Brit. J. Pharmacol. (1955), **10**, 160.

PROTECTION AGAINST ANAPHYLACTIC SHOCK BY VARIOUS SUBSTANCES

BY

H. HERXHEIMER

From the Surgical Unit, University College Hospital Medical School, London

(RECEIVED SEPTEMBER 8, 1954)

In view of the close relationship between anaphylactic shock and allergic disease, it is not surprising that many substances that antagonize anaphylactic shock (antihistamines, aminophylline, atropine and many sympathomimetic amines—Feinberg, Malkiel, Bernstein, and Hargis, 1950; Herxheimer and Rosa, 1953—) are also of great therapeutic value in allergic disorders. Anti-anaphylactic action is, however, not confined to such substances. Claims that a number of other drugs, differing widely in composition, have such an effect have been critically reviewed by Hill and Martin (1932). Because of the potential therapeutic value of anti-anaphylactic drugs, it was decided to investigate a number of substances reviewed by them and also some others.

METHODS

Anaphylactic shock was produced in guinea-pigs by the "microshock" method (Herxheimer, 1952) in which the time from exposure to an antigenic aerosol to convulsion point (preconvulsion time) is regarded as a measure of the severity of the shock. If the time required to develop shock is significantly prolonged under the influence of a drug, this drug is regarded as having a protective effect. The degree of protection is calculated from the expression $100\left(1-\frac{C}{T}\right)$, where C is the preconvulsion time in the control experiment and T the preconvulsion time under the influence of the drug (Armitage, Herxheimer and Rosa, 1952).

The substances investigated were (a) drugs with a hypnotic or sedative action—morphine, chloral hydrate, phenobarbitone, chlorpromazine, (b) potentially spasmolytic drugs—pethidine, khellin, "Buscopan" (hyoscine-*N*-butyl bromide; Wick, 1951), methantheline (2-diethylaminoethyl xanthen-9-carboxylate methobromide, "Banthine") and propantheline (2′-di*iso*propylaminoethyl xanthen-9-carboxylate methobromide, "Probanthine"), (c) various other substances—salicylic acid, phenylbutazone ("Butazolidin"), barium chloride, sodium cyanate, caffein, ascorbic acid, cyanocobalamin, phenylephrine, neosynephrine, dibenzyline, and heparin.

RESULTS

The substances which had no anti-anaphylactic action are listed in Table I. Morphine and caffeine had a protective effect in high doses only (50 mg. and 100 mg./kg. respectively). Buscopan, methantheline, propantheline, pethidine, and sodium cyanate had an anti-anaphylactic effect (Table II).

TABLE I

SUBSTANCES SHOWING NO ANTI-ANAPHYLACTIC ACTION AT SPECIFIED DOSE-LEVELS

Substance	Dose (mg./kg.)	Route of Admin.
Ascorbic acid	10, 20	i.m.
Barium chloride	10	i.p.
Chloral hydrate	300	,,
Chlorpromazine	3	i.m.
Cyanocobalamin	0·05, 1·0	,,
Dibenzyline	5, 10	,,
Heparin	5,000 (u./kg.)	i.p.
	10,000 ,,	
	20,000 ,,	
Khellin	20, 40	i.m.
Phenobarbitone	1	i.p.
Phenylbutazone	50	i.m.
Phenylephrine	0·2, 0·5, 1·0	,,
Salicylic acid	40	,,

DISCUSSION

Sedatives were included in this investigation because they are sometimes clinically effective in allergic disorders. The action of morphine seemed of particular interest, since its use in asthma is condemned by many because of its depressant action on the repiratory centre. It is also a histamine liberator (Feldberg and Paton, 1949; Nasmyth and Stewart, 1949). In the present experiments morphine did not protect against anaphylactic shock except in a very high dose. The absence of any such effect with lower doses makes it probable that it has no specific anti-anaphylactic action. The effect of this high dose is possibly due to an indirect toxic influence. The claim that chloral hydrate has an anti-anaphylactic action (Banzhaf and Famulener, 1908) has not been confirmed by the present experiments. It has been

TABLE II

PERCENTAGE PROTECTION AFFORDED BY VARIOUS DRUGS AGAINST MICROSHOCK

(n, No. of animals; *, significant protection)

Drug	Dose (mg./kg.)	n	Mean±S.E.
"Buscopan" ..	0·01	4	10·5±13·4
	0·1	7	43·0± 5·9*
	0·5	6	31·3± 7·7*
	1·0	5	48·6±10·1*
	5·0	7	62·0± 4·9*
	20·0	7	66·3± 5·5*
	50·0	5	37·0±13·7
	80·0	7	76·7± 4·1*
Caffeine	100	5	51·2± 7·0*
Methantheline ..	2	4	27·0±15·8
	5	7	59·6± 6·5*
	10	6	63·0± 4·7*
	25	5	69·2±13·6*
Morphine	50	4	51·2± 7·9*
Pethidine	10	5	16·0± 5·8
	20	5	43·4± 9·6*
	40	6	50·3± 7·2*
Propantheline ..	0·25	5	14·6±13·4
	0·5	6	41·2± 8·8
	1·0	5	65·2± 8·6*
	10	6	73·8± 4·1*
	20	6	62·8± 4·1*
Sodium cyanate ..	50	3	65·0± 8·7*
	100	7	59·7± 9·3*
	200	4	78·0± 5·3*

said that chlorpromazine, a near relative of promethazine, has no antihistaminic action and that it is a centrally active sedative. The present experiments confirm that, unlike promethazine, it has no anti-anaphylactic effect. In other, unpublished experiments, it was confirmed that it did not suppress histamine shock in the guinea-pig except in doses as high as 10 mg./kg.

Buscopan, methantheline and propantheline all have an atropine-like effect. As atropine has an anti-anaphylactic action, a similar effect of these substances might be expected. It is remarkable that high doses were tolerated by the animals without any sign of toxicity. Significant protection was present with very small doses (0.1 mg./kg. buscopan and 0.25 mg./kg. propantheline) and became very pronounced with higher doses. Methantheline, given intravenously, has been claimed to decrease asthmatic obstruction in man (Sjoerdsma and Dodge, 1954). Buscopan has had a similar effect in a few cases of chronic asthma in which I have tried it. According to some authors khellin is beneficial in bronchial asthma, but this has not been confirmed by others. Pethidine has, in addition to its sedative effect, a spasmolytic action, and it is sometimes used as an anti-asthmatic drug. In the present experiments it had, in contrast to khellin, a definite anti-anaphylactic action, although this became pronounced only with rather high doses.

Salicylic acid and phenylbutazone were investigated because of the frequent experience that salicylates, for instance aspirin, can cause a temporary improvement in an asthmatic attack. The lack of any anti-anaphylactic effect contrasts with this clinical experience. Most of the various substances listed in group (c) were also ineffective. Barium chloride (Pfeiffer and Jarisch, 1913) has been claimed to have an anti-anaphylactic effect. Dibenzyline, the only anti-adrenaline agent in this series, was tested because an antihistaminic action has been attributed to it (Kind, 1954). Phenylephrine was included because its anti-anaphylactic effect does not seem to have been investigated before. Heparin (Williams and van de Carr, 1927) and the vitamins ascorbic acid (Hoffmann, 1942) and cyanocobalamin (Traina, 1950; Ogasawa, Asta and Hisada, 1953) did not show any effect. It is possible that these substances, which play an important part in the normal metabolism of some organs, would exert an influence on anaphylactic shock if they were given in repeated doses over a longer period. Caffeine has been used as an anti-asthmatic drug for a long time. Its anti-anaphylactic action is doubtful, as only the very large amount of 100 mg./kg. had a significant effect.

The only substance in group (c) with a marked anti-anaphylactic effect is sodium cyanate (Schütz, 1949). Hawkins (1953) has shown that it has a relaxant effect on the isolated tracheal ring of the guinea-pig (Fig. 1). There is, at present, no explanation for its action. Its application in human therapy appears hardly advisable because of its toxic effects.

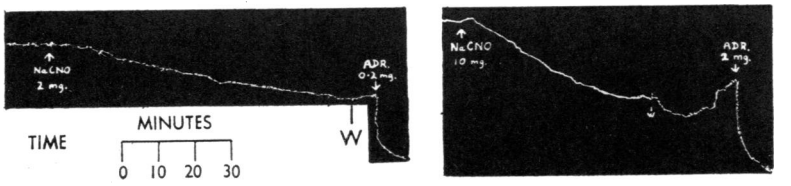

FIG. 1.—Action of sodium cyanate (2 mg. and 10 mg.) on isolated tracheal chains of the guinea-pig, followed by adrenaline (0.2 mg. and 2 mg.) after washing. Bath volume 50 ml. At W, sodium cyanate replaced by fresh Ringer solution. (Hawkins, 1953, unpublished tracing.)

SUMMARY

The anti-anaphylactic effect of nineteen substances has been investigated by the microshock method. Most of them were ineffective, but methantheline, propantheline, buscopan, and sodium cyanate had a strong anti-anaphylactic action.

This work was assisted in part by a personal grant from the Medical Research Council, and by a grant for technical assistance from the Asthma Research Council. I am indebted to Dr. P. Armitage for the statistical analysis of the results.

REFERENCES

Armitage, P., Herxheimer, H., and Rosa, L. (1952) *Brit. J. Pharmacol.*, **7**, 625.

Banzhaf, E. J., and Famulener, L. W. (1908). *Proc. Soc. exp. Biol., N.Y.*, **5**, 62.

Feinberg, S. M., Malkiel, S., Bernstein, T. B., and Hargis, B. J. (1950). *J. Pharmacol.*, **99**, 155.

Feldberg, W., and Paton, W. D. M. (1949). *J. Physiol.*, **111**, 19*P*.

Hawkins, D. F. (1953). Unpublished experiments.

Herxheimer, H. (1952). *J. Physiol.*, **117**, 251.

—— and Rosa, L. (1953). *Brit. J. Pharmacol.*, **8**, 177.

Hill, Justina H., and Martin, L. (1932). *Medicine*, **11**, 141.

Hoffmann, V. (1942). *Arch. exp. Path. Pharmacol.*, **199**, 631.

Kind, L. S. (1954). *J. Allergy*, **25**, 33.

Nasmyth, P. A., and Stewart, H. C. (1949). *J. Physiol.*, **111**, 19*P*.

Ogasawa, K., Asta, S., and Hisada, S. (1953). *Lancet*, **1**, 598.

Pfeiffer, H. S., and Jarisch, A. (1913). *Z. ImmunForsch.*, **16**, 38.

Schütz, F. (1949). *Experientia*, **5**, 133.

Sjoerdsma, A., and Dodge, H. T. (1954). *Amer. J. med. Sci.*, **227**, 255.

Traina, V. (1950). *Nature, Lond.*, **165**, 439.

Wick, H. (1951). *Arch. exp. Path. Pharmak.*, **213**, 485.

Williams, O. B., and van de Carr, F. R. (1927). *Proc. Soc. exp. Biol., N.Y.*, **24**, 798.