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Note

A gas chromatographic study of the metabolism of tarugan

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Tarugan, 1-phenyl-2,3-dimethyl-4-(2′-phenyl-3′-methylmorpholinomethyl)-pyrazolone, is a constituent of some pharmaceutical preparations (morazone, novartrine, pirisal, tarugan) with antiphlogistic and analgesic properties, and is administered to man at a dosage of about 100 mg/day.

We have studied the rate of excretion of this drug in man; in the urine are found tarugan itself and also its metabolite phenmetrazine (Fig. 1). The detection and determination of these substances was carried out by spectrophotometry and by gas and thin-layer chromatography.

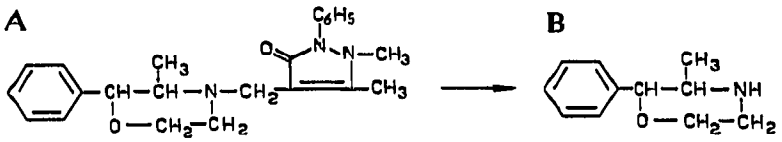

Fig. 1. Structural formulae of tarugan (A) and its metabolite phenmetrazine(B).

EXPERIMENTAL

Tarugan hydrochloride, recrystallized from methanol–acetone (1:1), melts at 169–170°. The free base extracted with chloroform from an aqueous solution of the hydrochloride, made alkaline to pH 10, dried under vacuum and recrystallized from methanol, melts at 150–151° (ref. 1).

Drug administration

Three men, 40–50 years old and ranging from 65 to 75 kg in body weight received 100 mg of tarugan hydrochloride orally. Urine samples were collected at 0 (blank), 2, 4, 8 and 20 h.

Sample extraction

To 10 ml of urine in a glass centrifuge tube was added 0.5 ml of 1 *N* HCl, and the mixture was extracted three times with 5–3 ml of diethyl ether. The extracts were discarded and the urine, made alkaline with 0.5 ml of 5 *N* NaOH, was extracted again as above. The ethereal extracts were dried with Na_2SO_4 and concentrated to 5 ml.

UV spectra

The spectrum of tarugan in diethyl ether was recorded in the 340–220 nm region with a Beckman DK-2 spectrophotometer. A maximum was found at 285 nm with $\varepsilon = 11{,}500$. At this wavelength, no interference was found from the blank or from the metabolite phenmetrazine and quantitative determinations were carried out on the 5-ml ethereal extracts.

Thin-layer chromatography

The ethereal extracts, concentrated to 5–10 μl, were placed on cellulose plates (Merck) together with reference compounds and developed with *n*-butanol–formic acid–water (20:1:2) and sprayed with bromocresol green at pH 5.5. Spots with $R_F = 0.70$ for tarugan and $R_F = 0.50$ for phenmetrazine were obtained.

Gas chromatography

The gas chromatographic determination was carried out only for phenmetrazine because tarugan does not give a peak even at high temperatures (up to 250°) on a 1% SE-30 column.

The ethereal extracts of the urine samples were examined on two columns of different polarities under the following conditions. Column 1: 2 m × 4 mm I.D. containing 10% Apiezon L on alkalinized Chromosorb W at a temperature of 190°, an injector temperature of 160° and a flow-rate of 40 ml/min; the retention index was 1450. Column 2: 2 m × 4 mm I.D. containing 2% Carbowax 20M on alkalinized Chromosorb W at a temperature of 160°, an injector temperature of 160° and a flow-rate of 40 ml/min; the retention index was 2140. The quantitative determination was made using *n*-hexadecane as the internal standard. Blank samples of urine obtained from the subjects before the administration of the drug were injected in order to control interferences from other peaks.

RESULTS AND DISCUSSION

The thin-layer chromatograms of the urine samples of men treated with tarugan showed two spots corresponding to tarugan, excreted as such, and its metabolite phenmetrazine. The tarugan was confirmed and quantitatively determined by spectrophotometry, and the phenmetrazine by gas chromatography on the two columns as described above. The presence of phenmetrazine in these samples indicates that it is formed in the body by cleavage of the N–C bond in the molecules of tarugan in a similar manner to

TABLE I

AMOUNT OF TARUGAN (μg) FOUND IN URINES COLLECTED AT VARIOUS TIMES

Amount of tarugan administered: 100 mg.

Subject No.	*Time after administration (h)*				*Proportion of tarugan excreted (%)*
	2	*4*	*8*	*20*	
1	56	32	154	127	0.37
2	273	550	27	147	0.99
3	934	300	52	150	1.44

TABLE II

AMOUNT OF PHENMETRAZINE (μg) FOUND IN URINES COLLECTED AT VARIOUS TIMES

Amount of tarugan administered: 100 mg.

Subject No.	*Time after administration (h)*				*Proportion of tarugan excreted as phenmetrazine (%)*
	2	*4*	*8*	*20*	
1	126	238	720	1570	1.57
2	200	424	646	1000	1.03
3	215	444	519	1270	1.36

the cleavage of methylamphetamine and phendimetrazine to yield their metabolites amphetamine and phenmetrazine, respectively[2,3]. This reaction was also confirmed *in vitro* by heating a solution of tarugan in 6 *N* HCl for 1 h at 100°; phenmetrazine was formed in a yield of about 60%.

In Table I are reported the amounts of tarugan determined in the urine samples. It was detected 2 h after administration, and the total amount of the drug recovered as such during the 20 h was *ca.* 1%.

In Table II are given the amounts of phenmetrazine excreted and in Fig. 2 the cumulative excretion curves of both substances (mean values) are compared.

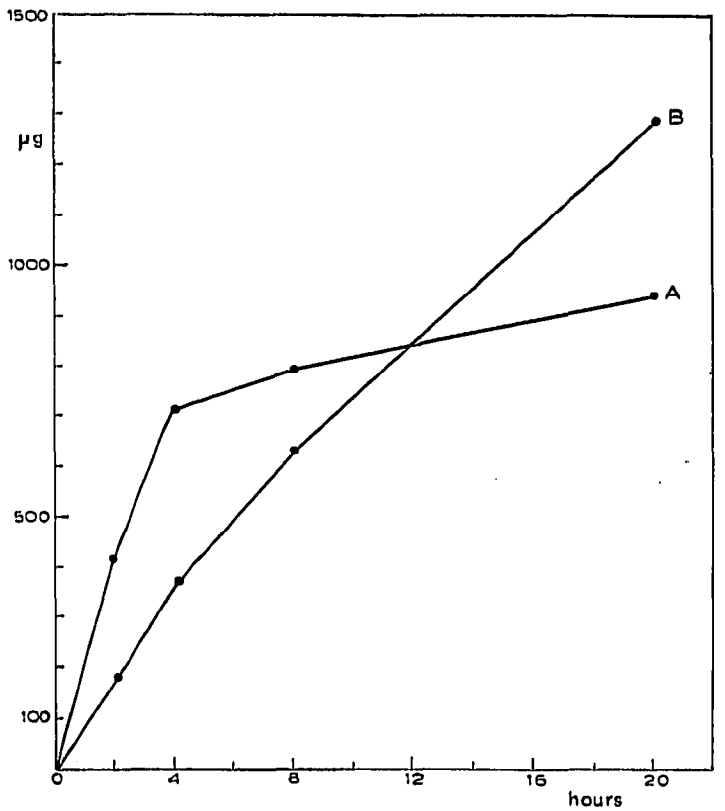

Fig. 2. Mean values of cumulative excretion of tarugan (A) and phenmetrazine (B).

The amount of the metabolite phenmetrazine excreted was initially less than that of tarugan, but it was later excreted in greater amounts and even in samples of urine examined 48 h after the administration it was found in trace amounts (*ca.* 0.05 μg/ml).

These results show that after the administration of a simple therapeutic dose of tarugan to man, not only the unchanged drug but also a comparable amount of its metabolite phenmetrazine are found in the urine.

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