An interaction between desipramine and phenylbutazone

SIR,—Imipramine and other tricyclic antidepressant agents are known to be inhibitors of liver microsomal enzymes (Kato, Chiesara & Vassanelli, 1963). I now report a novel effect of desipramine on the intestinal absorption of phenylbutazone.

Female, Sprague–Dawley rats, 150 g, were injected with desipramine (3·75–15 mg/kg i.p.), and 1 hr later phenylbutazone was given either intraperitoneally (20 mg/kg) or orally (40 mg/kg).

At specified times, the rats were decapitated and the blood collected in centrifuge tubes containing 0·1 ml of 2% heparin. After centrifugation, the phenylbutazone and oxyphenylbutazone were measured in the plasma (Herrmann, 1959).

Desipramine had no effect on the rate of decline of plasma levels of phenylbutazone during 4 hr, and only a small effect on these levels after 6 hr, when the phenylbutazone was administered intraperitoneally (Table 1). However, when phenylbutazone was given orally, pretreatment with desipramine or imipramine (15 mg/kg, i.p.) decreased the level of phenylbutazone in the blood plasma (Table 2).

A dose of 3·75 mg/kg of desipramine reduced the plasma concentration of phenylbutazone (40 mg/kg orally 1 hr later) by 45% from the control value ($95 \pm 3{\cdot}5$ to $53 \pm 5\,\mu$g/ml; $P < 0{\cdot}01$), while a dose of 15 mg/kg of desipramine lowered the plasma level of phenylbutazone by 82% (to $17 \pm 3\,\mu$g/ml; $P < 0{\cdot}01$). Phenylbutazone was measured 2 hr after oral dosage. The decreased plasma levels of orally administered phenylbutazone after desipramine pretreatment were not due to an increased metabolism of phenylbutazone since

TABLE 1. PLASMA LEVELS OF PHENYLBUTAZONE (I.P.) IN CONTROL AND IN DESIPRAMINE PRETREATED RATS

Time (hr) after phenylbutazone (20 mg/kg i.p.)	Plasma phenylbutazone (μg/ml) ± s.e.	
	Saline	Desipramine (10 mg/kg i.p.) 1 hr before phenylbutazone
1	85·7 ± 6·3	87·5 ± 7·3
2	71·3 ± 3·6	67·3 ± 3·8
3	57·5 ± 2·6	59·9 ± 3·6
4	54·7 ± 3·7	52·8 ± 3·7
6	34·7 ± 3·0	*49·5 ± 2·9
7	34·2 ± 3·4	43·3 ± 5·3
8	21·0 ± 2·4	33·8 ± 2·4

* = $P < 0{\cdot}01$

TABLE 2. PLASMA LEVELS OF PHENYLBUTAZONE (ORAL) IN CONTROL AND IN DESIPRAMINE OR IMIPRAMINE PRETREATED RATS

Time after phenylbutazone (40 mg/kg oral)	Plasma phenylbutazone (μg/ml) ± s.e.		
	Saline	Imipramine (15 mg/kg, i.p.)†	Desipramine (15 mg/kg, i.p.)†
20 min	28·0 ± 3·4	25·1 ± 3·6	**15·2 ± 2·6
1 hr	109·6 ± 5·8	*40·9 ± 4·3	*28·5 ± 3·1
2 hr	98·7 ± 3·0	*31·6 ± 5·4	*33·6 ± 3·8
4 hr	87·9 ± 5·3	*47·2 ± 3·5	*50·4 ± 6·8

† = Given 1 hr. before phenylbutazone.
* = $P < 0{\cdot}01$. ** = $P < 0{\cdot}05$.

oxyphenylbutazone levels were also lowered by pretreatment with desipramine from a control value of 22 ± 5 μg/ml to 2 ± 1·5 μg/ml at a dose of desipramine of 15 mg/kg indicating a possible effect of desipramine on phenylbutazone metabolism. This inhibitory effect on metabolism was also noticed after 6 hr when phenylbutazone was given intraperitoneally (Table 1).

These findings suggest desipramine interferes with the intestinal absorption of phenylbutazone. The effect of desipramine on the metabolism of phenylbutazone appears to be important in the light of the high doses required and the minor influence on the phenylbutazone and oxyphenylbutazone blood levels.

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Guanethidine and carbachol on the isolated frog rectus: a non-competitive interaction

SIR,—Guanethidine has been found to inhibit contractions caused by direct nerve and by direct muscle stimulation (Dixit, Gulati & Gokhale, 1961; Kroneberg & Stoepel, 1962; Green & Hughes, 1966; Chang, Chen & Cheng, 1967). Its main effect appeared to be on muscle fibres (Chang & others, 1967). On the other hand, in experiments in which avian and frog muscle were used, Rand & Wilson (1967b) concluded that guanethidine was a competitive antagonist of acetylcholine in these preparations. Gokhale, Gulati & others (1963), Chang & others (1967) and Rand & Wilson (1967b) attempted to modify the responses of the frog rectus to single doses of acetylcholine, but failed to analyse the dose-response curves before and after exposure to guanethidine. In recent work, Feinstein & Paimre (1967) used the same preparation to compare the effects which the competitive antagonist (+)-tubocurarine and the non-competitive antagonist tetracaine exerted on contractions elicited by carbachol, and found that while the first drug produced a parallel shift to the right of the dose-response curves, the second mainly reduced maximum contractility.

The object of the present work was to find out whether guanethidine was a competitive or non-competitive inhibitor of carbachol.

In Ringer solution, with oxygen bubbled through it, contractions of isolated rectus abdominis muscle of *Rana esculenta* were elicited by carbachol, of which the end-concentrations were $0{\cdot}2 \times 10^{-6}$ g/ml and the 2, 4, 8, 16-fold of it. The carbachol concentration was always doubled, without washing, when the effect of the preceding concentration had fully developed, and the dosing was continued until the maximum contraction developed. Five and 10 min after addition of the antagonists tubocurarine and guanethidine, respectively, the above procedure was repeated.