Brit. J. Pharmacol. (1952), 7, 625.

THE PROTECTIVE ACTION OF ANTIHISTAMINES IN THE ANAPHYLACTIC MICROSHOCK OF THE GUINEA-PIG

BY

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(Received June 5, 1952)

It has been known for some time that the antihistamines protect against anaphylactic shock. Bovet, Horclois, and Walthert (1944) have shown this for mepyramine (neoantergan, Anthisan), and, subsequently, it has been shown for many other antihistamines. These authors observed protection from the fatal outcome of shock. An exact threshold dosage for this protection could not be determined, because the amounts of antigen and antibody which react together and thus lead to fatal shock are variable. An exact quantitative comparison of the various antihistamines is therefore, as Feinberg *et al.* (1950a) have pointed out, not possible. Feinberg *et al.* (1950b) attempted an approximate comparison by contrasting the number of deaths in anaphylactic shock with the number of protected guinea-pigs. We have selected from their material the more familiar antihistamines and reproduced their results in Table I, from which it will be seen that there are certain differences: promethazine, chlorcyclizine, chlortrimeton, and, perhaps, mepyramine seem to have a strong protective action. This group is followed by tripelennamine and diphenhydramine, whose action is weaker ; antazoline is the weakest. These differences, however, are uncertain, as only one or two doses of most drugs were tried. Within the groups, differentiation is impossible.

We used the microshock method (Herxheimer, 1952a) in order to obtain a quantitative comparison. A mild repeatable shock of constant strength was applied by inhalation of the aerosolized antigen. The fatal outcome was prevented by removing the animal from the aerosol just before convulsions would have occurred. The time required to reach this point is called the preconvulsion time. After one exposure re-formation of antibodies takes place which are removed by the next exposure. The longer the interval between two exposures the more antibodies are re-formed. By varying the interval for each animal we could determine the period required for the formation of sufficient antibody to produce a given preconvulsion time on re-

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TABLE I

DEATH RATE OF GUINEA-PIGS IN ANAPHYLACTIC SHOCK UNDER THE PROTECTIVE INFLUENCE OF ANTIHISTAMINES (AFTER FEINBERG *et al.*, 1950B)

The first figure indicates the number of deaths, the second figure the total number of animals used

Substance	Dosage			
	0.1	1.0	3.0	5.0 mg./kg.
Diphenhydramine		13/20	3/10	
Tripelennamine		10/20	3/10	1/8
Mepyramine	6/10			
Antazoline		10/10		
Promethazine			0/5	
Chlortrimeton			1/5	
Chlorcyclizine		3/10	0/5	

exposure. If this period is adopted as the interval between exposures, the preconvulsion time will remain approximately constant. Its increase under drug influence therefore signifies a protective effect.

METHOD

We used groups of 4–9 guinea-pigs for each single experiment. The animals were sensitized by intramuscular injection of 0.7–0.8 ml. of a 5 per cent solution of crystalline egg albumin. After 21 days the animals were exposed to aerosolized antigen, and the preconvulsion time was determined. At the first exposure half the usual antigen concentration was used, because the preconvulsion time may be very short (less than 40 sec.) and the first signs of dyspnoea may be followed rapidly by convulsions and death. Further exposures were carried out at intervals of 2–3 hours or 24 hours. These led to a partial desensitization and thus to an increase in preconvulsion time. When the preconvulsion time had reached 80–120 seconds, the next exposure was carried out after 3–4 days. In some animals it then remained fairly constant, but in others it increased further. For the latter animals the interval was increased to 6–7 days, and usually this proved to be the correct period for maintaining a constant preconvulsion time. When exposures with the appropriate intervals had been repeated, groups of animals with the same intervals were formed and the drug experiments started. Each exposure under the influence of a drug was followed by a control exposure without it. The mean of the preconvulsion times before and after drug exposure was contrasted with the preconvulsion time under drug influence. The drawbacks of this method are, as pointed out elsewhere (Herxheimer, 1952a), the individual variability of guinea-pigs and the difficulty of assessing the convulsion point accurately. Some animals showed great variations between two preconvulsion times, varying sometimes from 90 to as long as 170 seconds, or vice versa. Such extreme fluctuations in the control times, although rare, increase the inherent variability in results from different animals and necessitate a large number of experimental groups.

We examined not only the influence of a number of antihistamines, but also that of atropine sulphate, procaine, and procaine amide. The last two were given intraperitoneally 20 min. before exposure, the others intramuscularly 60–90 min. before exposure. The latter period was chosen because Bain (1949) found that the maximum effect of various antihistamines was reached 2–3 hours after oral administration. Clinically, a pronounced drug effect is observed with most antihistamines one hour, and with Promethazine 1.5 hours, after they have been taken by mouth. As intramuscular injection must be

expected to reach its maximum effect after a much shorter time, we felt that exposure 60–90 min. after injection would show the drug effect near its maximum.

In three experiments not included in the results reported in this paper, we gave antihistamines (promethazine, 0.5 and 2.0 mg./kg.; diphenhydramine, 3.0 mg./kg.) intraperitoneally 45–60 min. before exposure. The results differed little from those produced by intramuscular injection. We are aware of the fact that protection can also be achieved by administration of the drug in the form of an aerosol. Our results with this method will be reported separately.

In three other experiments not included in the results reported in this paper we used animals sensitized by injection to horsehair and dander extract or to castor-bean extract (Bencards), and shocked by the aerosol of the same extract. The degree of protection achieved against these antigens was of the same order as in our other experiments, but the number of experiments is too small to permit a comparison.

RESULTS

The results and their statistical analysis are shown in Tables II–VI and Fig. 1. The method used for measuring the protective effect of a single dose of a drug is illustrated in Table II, which shows the results for the group of six guinea-pigs

TABLE II

EXAMPLE OF THE METHOD OF CALCULATION OF PERCENTAGE PROTECTION

The protection given by 12 mg./kg. of chlorcyclizine

(1) Animal	(2) Control preconvulsion time (mean of 2 controls) in sec. C	(3) Drug preconvulsion time in sec. T	(4) Percentage protection $100\,(1-C/T)$
1	140	480	71
2	117	450	74
3	74	180	59
4	113	240	53
5	92	230	60
6	118	180	34

Mean protection: 58.5%. Standard deviation: 14.3. Standard error of mean: ± 5.9

treated with the highest dose (12 mg./kg.) of chlorcyclizine. Column (2) shows the mean, C, of the preconvulsion times before and after treatment, and column (3) shows the preconvulsion time, T, under the influence of the drug. As a measure of "percentage protection" we have calculated, in column (4), the quantity $100\,(1-C/T)$. If the control and treatment preconvulsion times, C and T, are equal, the percentage protection is zero; if the drug gives complete protection, T is effectively infinite, and the percentage protection is 100. Occasionally, with individual animals at low doses, T is less than C, and the percentage protection is negative.

Table III shows, for each dose, the mean of the individual values of percentage protection, and the standard error of the mean. For each drug the mean responses tend to increase with increasing dose. The exact nature of the relationship between percentage protection and dose is rather speculative, but in view of the upper limit of 100 per cent to the scale of protection, and the likely lower limit of zero at small doses, some sort of sigmoid relationship might be expected. The results for some

TABLE III

MEAN PERCENTAGE OF PROTECTION AND STANDARD ERROR FOR EACH DOSE

	Dose mg./kg.	No. of animals	Mean percentage protection ± standard error	Estimated mean from fitted curve
Antazoline (antistine) ..	0.2	9	−20.9±17.2	8
	0.3	5	5.4± 9.3	17
	0.5	5	47.2± 3.6	40
	1.0	6	42.5± 6.6	58
	3.0	7	73.9± 3.9	67
	3.0	5	61.6± 7.9	67
	12.0	4	52.8± 2.3	57
	20.0	6	39.7± 6.1	40
Atropine	0.11	7	1.4±12.7	1.3
	0.22	8	18.0± 9.3	6.8
	0.325	7	14.7± 5.1	19.0
	0.65	6	60.2± 6.8	49.2
	1.3	6	43.8± 9.1	58.7
	2.6	7	55.0± 8.2	59.9
	6.35	4	45.5±15.8	60.0
Chlorcyclizine (histantin) ..	0.025	6	−4.7±10.2	5.6
	0.05	5	2.0±18.7	10.7
	0.08	8	−19.0±16.4	15.8
	0.2	7	29.9± 2.8	29.4
	1.0	6	48.5±10.4	50.8
	6.0	5	58.2± 2.4	58.5
	12.0	6	58.5± 5.9	59.3
Chlortrimeton	0.01	6	−6.5±23.5	11.0
	0.05	4	22.0±10.2	21.8
	1.0	6	58.7± 9.4	55.8
	2.8	5	67.4± 3.9	68.1
Diphenhydramine (benadryl)	0.025	5	−7.8±10.3	2.6
	0.05	6	−18.7±10.3	5.5
	0.2	6	31.0±10.2	13.6
	0.9	7	33.3± 3.2	31.4
	2.0	6	17.3±11.5	44.9
	6.0	6	44.7± 9.7	64.2
	12.0	5	80.8± 4.0	74.6
	12.0	5	73.2± 3.4	74.6
Mepyramine (neoantergan, anthisan)	0.01	5	14.6± 3.5	6.3
	0.025	7	5.7±11.9	12.9
	0.05	7	25.7± 6.6	20.8
	0.1	6	32.8± 7.7	31.0
	0.167	6	22.5± 8.0	39.3
	0.4	6	59.7± 5.5	52.9
	1.0	7	64.0± 6.3	63.2
	3.0	7	78.6± 5.7	70.1
	6.0	5	57.6± 7.2	72.3
Promethazine (phenergan) ..	0.01	5	−10.4±10.8	0.4
	0.025	6	22.0± 6.8	4.1
	0.05	9	1.7±15.7	18.4
	0.1	8	46.3± 3.3	47.2
	0.1	9	44.0± 6.8	47.2
	0.25	7	78.9± 5.3	66.9
	0.5	7	72.6±10.8	69.4
	0.75	6	68.8± 7.4	69.8
	0.75	7	75.6± 5.1	69.8
	1.5	7	66.0± 6.7	70.0
	3.0	7	76.6± 7.0	70.0
Tripelennamine (pyribenzamine)	0.01	6	50.5± 5.2	42.6
	0.01	4	27.8± 9.1	42.6
	0.02	6	24.2±11.3	45.4
	0.05	6	54.0± 6.3	49.1
	0.25	5	42.2±11.9	55.7
	1.0	5	62.2± 8.2	61.1
	3.0	5	54.2± 8.4	65.3
	30.0*	6	87.2± 9.3	73.3

* This dose caused violent convulsions lasting about 20 minutes. Exposure to antigen aerosol was carried out 40 minutes later.

drugs suggest an upper limit at less than 100 per cent. We have therefore followed the procedure of guessing an upper limit to the percentage protection for each drug, and fitting a logistic curve relating percentage protection to log-dose. The equation of the curve may be written

$$Y=\frac{L}{1+e^{-b(x-x_0)}}$$

where Y is the mean percentage protection expected at a dose whose logarithm is x units, L is the assumed upper limit to Y, and the two constants b and x_0 are estimated from the data. Of these, b represents the steepness of the increase of Y with x, and x_0 is the logarithm of the dose required to give a protection of 0.5 L per cent. More precisely, the maximum gradient of the curve, which occurs at a response of 0.5 L per cent, is measured by $b'=0.25Lb$; b' is a convenient measure of the relative steepness or " slope " of the different curves.

This procedure was not suitable for antazoline, for which the responses appear to rise to a maximum at a dose of about 3 mg./kg. and then decrease at higher doses. For this drug a freehand curve has been fitted to the results.

The method used for fitting the logistic curve is similar to that suggested by Emmens (1940, pp. 221–3). A more precise method (that of maximum likelihood) has been described by Finney (1952, Section 47 and Appendix II), in which the upper limit L is estimated from the data ; the present data are too variable, and the suitability of the logistic curve too questionable, to justify undue refinement. The assumed values of L, and the estimated values of the " slope," b', and of x, are shown in Table IIIa. The high values of χ^2 given in Table IIIa show that the fit of some of the curves is bad in the strict statistical sense. The total value of χ^2 is 87.0 on 40 degrees of freedom ($P<0.001$) : the observed mean responses diverge from the fitted curves to a greater degree than would be expected by chance. This divergence may occasionally be due to the use of an inadequate model ; for some drugs the response curve may reach an upper limit more suddenly than does the logistic, or, like that

TABLE IIIa

ESTIMATED CONSTANTS FOR EACH LOGISTIC CURVE, WITH MEASURE OF GOODNESS OF FIT

Drug	Assumed upper limit L for % protection	Estimated " slope" b′ ± standard error	Estimated log-dose x_0 giving protection of $\frac{1}{2}L\%$ ± standard error	χ^2 index for goodness of fit, with No. of degrees of freedom	Significance of χ^2
Antazoline	—		(Curve fitted by eye)		
Atropine	60	113.7±39.8	−0.39±0.06	8.7 on 5 d.f.	$0.1<P<0.2$
Chlorcyclizine	60	37.2±16.9	−0.69±0.11	5.8 on 5 d.f.	$0.3<P<0.5$
Chlortrimeton	100	29.1±11.8	−0.20±0.27	0.1 on 2 d.f.	$0.90<P<0.95$
Diphenhydramine ..	100	41.2± 6.2	0.42±0.09	22.1 on 6 d.f.	$0.001<P<0.01$
Mepyramine	75	38.1±12.2	−0.83±0.15	18.8 on 7 d.f.	$0.001<P<0.01$
Promethazine	70	102.5±30.1	−1.12±0.05	17.1 on 9 d.f.	$0.02<P<0.05$
Tripelennamine ..	100	9.4± 4.4	−1.20±0.47	14.4 on 6 d.f.	$0.02<P<0.05$
			Total	87.0 on 40 d.f.	

for antazoline, may even fall slightly with increases of the dose beyond some optimum level. Usually, however, there is no *systematic* divergence from the logistic curve, and the discrepancies are probably due to heterogeneity between the groups of animals allotted to different doses. The standard errors of the estimated quantities given in Table IIIa take into account this heterogeneity; the heterogeneity factor, 87.0/40=2.175, has been used for each drug (Finney, 1952). The estimated mean response at each dose is shown, for comparison with the observed value, in Table III; the fitted curves are also plotted in Fig. 1.

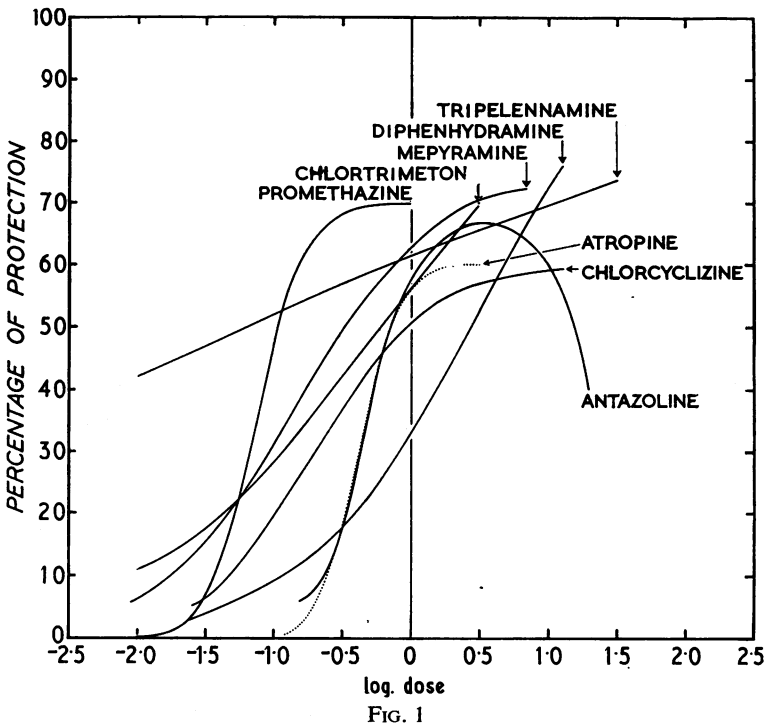

FIG. 1

Some protection against anaphylactic shock (expressed as increase of preconvulsion time) was given by all the antihistamines which we tried. This protection, however, was never complete except at very high dosages, which would be toxic for man, and even then it was present in some animals only. The degree of protection depends on the dosage. With all but one substance (tripelennamine) the smallest doses used gave little or no protection (Fig. 1). Table IV shows the lowest doses at which the mean protection was significant. This dosage differs from one substance to another, and is lower than the therapeutic dosage used in man. As the dose is increased, protection rapidly becomes more pronounced, but for most substances it seems to approach a maximum value below 100 per cent. For each substance the dose beyond which there is no significant increase in protection is shown in Table V. Again, there are considerable differences between substances, but, except for atropine, these doses are of a similar order to the therapeutic doses

TABLE IV

LOWEST DOSE AT WHICH SIGNIFICANT PROTECTION OCCURS

(Chlortrimeton has been omitted from this Table, as no intermediate doses between 0.05 and 1 mg./kg. have been tried)

	mg./kg.
Antazoline	0.5
Atropine	0.325
Diphenhydramine	0.2
Chlorcyclizine	0.2
Promethazine	0.025
Mepyramine	0.005(?)*
Tripelennamine	0.005*

* See addendum.

TABLE V

LOWEST DOSE BEYOND WHICH NO SIGNIFICANT INCREASE IN PROTECTION OCCURS

(Chlortrimeton has been omitted from this Table, as no intermediate doses between 0.05 and 1 mg./kg. have been tried)

	mg./kg.
Antazoline	3.0*
Chlorcyclizine	1.0
Atropine	0.65
Mepyramine	0.4
Diphenhydramine	†
Promethazine	0.25
Tripelennamine	‡

* Higher doses lead to a decrease of protection.
† Observed protection remains fairly constant between 0.2 and 6.0 mg./kg. with a significant rise at the excessive dose of 12.0 mg./kg.
‡ Observed protection remains fairly constant between 0.01 and 3.0 mg./kg., with a significant rise at the excessive dose of 30.0 mg./kg.

used in man. Thus, doses far in excess of those used in man usually failed to give complete protection. With antazoline, the excessive dose of 20 mg./kg. gave less protection than 3 mg./kg. and 12 mg./kg.

Atropine, which has a weak antihistaminic action, ranges with the weaker group of substances tried. Protective effect in anaphylactic microshock exists at 0.325 mg./kg. and starts possibly at 0.22 mg./kg., doses which would be toxic in man. Procaine also has a protective effect, but it is weaker than any of the other substances. Whether procaine amide has a protective action is uncertain (Table VI).

TABLE VI

PROTECTIVE EFFECT OF PROCAINE AND PROCAINE AMIDE

Drug	Dose mg./kg.	No. of animals	Mean % protection ± standard error	Standard deviation
Procaine	3	5	−12.6±10.5	23.6
	6	5	35.6±14.7	32.8
	10	3	32.0±15.2	33.9
	25	5	36.2±11.7	26.1
Procaine amide	3	5	15.0±14.5	32.4
	10	3	45.0± 1.7	3.0
	25	5	6.4±15.6	34.8
	50	5	15.6±24.7	55.3

The individual reaction of the animals to the same drug varied considerably. As a rule, the animals which were strongly protected by one antihistamine were also protected by the others. There were, however, exceptions to this rule: Animal 180, for instance, was well protected by medium doses of tripelennamine and chlortrimeton, but not by a large dose (3.0 mg.) of promethazine. Animal 158 was well protected by 0.01 mg. tripelennamine, but not by 2.0 mg. diphenhydramine. Animal 174 was little influenced by 0.25 mg. tripelennamine, but well protected by 0.1 mg. promethazine. Animal 186 was not protected by 0.25 mg. tripelennamine or 0.2 mg.

diphenhydramine, but well protected by 0.5 mg. of the much weaker antazoline. We noticed these differences only when we had completed most of our experiments. As the total number of animals used was large, and as animals were changed haphazardly for each experiment, it was rare that the same animal was used with corresponding doses of different antihistamines. If the experiments had been arranged with a view to observing individual differences, we might have seen more such examples. This difference in individual responses is interesting, as it occurs also in man.

Discussion

Our results seem to be in approximate agreement with those of Feinberg *et al.* (1950b). Some antihistamines (promethazine, mepyramine, and chlortrimeton) have, in non-toxic doses, a much stronger action than others. The weaker group, in our experiments, included tripelennamine, diphenhydramine, chlorcyclizine, and antazoline. Chlorcyclizine was included by Feinberg *et al.* in their stronger group. Apart from these gross differences in strength, each substance appears to possess some characteristic behaviour by which it differs from all others. Tripelennamine, for instance, protects in smaller amounts than the others, but the protection afforded by a medium dose is unexpectedly weak, like that of chlorcyclizine. At an extreme range, however, which is toxic even for guinea-pigs, it becomes efficient. Diphenhydramine gives a very weak protection even in high dosage, but at an extreme range its protection becomes efficient. The protection by chlorcyclizine is somewhat better, but it does not improve at extreme range. Naturally, these differences can only be detected by experiments with graded dosage. They show that these substances not only have a protective action, but that they differ from each other in characteristic details. These can be best seen from Fig. 1. They can be summarized as follows: The highest degree of protection is given, in doses tolerable for man, by promethazine, mepyramine, and (to a slightly lesser degree) chlortrimeton. This effect is achieved by promethazine with a smaller amount than by mepyramine and by mepyramine with a smaller amount than by chlortrimeton. Tripelennamine and diphenhydramine achieve the same high protection but only with amounts toxic for man. The other substances do not give such a high degree of protection whatever their dose, and for this lesser degree of protection greater amounts are required.

We shall now consider how far anaphylactic microshocks can be compared to attacks of asthma in man. Many authors agree that there is no principal difference between anaphylactic shock in the animal and allergic disease in man. We share this opinion, especially in view of the work of Schild *et al.* (1951), who found that isolated human bronchi of an asthmatic patient reacted in exactly the same way as organs of sensitized animals. The microshocks in our experiments were reactions due to antigen introduced into the respiratory passages of a sensitized animal. The allergic asthma attack in man is caused in the same way. The only, and perhaps important, difference is that in the animal sensitization has been carried out by injection, whereas in man sensitization occurs because there is a congenital tendency (" Anlage ") which is absent in the guinea-pig. In view of this difference we cannot regard both phenomena as exactly the same, but they are closely related. We have been able to elicit the same microshock also when the sensitization was carried out by inhalation instead of by injection. The antigen used was extract of horsehair and dander, and sensitization was not achieved with the same regularity as by

injection. The similarity of both phenomena is evident also from their external appearance. The increasing dyspnoea, the standing of the animals on their front feet to support inspiration, the gasping for air, and the cyanosis are so similar to the acute asthmatic attack that the animal assumes an almost human expression. The onset and course of the dyspnoea have clearly the same mechanism. This statement is supported by the anatomical findings if the animal dies: there is always gross emphysema and also some oedema of the mucous membrane even if the attack is the first of this kind experienced by the animal (Herxheimer and Pagel, unpublished experiments). The degree of oedema is not sufficient to cause fatal emphysema ; bronchial muscular spasm must be the main cause. These findings are very similar to those in human asthma ; there the picture is often complicated by chronic bronchitis, but in patients in whom an acute attack of unusual violence has caused death during an otherwise asthma-free interval (for instance, after a wasp sting or an intracutaneous skin test), the same picture of almost pure emphysema can be seen. These many similarities between the microshock in the guinea-pig and the asthma attack in man justify, in our opinion, their comparison under the influence of drugs.

Such a comparison reveals many parallels. The most striking parallel is the limitation of the protective effect. The antihistamines protect against mild asthmatic attacks, especially against nocturnal attacks in chronic asthma. They are useless in acute or severe attacks, which they neither prevent nor influence (Herxheimer, 1952b). In induced asthma mild attacks can be prevented (Herxheimer, 1949), but moderate or severe attacks cannot. If in a patient an anti-asthmatic effect has been achieved with, say, 25 mg. promethazine, and the asthmatic obstruction becomes more severe, the dose can be successfully increased to 50 or 100 mg. If the obstruction becomes more severe still, a further increase of the dose usually does not give an additional benefit. In all these examples there is a beneficial effect, but it is limited as in the guinea-pig, and an increase in dosage beyond a certain limit is of no value. In both man and guinea-pig there is protection, but a partial protection only.

Another parallel is found in the great individual differences in the drug action. In man we find a number of patients who respond well to several antihistamines, but there are others who respond only to one and not to others. The guinea-pig shows a similar behaviour. Individual animals may occasionally respond very little, if at all, to some particular antihistamine. This variability can also be seen in their response to low dosage. A high dose of an antihistamine usually protects all animals of one group, though at a varying degree. If this dose is decreased to such a level that the mean protection is just significant, it will be seen that some of the individual animals in this group are not at all protected. This is a regular occurrence at such borderline doses.

Further similarities emerge if dosage and order of efficiency are compared. The smallest dosage which affords very pronounced protection in the guinea-pig is usually smaller than that used clinically in man, often one-half to one-third as large, but in man the drug is given orally. As the drugs were given intramuscularly to our animals, the difference does not seem considerable. The order of efficiency, weight for weight, is difficult to assess clinically ; it can be found approximately in those patients who respond well to a number of antihistamines. From such comparisons we have found that promethazine is about 6–7 times stronger than mepyramine.

Diphenhydramine and chlorcyclizine are much weaker, and antazoline is practically useless in asthma. With chlortrimeton and tripelennamine we have not sufficient clinical experience, but it seems to us that the former is almost as strong as promethazine, and the latter stronger than diphenhydramine and chlorcyclizine. Bain (1950) also found similar differences between some of these drugs, although he tested them against skin responses to histamine. In our animal experiments a similar order emerges to that found clinically. A comparison with the procaine action has the same result. In the guinea-pig its action is weaker than that of the weakest antihistamine. In man an anti-asthmatic effect can be observed only after intravenous administration ; it is weak and fleeting. There is some considerable difference between the effect of atropine in the guinea-pig and in man. In human asthma its action is almost negligible. The reason for this difference is probably that the equivalent of the effective dose in the guinea-pig would have toxic effects in man.

The similarity of the drug action in guinea-pig and man throws further light on our views on antihistamine treatment of human asthma. The varying and erratic results of the treatment of sometimes quite unsuitable cases have led some observers to regard this therapy as useless or, at least, as disappointing. This view has tempted some of them to explain some undeniable successes as due to suggestion or to the sedative effect of the antihistamines. One of us (Herxheimer, 1949, 1952b) has given reasons why neither of these explanations could be valid. Our present experiments confirm this view: Suggestions could not have increased the preconvulsion time in guinea-pigs, nor could sedation alone have had this effect. We have given 0.1 mg./kg. of pentobarbitone to a group of guinea-pigs and have not found any change in the preconvulsion time, although the animals showed signs of being tired: they were unsteady on their feet and, at times, closed their eyes. Similar symptoms were noted also after antihistamines, but only after large doses (3 mg./kg.). The animal experiments thus confirm the conclusions drawn from clinical experience.

Our experiments do not show how the antihistamines achieve their protective action. They may counteract oedema of the mucous membrane or muscular spasm, or both. Their action in allergic rhinitis makes it probable that they reduce oedema. The experiments of Schild *et al.* (1951), and our present experiments in which oedema cannot have played a dominant part, make it probable that they also counteract muscular spasm to some degree.

SUMMARY

1. Antihistamines have a protective effect in the mild anaphylactic shock of the guinea-pig.

2. This effect begins with doses in the region from 0.01–0.5 mg./kg. and approaches its maximum with doses from 0.25–3.0 mg./kg. The protective effect consists in delaying the onset of the asthmatic dyspnoea due to the shock. It does not prevent the onset of dyspnoea except in a few animals in which protection is complete.

3. There are considerable differences in the protective strength of the antihistamines tested. There is a stronger group (promethazine, mepyramine, and chlortrimeton) affording a higher degree of protection, and a weaker group (tripelennamine, diphenhydramine, chlorcyclizine, and antazoline). Each of these substances has characteristics of its own.

4. The anti-anaphylactic action of atropine is similar to that of the weaker group. The protective action of procaine is still smaller.

5. Parallels exist between the action of the antihistamines in the guinea-pig and in man. In both, moderate doses give a moderate protection which is improved with an increase in dosage until a limit is reached. In both, there are considerable variations of the effect in the individual animal or patient. In both, the classification of the drugs in groups according to their strength is about the same.

6. As sedative and psychological effects of the antihistamines cannot account for their action in the guinea-pig, it is unlikely that these factors are the reason for their beneficial action in man.

ADDENDUM

Very recently, we have had the opportunity of investigating the protective effect of smaller amounts of tripelennamine and mepyramine than were previously used. We have also examined a wide range of dosage of a new antihistamine, provisionally named 295/C/51 by Burroughs, Wellcome & Co. These results are shown in Table VII. The experiments with tripelennamine confirm our expectation that some protection is conferred by a dose of 0.005 mg./kg. With mepyramine we found a higher level of protection than before with all three doses used. We cannot explain this difference, but as these experiments were carried out three months later than the

TABLE VII

Drug	Dose mg./kg.	Log dose	No. of animals	Mean percentage protection ± standard error
Mepyramine	0.001	−3.00	7	−17.57 ± 9.22
	0.005	−2.30	6	39.17 ± 6.06
			6	17.67 ± 6.64
	0.01	−2.00	6	62.67 ± 5.92
			7	65.71 ± 3.09
	1.0	0	6	80.67 ± 2.82
Tripelennamine	0.001	−3.00	6	−31.83 ± 24.50
	0.005	−2.30	5	12.40 ± 10.56
			6	18.67 ± 8.39
	0.01	−2.00	4	16.75 ± 11.74
BW 295/C/51	0.00033	−3.48	5	−5.40 ± 12.06
	0.001	−3.00	4	−29.50 ± 35.24
			4	27.50 ± 7.97
			5	31.60 ± 5.42
	0.005	−2.30	6	50.00 ± 6.03
			5	66.60 ± 2.16
	0.01	−2.00	3	56.33 ± 5.46
			4	11.25 ± 7.72
			7	57.43 ± 3.94
	0.05	−1.30	6	73.17 ± 4.05
			6	44.00 ± 8.58
	0.1	−1.00	7	74.00 ± 9.21
	0.5	−0.30	6	67.50 ± 6.44
			5	81.40 ± 2.73
	1.5	0.18	7	79.01 ± 2.7
	3.0	0.48	7	88.43 ± 1.31

main group, it seems possible that seasonal changes in the reactivity of the animals may have had some effect. The substance 295/C/51 is of particular interest, because it affords protection at a lower level (0.001 mg./kg.) than all the other substances investigated, and because the maximum protection lies above 80 per cent, i.e. higher than that given by the stronger group of the other antihistamines. The impression that this drug has, weight for weight, a stronger antihistaminic action than, for instance, promethazine is confirmed by preliminary clinical observations.

One of the authors (H.H.) was in receipt of a part-time grant of the Asthma Research Council. We wish to thank Mr. T. West for his help in assessing the preconvulsion time.

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