

THE EFFECT OF SOME NEW ANTIHISTAMINES ON THE ANAPHYLACTIC MICROSHOCK OF THE GUINEA-PIG

BY

H. HERXHEIMER AND E. STRESEMANN

From the Asthmapoliklinik, Free University, West Berlin, Germany

(Received May 14, 1963)

The dose/response curves for the protective effects of the new antihistamine compounds trimeprazine, 10-(3-diethylamino-2-methylpropyl)phenothiazine 1,1-dioxide hydrochloride (oxomemazine hydrochloride), cyproheptadine, homochlorcyclizine and methotrimeprazine against the anaphylactic microshock of the guinea-pig were similar to that of promethazine. The first three compounds, however, protected at lower doses than promethazine (5 to 10 $\mu\text{g/kg}$). The protective effect of cyproheptadine lasted longer than 24 hr.

The antianaphylactic effects of promethazine, mepyramine, chlorcyclizine, tripeleennamine and diphenhydramine have been investigated by Armitage, Herxheimer & Rosa (1952). In this paper we describe investigations of a few of the newer antihistamines.

METHODS

The microshock method (Herxheimer, 1952) was used and the protection against anaphylactic shock was calculated according to Armitage *et al.* (1952) with the formula $p = 100(1 - c/t)$, in which p is the percentage of full protection, c the control preconvulsion time and t the preconvulsion time of the animal under the influence of the drug.

The compounds investigated were trimeprazine, methotrimeprazine, cyproheptadine, homochlorcyclizine and 10-(3-diethylamino-2-methylpropyl)phenothiazine 1,1-dioxide hydrochloride (oxomemazine hydrochloride, 6847 R.P.). They were injected intramuscularly in aqueous solution; the exposure to the antigen (an aerosol of 5% albumen solution) was done 1 hr later. For cyproheptadine, the exposure was delayed by between 1 and 48 hr in order to investigate the duration of the effect.

RESULTS

The results are given in Tables 1 and 2 and Figs. 1, 2 and 3. Fig. 2 was prepared by smoothing out the values of \bar{x} in Table 1 and in Fig. 1 in the following way: a regression line was drawn through every three neighbouring points, and the value on the ordinate of each middle point was regarded as the fitted value. From these fitted values Fig. 2 has been constructed. With this procedure, the two values corresponding to extreme doses of each compound had to be omitted.

Originally it had been intended to use this fitting as a preliminary to the construction of a logistic function. The attempt to do so showed, however, that the closeness of fit was inadequate and the construction was therefore abandoned. As can be

TABLE 1
THE PROTECTIVE EFFECT OF VARIOUS ANTIHISTAMINES IN THE ANAPHYLACTIC
MICROSHOCK OF GUINEA-PIGS

Antihistamine values (\bar{x}) are means of the percentages of guinea-pigs showing full protection. * From Armitage *et al.* (1952). $\sigma = \sqrt{\frac{s(\bar{x} - \bar{x})^2}{n}}$. The *P* values were calculated by Student's one-tailed "*t*" test (Fisher & Yates, 1960)

		Dose (mg/kg)										
		0.005	0.01	0.05	0.1	0.2	0.25	0.5	1.0	2.0	3.0	6.0
Cyproheptadine	\bar{x}	16.5	21.4	36.6	45.8	—	—	60.2	65.9	71.1	83.5	—
	<i>n</i>	12	17	21	11	—	—	25	15	18	19	—
	σ	29.5	23.1	23.4	26.0	—	—	25.4	21.1	25.7	12.2	—
	<i>P</i>	<0.05	<0.01	<0.01	<0.01	—	—	<0.01	<0.01	<0.01	<0.01	—
Trimeprazine	\bar{x}	13.1	29.0	35.5	—	49.6	54.1	—	64.4	70.8	87.1	63.0
	<i>n</i>	11	22	17	—	8	16	—	16	13	8	26
	σ	25.2	21.0	20.0	—	15.2	15.8	—	11.3	12.8	8.6	14.1
	<i>P</i>	>0.05	<0.01	<0.01	—	<0.01	<0.01	—	<0.01	<0.01	<0.01	<0.01
Methotrimeprazine	\bar{x}	—	—	2.0	29.6	—	—	45.5	56.3	71.9	74.2	—
	<i>n</i>	—	—	14	20	—	—	34	32	9	14	—
	σ	—	—	7.5	23.7	—	—	27.3	25.5	9.1	16.5	—
	<i>P</i>	—	—	>0.15	<0.01	—	—	<0.01	<0.01	<0.01	<0.01	—
Homochlorcyclizine	\bar{x}	—	4.8	—	22.2	—	25.0	48.5	51.9	62.4	68.5	—
	<i>n</i>	—	10	—	18	—	14	20	17	21	30	—
	σ	—	39.0	—	22.3	—	15.9	28.1	16.6	18.0	19.0	—
	<i>P</i>	—	>0.30	—	<0.01	—	<0.01	<0.01	<0.01	<0.01	<0.01	—
Oxomezazine	\bar{x}	8.0	34.3	41.3	53.7	—	55.3	65.4	59.4	79.6	72.8	—
	<i>n</i>	13	15	10	13	—	17	16	17	10	25	—
	σ	36.6	16.7	26.4	23.5	—	20.6	18.3	7.8	7.9	16.6	—
	<i>P</i>	>0.2	<0.01	<0.01	<0.01	—	<0.01	<0.01	<0.01	<0.01	<0.01	—

		Dose (mg/kg)								
		0.01	0.025	0.05	0.1	0.25	0.5	0.75	1.5	3.0
Promethazine*	\bar{x}	—10.4	22.0	1.7	46.3, 44.0	78.9	72.6	68.8, 75.6	66.0	76.6
	<i>n</i>	5	6	9	8, 9	7	7	6, 7	7	7
	σ	24.1	16.6	47.0	9.3, 20.4	14.0	28.5	18.1, 13.5	17.6	18.4
	<i>P</i>	>0.2	<0.0125	>0.4	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

seen from Figs. 1 and 2, there are some slight differences between the newer compounds and promethazine, the most effective of the older antihistamines, which has been plotted for comparison from results obtained in an earlier investigation (Armitage *et al.*, 1952). Cyproheptadine, oxomemazine and trimeprazine have a protective effect in doses of 5 or 10 μ g/kg, whereas promethazine starts only at 25 μ g/kg. Homochlorcyclizine seems a little weaker than the other compounds at all doses, and methotrimeprazine in its lower doses. At 2 and 3 mg/kg the

TABLE 2
DURATION OF PROTECTION BY A SINGLE DOSE OF 3 MG/KG OF CYPROHEPTADINE
Statistical evaluation as in Table 1

		Duration (hr)					
		2	4	8	16	24	44 to 48
\bar{x}		78.8	79.0	61.8	56.1	42.8	6.9
<i>n</i>		10	16	23	14	19	9
σ		13.49	14.79	17.74	14.76	21.84	22.60
<i>P</i>		<0.01	<0.01	<0.01	<0.01	<0.01	>0.15

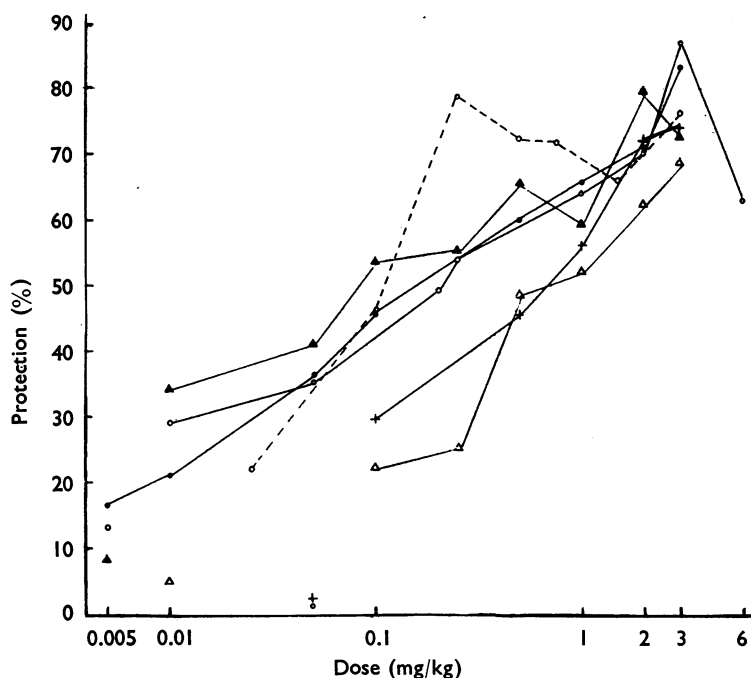


Fig. 1. The protective effect of various antihistamines in anaphylactic microshock of guinea-pigs. Ordinate: percentage protection. Abscissa: dose in mg/kg of guinea-pig. ●=cyproheptadine; ○—○=trimeprazine; +=methotrimeprazine; △=homochlorcyclizine; ▲=oxomemazine; and ○---○=promethazine. Points not connected by continuous or dotted lines represent values which were not statistically significant.

differences between all compounds examined were small, the maximal protection lying between 70 and 85%. The duration of action was investigated only for cyproheptadine and was found to be surprisingly long. After 24 hr there was still a protection of 40%, and only after 44 to 48 hr had the protection disappeared (Fig. 3).

DISCUSSION

The investigation of these five new compounds has not shown great differences in comparison with older antihistamines. It seems that promethazine is somewhat more effective in the medium range of doses, and that three of the new compounds have an effect in very low doses, 5 to 10 μ g/kg. Their maximal effect lies, as with the older compounds, near 80% protection. With more than 3 mg/kg, the percentage protection tends to fall, as seen with trimeprazine, and as Armitage *et al.* (1952) have observed with antazoline. Of the two compounds which have a strong anti-5-hydroxytryptamine effect, homochlorcyclizine is the weaker antihistamine. The antihistamine effect of the other, cyproheptadine, is extremely strong: 5 μ g gave slight but definite protection, and the effect of higher doses was greater than 80% and lasted longer than 24 hr, that is longer than the effect of promethazine. This compound therefore differs in these respects from all the others. Its long-

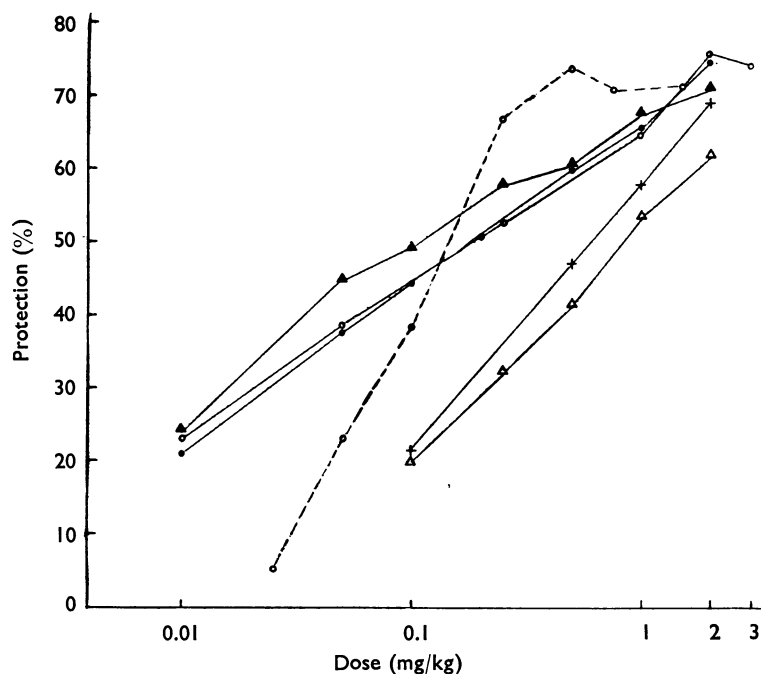


Fig. 2. The protective effect of various antihistamines in anaphylactic microshock of guinea-pigs. Symbols as in Fig. 1. Lines are smoothed curves corresponding to those in Fig. 1; for method of calculation, see text.

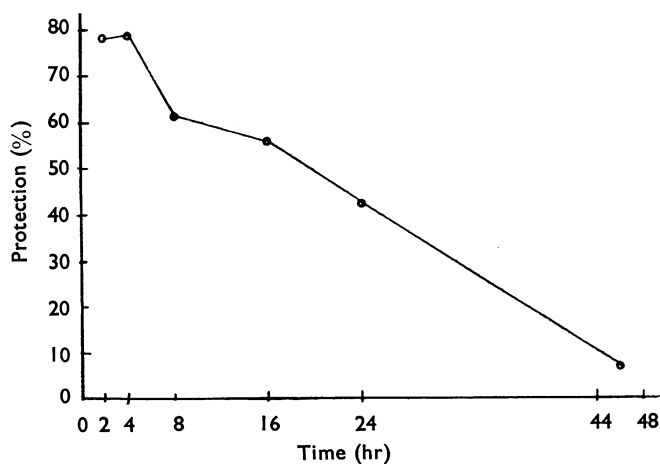


Fig. 3. Duration of action of cyproheptadine (3 mg/kg) in protecting against anaphylactic microshock of guinea-pigs.

lasting action is apparent also from the reports of patients and healthy subjects, many of whom have found that the well-known fatiguing effect of antihistamines may persist after 5 or 10 μ g cypheptadine for 36 hr or longer.

We are much indebted to Professor P. Armitage (London) and Professor K. Freudenberg (Berlin) for their advice about the statistical evaluation of our results.

REFERENCES

- ARMITAGE, P., HERXHEIMER, H. & ROSA, L. (1952). Protective action of antihistamines in the anaphylactic microshock of the guinea-pig. *Brit. J. Pharmacol.*, 7, 625-632.
- FISHER, R. A. & YATES, F. (1960). In *Scientific Tables*. Basel: Geigy.
- HERXHEIMER, H. (1952). Repeatable "microshocks" of constant strength in guinea-pig anaphylaxis. *J. Physiol. (Lond.)*, 117, 251-255.