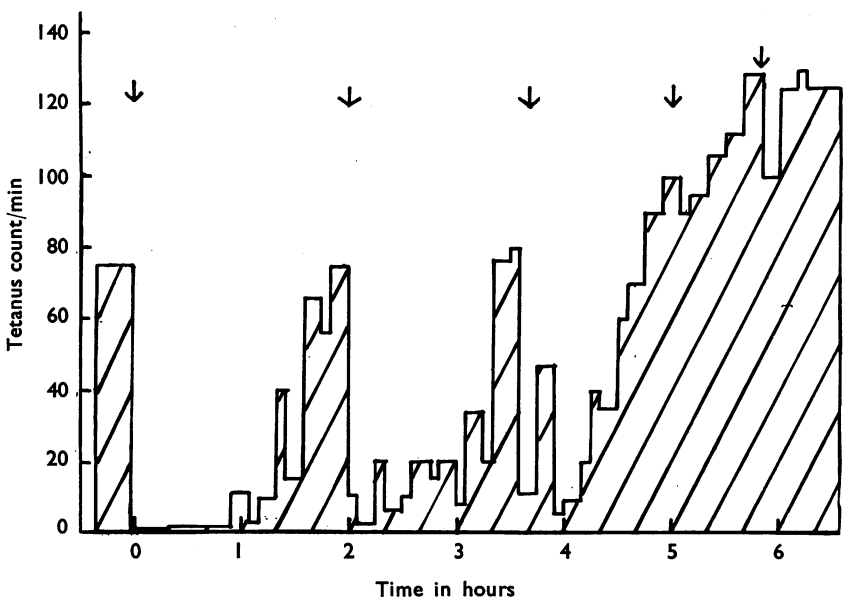

Fig. 1. Tachyphylaxis to chlorpromazine in experimental tetanus. The time course of tetanus activity in a rabbit receiving 1 mg/kg injections of chlorpromazine at the arrows is shown. A distinct tachyphylaxis developed.

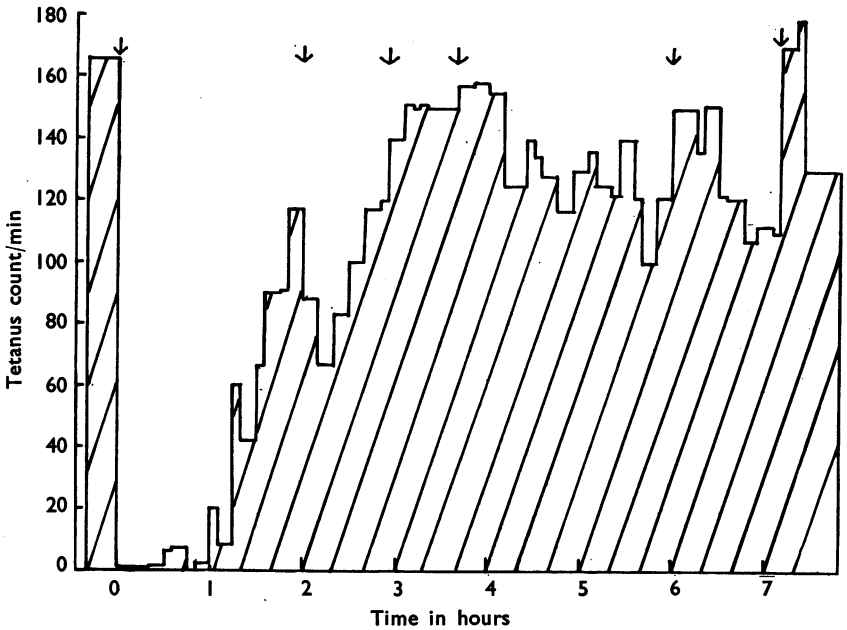

Fig. 2. Tachyphylaxis to acepromazine in experimental tetanus. The time course of tetanus activity in a rabbit receiving 1 mg/kg injections of acepromazine at the arrows is shown. A marked tachyphylaxis developed.

In all except one experiment (BE 59), chlorpromazine (n=6) (1 mg/kg) was followed by a decrease in activity, however slight or transient (Table 1). On the other hand, acepromazine in the same dose invariably caused immediate stimulation in the third or subsequent injection. In 2 further experiments a smaller dose of acepromazine (0.2 mg/kg) also showed tachyphylaxis even though the total dose did not exceed 1 mg/kg, a dose which, when given initially, abolished tetanus activity almost completely.

TABLE 1

REDUCTIONS IN TETANUS ACTIVITY FOLLOWING SUCCESSIVE DOSES OF ACEPROMAZINE AND CHLORPROMAZINE

Reductions in activity for the 1st hour after each injection were calculated in comparison with the level of activity immediately before *that* injection. Negative values indicate stimulation

		Percentage reduction								
		Chlorpromazine injection					Acepromazine injection			
Animal	Dose (mg/kg)	1	2	3	4	Dose (mg/kg)	1	2	3	4
B58	1·0	93	58	93	43	1·0	92	31	−26	—
B59	1·0	97	84	71	−11	1·0	98	21	−28	4
B64	1·0	82	61	39	68	1·0	85	−40	−19	15
B65	1·0	96	92	68	54	1·0	87	−3	−24	11
						Mean	90	2	−24	10
B82	1·0	91	61	—	—	0·2	70	25	17	28
B83	1·0	87	68	66	81	0·2	54	18	6	8
Mean		90	66	63	43	Mean	62	21	11	18

TABLE 2

REDUCTIONS IN TETANUS ACTIVITY FOLLOWING SUCCESSIVE DOSES OF ACEPROMAZINE AND CHLORPROMAZINE

Reductions in activity for the 1st hour after each injection were calculated in comparison with the level of activity immediately before the 1st injection. Negative values indicate stimulation

		Percentage reduction								
		Chlorpromazine injection					Acepromazine injection			
Animal	Dose (mg/kg)	1	2	3	4	Dose (mg/kg)	1	2	3	4
B58	1·0	93	67	93	55	1·0	92	44	25	—
B59	1·0	97	83	65	−40	1·0	98	45	9	13
B64	1·0	82	75	57	80	1·0	85	8	25	52
B65	1·0	96	95	82	79	1·0	87	31	22	18
						Mean	90	32	20	28
B82	1·0	91	61	—	—	0·2	70	52	50	46
B83	1·0	83	68	66	81	0·2	54	50	37	36
Mean		90	75	73	51	Mean	62	51	43	45

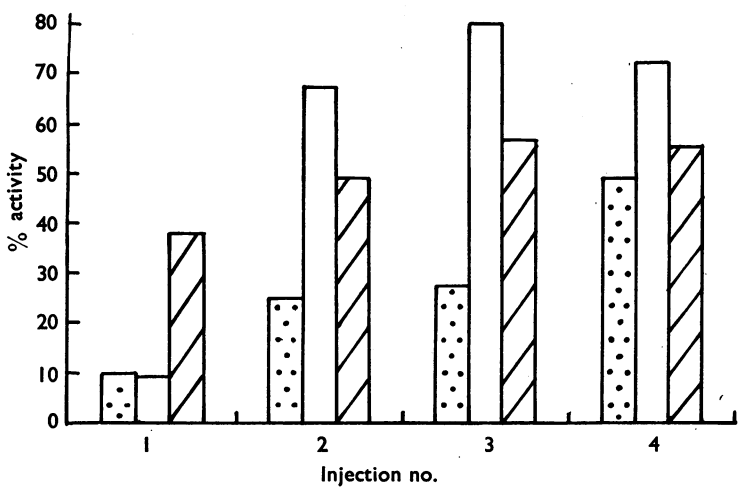

Fig. 3. Tachyphylaxis to the anti-tetanus activity of acepromazine and chlorpromazine. Mean results are plotted for 1 mg/kg chlorpromazine (dotted columns) (6 animals), 1 mg/kg acepromazine (white columns) (4 animals) and 0.2 mg/kg acepromazine (hatched columns) (2 animals). The interval between injections varied from animal to animal, being between 1·5 and 2 hr. Percentage activity values were calculated for the 1st hour after each injection compared with the level of activity before the 1st injection. Although tachyphylaxis developed with all doses, activity did not exceed the control level.

From Table 2 and Fig. 3, it can be seen that tachyphylaxis developed more rapidly with acepromazine than it did with chlorpromazine.

The immediate stimulation which often followed acepromazine injections is shown when the results in Table 1 are plotted (Fig. 4).

Once the tetanus-suppressing activity of either drug began to diminish, increasing the dose by up to five times not only failed to reduce activity but usually stimulated it.

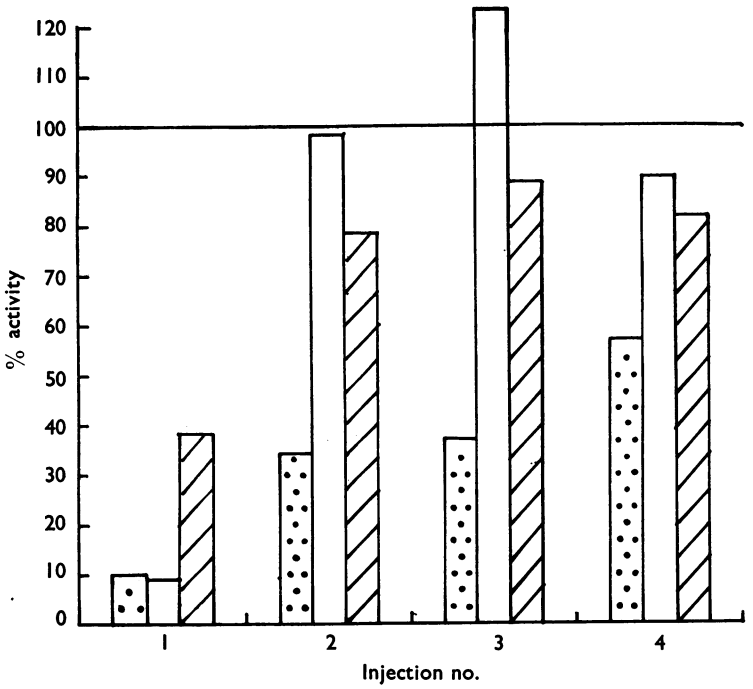

Fig. 4. Tachyphylaxis to the anti-tetanus activity of acepromazine and chlorpromazine. Mean results are plotted for 1 mg/kg chlorpromazine (dotted columns) (6 animals), 1 mg/kg acepromazine (white columns) (4 animals) and 0·2 mg/kg acepromazine (hatched columns) (2 animals). The interval between injections varied from animal to animal, being between 1·5 and 2 hr. Percentage activity values were calculated for the 1st hour after each injection, compared with level of activity before *each* injection. Considerable stimulation occurred after the 3rd 1 mg/kg dose of acepromazine, but activity did not exceed the control level.

Control injections of saline did not produce any consistent change in activity in two animals.

Cross-tachyphylaxis. In 3 experiments in which tachyphylaxis had developed to chlorpromazine, acepromazine failed to reduce tetanus (Fig. 5) and vice versa.

Effect of other drugs after tachyphylaxis had developed. When tachyphylaxis to these phenothiazines had developed, both thiopentone (Fig. 5) and mephenesin retained their usual suppressant effect on tetanus.

Optimal anti-tetanus dose of chlorpromazine and acepromazine. The experiments demonstrating tachyphylaxis suggest that there may be an optimum dose of chlorpromazine and of acepromazine for controlling tetanus, and that to exceed this may not merely offer no advantage but may even be positively disadvantageous.

Three doses of chlorpromazine (1.0, 5.0, 10.0 mg/kg) and of acepromazine (1.0, 2.5, 5.0 mg/kg) were therefore given singly to 3 animals with local tetanus, and the percentage reduction of muscle activity calculated for both the first and second hours after each injection. From the results shown in Fig. 6, it appears that there

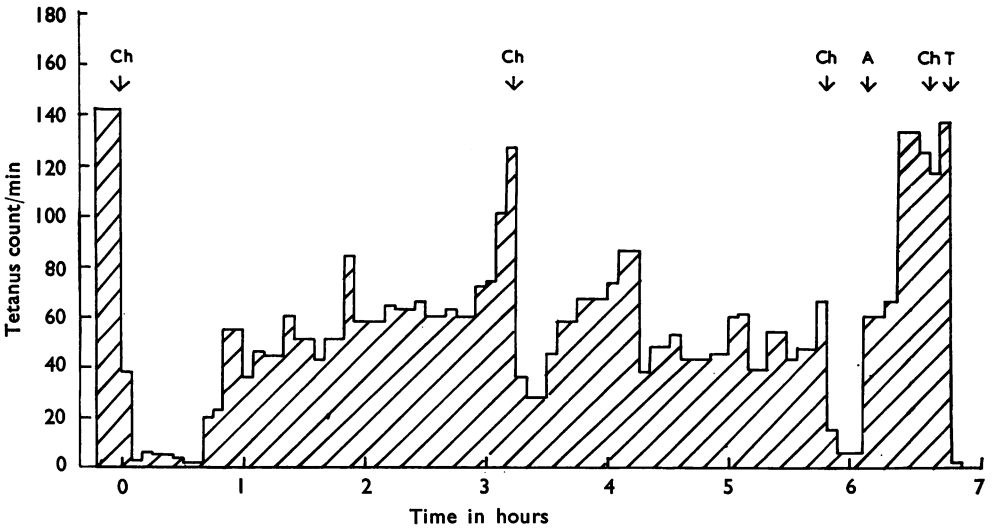

Fig. 5. Cross-tachyphylaxis to the anti-tetanus activity of acepromazine and chlorpromazine. The effect of acepromazine 1 mg/kg (A) and chlorpromazine 1 mg/kg (Ch) on the time-course of tetanus activity is shown. Acepromazine stimulation after chlorpromazine and the normal effect of thiopentone 6 mg/kg (T) are shown.

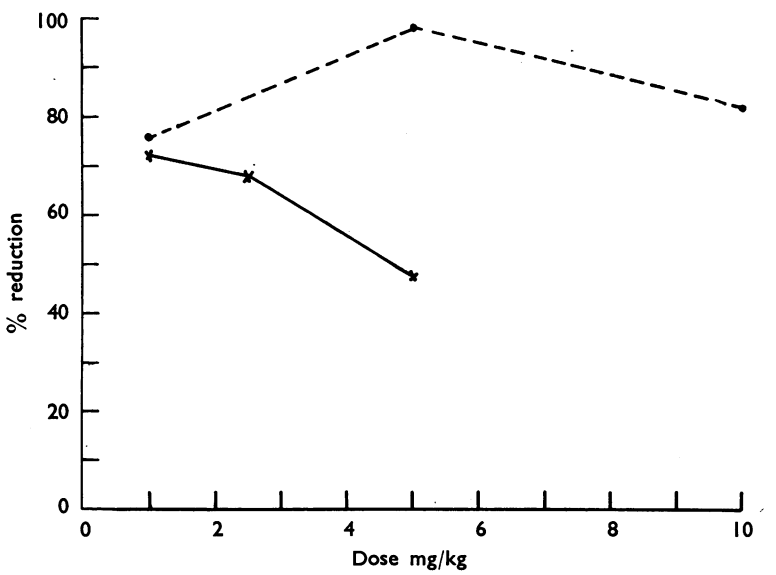

Fig. 6. Optimal doses for the anti-tetanus activity of acepromazine (×——×) and chlorpromazine (●--●). Percentage reductions were calculated for the 2 hr period after each injection. Each point is the mean of results obtained from at least 3 animals. A sharp decline in the activity of acepromazine above 1 mg/kg is shown.

seems to be an optimal dose for each compound in rabbits, 5 mg/kg for chlorpromazine and at, or just below, 1 mg/kg for acepromazine. Above 1 mg/kg chlorpromazine is more effective than acepromazine, whereas at lower doses the converse is true (Laurence & Webster, 1958b).

If the results of the above experiment are combined with those obtained in the assay of the anti-tetanus activity of these two drugs by Laurence & Webster (1958b), a full dose-response relationship can be plotted (Fig. 7). The slope for chlorpromazine is much steeper than that for acepromazine.

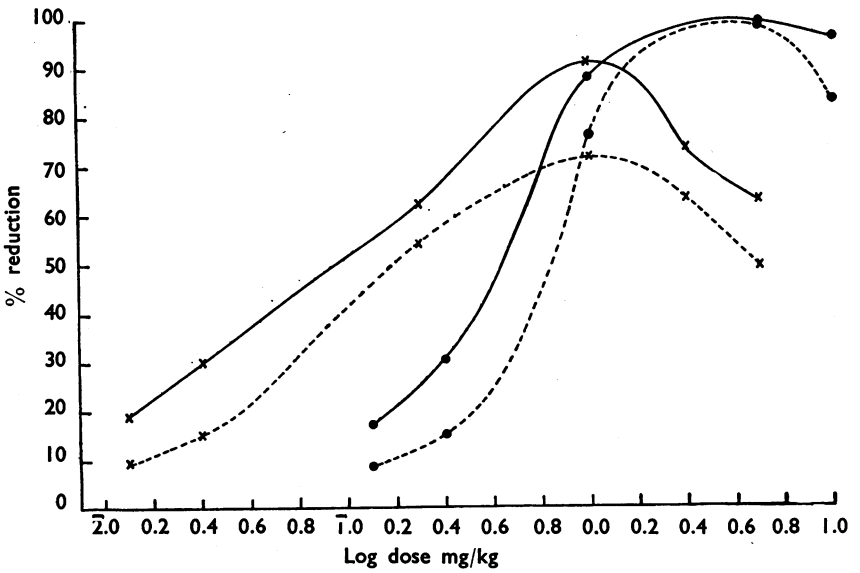

Fig. 7. Dose-response relationship for the anti-tetanus activity of acepromazine and chlorpromazine. Each point is the mean of at least 3 observations. Percentage reductions were calculated for the 1st (acepromazine ×——×; chlorpromazine ●——●) and 2nd hr (acepromazine × - - - ×; chlorpromazine ● - - - ●) after injection. Values for the two lower doses were estimated from data obtained in previous experiments.

The method of plotting results, used above, does not show whether the reduced effectiveness of large doses of acepromazine was due to a reduction in depth of suppression or in duration of action. From the plot of the time-courses of muscle activity following 1.0, 2.5 and 5.0 mg/kg acepromazine (Fig. 8), it can be seen that, although the initial depression of activity was similar with all three doses, the higher doses provided slightly less depression than did the optimal dose of 1 mg/kg. The duration of action, however, decreased with higher doses. The secondary depression of activity at 1.75 hr after 2.5 mg/kg of acepromazine was common to all three animals.

An experiment related to the possible clinical importance of tachyphylaxis. Since chlorpromazine has been advocated in the routine control of clinical tetanus (Laurence, Berman, Scragg & Adams, 1958; Adams *et al.*, 1959; Packard, Cartmill & Henry, 1958), it would be useful to know whether tachyphylaxis occurs in man.

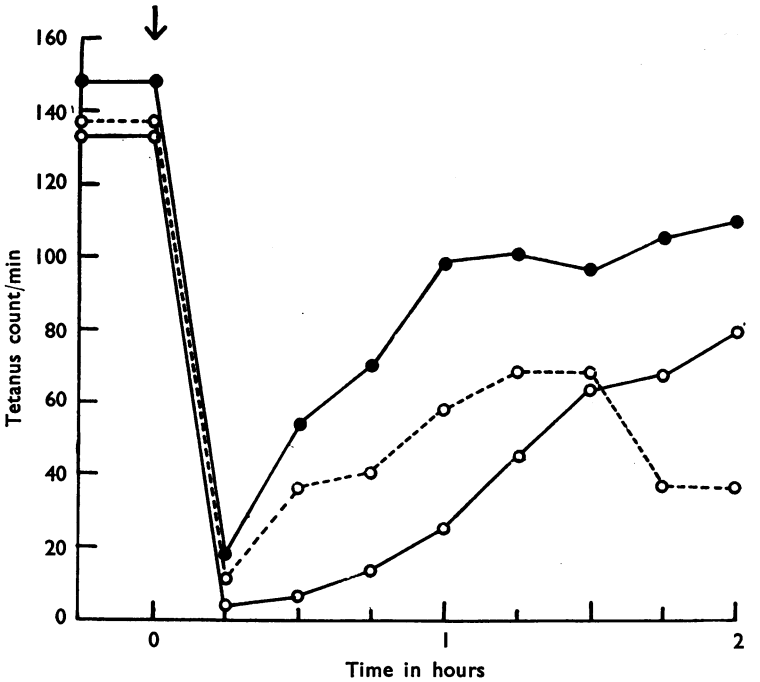

Fig. 8. Mean time-course of the anti-tetanus activity of varying doses of acepromazine given at the arrow (●——● 5 mg/kg; O - - - O 2·5 mg/kg; O——O 1 mg/kg). Mean results for 3 animals are plotted. Although a similar initial depression was obtained with each dose the subsequent rise in activity increased in proportion to dose.

It was recalled by one of us that chlorpromazine, even in large and frequently repeated doses, had notably failed to control very severe tetanus in one patient treated under the care of Professor E. B. Adams during a therapeutic comparison of chlorpromazine with barbiturates (Laurence *et al.*, 1958). This man received, over 5 hr, a total of approximately 16 mg/kg of chlorpromazine intravenously in 6 doses. His convulsions, inadequately controlled from the start, became worse and he died.

Chlorpromazine, on a similar mg/kg basis, was given to each of two rabbits with local tetanus at the same time intervals as the patient received his injections. Tachyphylaxis occurred in both experiments and chlorpromazine ceased to have any useful suppressant effect. The time-course of tetanus activity in one experiment is shown in Fig. 9. It is clear that doses of chlorpromazine, which have been used in man, are capable of inducing tachyphylaxis (and possibly stimulation) in experimental tetanus.

Qualitative differences between experimental tetanus and tetanus activated by phenothiazines. When tetanus was activated by a phenothiazine derivative, muscle activity differed from normal and often bore no relationship to the standard afferent stimulus used to activate it. Spontaneous tremors and twitches sometimes occurred

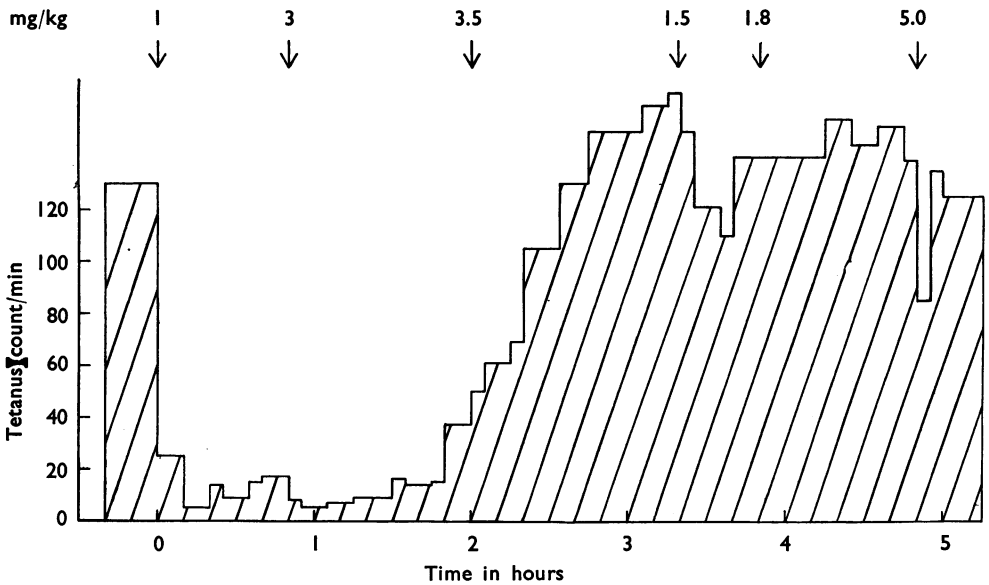

Fig. 9. Time-course of an experimental demonstration of the possible clinical importance of tachyphylaxis. Doses of chlorpromazine given to a patient with general tetanus expressed in mg/kg and injected into a rabbit at the arrows, with local tetanus at the same time-intervals as they were received by the patient, in whom they became ineffective. Stimulation occurred after the 3rd injection.

in both the tetanus and control limbs, and occasionally muscle activity in the control limb even exceeded that in the affected one.

As the depressant effect of a large dose (for example, 5 mg/kg or more) wore off, it was usually followed by an increase in activity above the control level and, if a second dose was given during the subsequent 24 hr, this was often followed by immediate activation. This activated tetanus could be abolished by mephenesin or a barbiturate drug.

In normal rabbits receiving large doses of acepromazine (5 mg/kg) or chlorpromazine (10 mg/kg), tremors and twitches sometimes occurred, but were only rarely associated with sustained regular hyperactivity.

Tachyphylaxis in the spinal rabbit. In order to discover whether tachyphylaxis could be demonstrated in the spinal animal with acepromazine, four rabbits underwent spinal section in the lower thoracic region under thiopentone and ether anaesthesia and tetanus toxin was injected intramuscularly 48 hr later. Following operation they required careful nursing with expression of urine from the bladder at least once daily. On recovery, the level of tetanus activity in the spinal animal was always substantially below that in the intact animal, and it was necessary to use an electrical cutaneous stimulus to maintain regular activity. Electrode polarity was regularly reversed to avoid alteration in the stimulus due to polarization of the electrodes.

When acepromazine was given, neither tachyphylaxis nor stimulation was now observed in any of the 4 animals, but tetanus was reduced by about 60%.

Other phenothiazines. As tachyphylaxis and stimulation are clearly undesirable properties of an anticonvulsant, a number of other phenothiazines, including perphenazine, trimeprazine, and methotrimeprazine (Veractil), were tested for potency (unpublished observations). Promethazine and promazine had been previously compared with chlorpromazine (Laurence & Webster, 1958b). The only compound, apart from acepromazine, found to be more potent than chlorpromazine was methotrimeprazine, which was about twice as potent. A single dose of 1 mg/kg abolished tetanus for 1 to 2 hr in two rabbits and, after 4 hr, the activity had returned to only 30% of normal. Further doses showed no or only slight tendency to stimulate activity and tachyphylaxis seemed less. A single injection of 5 mg/kg of methotrimeprazine completely abolished all activity for 4 hr, but tremors followed after 10 mg/kg.

These results suggest that methotrimeprazine may be superior as an anticonvulsant to chlorpromazine for use in clinical tetanus. Opportunity has since arisen to treat a case of clinical tetanus with methotrimeprazine. A dose of 25 mg given intravenously enabled the patient to increase the jaw separation from 1.1 cm to 2.5 cm with symptomatic relief. During succeeding days doses of 25 to 50 mg given intravenously to a daily total of 400 mg appeared to relieve spasms, but no opinion on its clinical merit can be made on the basis of this single case.

DISCUSSION

Tachyphylaxis occurs with certain drugs such as nicotine and ephedrine, although it is doubtful whether there is a common underlying mechanism. The tachyphylaxis to the anti-tetanus activity of repeated doses of 1 mg/kg of acepromazine and of chlorpromazine reported here may be explained on the assumption that these phenothiazine derivatives may both depress and stimulate the central nervous system and that the time courses of these two actions differ considerably. The interrelationship between inhibition and excitation is probably complex, and excitation may only become obvious when the normal balance between inhibition and excitation in the central nervous system has been disturbed, as in tetanus. Although it has been shown that there is an optimal effective dose for both acepromazine and chlorpromazine and that large doses may become ineffective or even stimulate activity, it seems unlikely that tachyphylaxis is simply due to the accumulation of doses to exceed the optimal and produce excitation. Tachyphylaxis still occurred to the repeated injections of small doses of acepromazine, despite the fact that the first injection was only slightly effective and that the total dose did not reach the optimal single depressant dose. Also when 1 mg/kg of acepromazine was injected after four similar doses an immediate stimulation was obtained whereas a single injection of 5 mg/kg produced depression.

This latter observation and the fact that a large dose of acepromazine given 24 hr after a number of smaller doses resulted in immediate stimulation instead of the expected depression suggest that excitation lasts much longer than inhibition. Consequently, even though the potential excitatory action of any one dose is

probably considerably weaker than the inhibitory action, since the phenothiazines are primarily depressants, persistence of excitation after depression has worn off will ensure an accumulated effect with repeated doses which will gradually reduce the depressant effect of succeeding doses and eventually counteract the inhibitory effect of any one dose and produce stimulation. This would explain why tachyphylaxis occurred to the repeated injection of small as well as large doses.

That phenothiazine excitation is a distinct effect and not simply a loss of initial inhibition is also suggested by the finding that the activity recorded once tachyphylaxis has developed differs from typical tetanus. Twitches or tremor, seldom seen in tetanus, were often recorded either alone or superimposed on tonic activity, but the characteristic reflex response to afferent stimulation, obtained in the tetanus animal, was absent. Activity also often developed in a previously quiescent control limb, sometimes exceeding that in the affected limb, and brief stimulation was obtained in normal animals with large doses of both compounds.

The relationship between chlorpromazine-induced tremors and hypothermia has been discussed by Domer & Feldberg (1960). The possibility that hypothermia may have played a part in some of the experiments reported here has not been excluded but is not considered to be important, even if it occurred, since excitation immediately followed some injections and single large doses of phenothiazines had less suppressant activity on tetanus than smaller doses.

Another reversal of central effect with increased doses has been recorded by Rinaldi & Himwich (1955), who found that chlorpromazine depressed the electrical activity of the brain and the arousal response by an action on the reticular system in doses up to 10 mg/kg, but that higher doses had the reverse effect. As neither tachyphylaxis nor stimulation could be obtained in spinal animals in the present experiments, although they probably occur in decerebrate preparations (unpublished observation), phenothiazine stimulation would appear to be limited to the reticular system of the brain-stem. If this is so, tachyphylaxis may be only another example of the numerous extrapyramidal side-effects, similar to parkinsonism, that have been widely reported in patients receiving large doses of chlorpromazine (Moyer, Wright & Finney, 1955; Hall, Jackson & Swain, 1956; Giacobin & Lassenius, 1955; and Goldman, 1955).

Phenothiazine stimulation of the reticular system may involve the adrenergic mechanism which has been shown to exist at this level of the nervous system (Bonvallet, Dell & Hiebel, 1954; Hiebel, Bonvallet & Dell, 1954; Rothballer, 1956; Bradley, 1957), for, as pointed out by Himwich (1958), the structural formulae and in particular the side-chain of chlorpromazine and adrenaline are very similar. This may account for the fact that the phenothiazine derivatives are, to varying extents, antiadrenaline agents, and why acepromazine, which is the more active antiadrenaline derivative (Schmitt, Mercier, Aurousseau, Hallot & Comoy, 1957; Mercier, Schmitt, Navarro, Gavend & Gavend, 1958), also produced the most stimulation. Any relationship between the antiadrenaline activity of the phenothiazines and their effects in tetanus must be speculative. Since the most common examples of tachyphylaxis occur in the use of the sympathomimetic amines, it is of interest that tachyphylaxis has been recorded to the hypotensive antiadrenaline effects of chlor-

promazine both in man and animals (Dundee, 1958 ; Cahn, George & Pierre, 1957 ; Roth, Irwin, Eckhart, Tabacknick & Govier, 1959).

These results show that there is an optimal frequency of administration as well as an optimal dose for continuous suppression of tetanus in rabbits. This may be of considerable clinical importance, for the pharmacology of the phenothiazine compounds in rabbits and in man seems to be similar. That tachyphylaxis and perhaps also activation of tetanus by chlorpromazine might occur in man is strongly suggested by the present work. Barr (1958) and Packard *et al.* (1958) have both suggested that tolerance may occur in man.

Because acepromazine was more active than chlorpromazine, it was given preliminary clinical trial (Adams *et al.*, 1959) before it had been found to have the potential disadvantages reported here. It did not appear to be more than an alternative to chlorpromazine. The present experiments suggest that, had acepromazine been subjected to formal clinical trial, it might have proved unsatisfactory because of the occurrence of tachyphylaxis and stimulation.

The only other phenothiazine derivative found to be more active against experimental tetanus than chlorpromazine was methotrimeprazine. The results reported here indicate that a possible superiority to chlorpromazine in the treatment of clinical tetanus may lie in its greater potency and in its tendency to induce less stimulation. It is of interest to note that this greater tetanus depressant activity is accompanied by an antiadrenaline activity approximately equal to that of chlorpromazine.

Because of the possibility of stimulation by phenothiazine derivatives it seems likely that the combination of a phenothiazine with some other depressant, such as a barbiturate, may be desirable clinically. Such a combination has already been used extensively to control convulsions and found to be more easily handled than chlorpromazine alone, despite the findings by Adams (1958) that it did not reduce mortality materially when the mixture was compared with either drug alone.

One of us (R. A. W.) is now Stothert Research Fellow of the Royal Society.

Most of this work was done whilst one of us (R. A. W.) was in receipt of a grant from May & Baker, who also contributed to experimental costs.

We are grateful to Dr. Mollie Barr, of the Wellcome Research Laboratories, for a gift of tetanus toxin.

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