Potentiation of noradrenaline toxicity by drugs with antihistamine activity

SIR,—The finding that antihistamine drugs potentiate the cardiovascular action of noradrenaline (Sherrod, Loew & Schloemer, 1947; Innes, 1958) has recently been interpreted in terms of an inhibition of noradrenaline uptake by peripheral tissues (Isaac & Goth, 1965).

While examining the interaction of drugs blocking catecholamine uptake with the changes of body temperature induced by noradrenaline and reserpine it was observed that in relatively low doses these drugs also increased the toxicity of noradrenaline.

Female Sprague-Dawley rats (150 ± 5 g) in groups of at least 5 for each dose, were kept at 22° and a relative humidity of 60%. They were treated intraperitoneally with the drugs 1 hr before receiving different doses of noradrenaline. Where death occurred was it almost immediate, but the LD 50 (Litchfield & Wilcoxon, 1949) was calculated from dose-mortality data obtained 24 hr after the treatment.

The drugs used were: (+)-chlorpheniramine hydrochloride, tripelennamine hydrochloride, desipramine, pyrilamine hydrochloride, noradrenaline bitartrate.

The results in Table 1, show that (+)-chlorpheniramine, tripelennamine and

TABLE 1. THE EFFECT OF DRUGS WITH ANTIHISTAMINE ACTIVITY ON THE TOXICITY OF NORADRENALINE GIVEN INTRAPERITONEALLY TO RATS 1 HR AFTER THE DRUGS

No. of rats	Drug pretreatment 7·5 mg/kg i.p.	LD 50 Noradrenaline (mg/kg i.p.)	95% confidence limits
18	Control	8·0	7·41–8·64
24	(+)-Chlorpheniramine	3·2	2·5 –4·1
51	Desipramine	4·1	3·46–4·98
33	Tripelennamine	5·3	4·45–6·31
30	Pyrilamine	8·2	7·19–9·35

desipramine, but not pyrilamine, significantly increased the toxicity of noradrenaline.

Desipramine shows a slight antihistamine property but it is a powerful inhibitor of the catecholamine uptake process (Glowinski & Axelrod, 1964; Iversen, 1965); on the contrary, pyrilamine exerts greater antihistamine activity than the other compounds, but it was inactive on the uptake of tritiated noradrenaline by the isolated rat heart (Isaac & Goth, 1965).

Thus antihistamine potency appears not to be related to the modified responses to noradrenaline. But some antihistamine drugs, blocking the uptake mechanisms, are able to intensify the effect and to enhance the toxicity of exogenous noradrenaline. This fact might be responsible for undesirable side-effects seen on occasions in clinical treatment, where antihistamines are given with sympathomimetic agents.

Istituto di Ricerche Farmacologiche "Mario Negri," A. JORI
Via Eritrea, 62, Milan,
Italy.

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