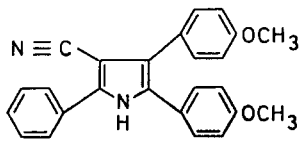
Pharmacokinetics of 4,5-bis(*p*-methoxyphenyl)-2-phenylpyrrole-3-acetonitrile in normal and polyarthritic rats

4,5-Bis(*p*-methoxyphenyl)-2-phenylpyrrole-3-acetonitrile (U-24,568, I) is a potent, orally-active anti-inflammatory agent in the adjuvant-induced polyarthritic rat (Kaiser & Glenn, 1972) and is more active than aspirin or ibuprofen in the treatment of rheumatoid arthritis, but also more toxic (Brooks, Schmid & others, 1970). Kaiser & Glenn (1972) developed a fluorometric method for the determination of I in biological materials and reported that: (a) plasma concentrations in the polyarthritic rat were linearly related to oral dose; (b) anti-inflammatory activity was linearly related to the logarithm of the average plasma concentration in a dosage interval at the equilibrium state; and (c) disappearance of I from circulation in normal rats was slow (half-life, ~11·4 h).



I

Marked reductions in liver microsomal drug metabolizing enzymes occur during the development of adjuvant-induced polyarthritic lesions in rats. Depression of the metabolism of at least 10 drugs involving 3 or more metabolic pathways has been reported (Quevauviller, Chalchat & others, 1968; Morton & Chatfield, 1970; Zak, Honc & Lukas, 1972; Whitehouse & Beck, 1973; Beck & Whitehouse, 1973). The present study compares pharmacokinetic parameters for I after single-dose administration to normal rats and multiple-dose administration to rats with established polyarthritis.

Each of 45 fasted normal male rats (Spartan[1]; mean weight, 192 g) received 52·1 mg kg^{-1} of I in 0·5 ml polysorbate 80 USP by gastric intubation. At specific times from 0 to 24 h subgroups of 5 rats were exsanguinated *via* the dorsal aorta, and serum collected for determination of I by the method of Kaiser & Glenn (1972).

Male rats (Spartan[1]; mean weight, 239 g) with severe established polyarthritis (15 days after intradermal injection into the tail of 0·5 mg *Mycobacterium butyricum*[2] in 0·1 ml mineral oil) were divided into 4 groups of 90 each. Animals received 29 oral doses of I at 0, 2·4, 6·8 or 11·4 mg kg^{-1}, b.i.d. in 0·5 ml polysorbate 80 U.S.P. After the last dose, plasma was obtained from 45 rats per group for determination of plasma inflammation units by the method of Glenn & Kooyers (1966). At specific times from 0 to 24 h, plasma was collected from subgroups of 5 rats each and analysed for I.

Table 1. *Pharmacokinetic parameters for the drug in rats.*

System	Regimen	Dose (mg kg^{-1})	% IPA*	$t_{\frac{1}{2}}$(h)	$T_{\frac{1}{2}}$(h)
Normal rats	Single dose	52·1	—	0·1	11·3
Polyarthritic rats	29th dose, b.i.d.	2·4	24	1·3	2·3
		6·8	57	0·9	8·1
		11·4	63	1·9	5·9
				Mean 1·4	5·4

* Percent inhibition of polyarthritis based on plasma inflammation units.

[1] Spartan Research, Haslett, Michigan.

[2] Difco Laboratories, Detroit, Michigan.

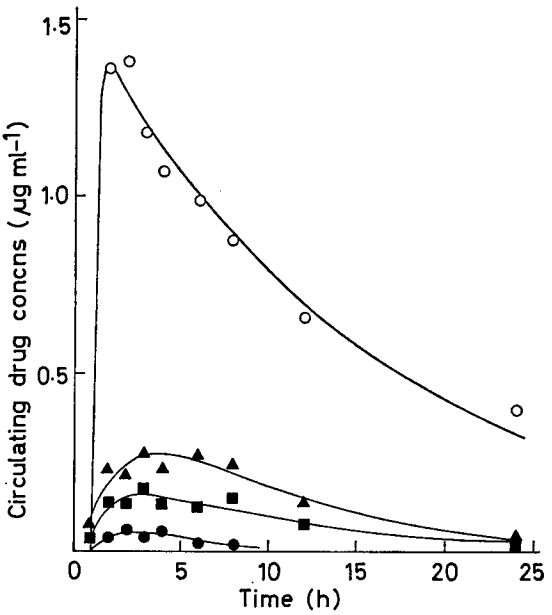


FIG. 1. Mean circulating drug concentrations following single dose (mg kg^{-1}) administration to normal rats (○, 52·1) and multiple dose (mg kg^{-1}) administration to polyarthritic rats (●, 2·4; ■, 6·8; ▲, 11·4) *versus* time. Solid lines represent predicted concentrations calculated from derived pharmacokinetic parameters.

Mean circulating concentrations of I for the various treatments are shown in Fig. 1. These observed data were fitted to a one compartment open model with the nonlinear least squares computer program of Metzler (1970). Solid curves in Fig. 1 indicate that this simple pharmacokinetic model was consistent with the data. Table 1 summarizes the half-lives for appearance ($t_{1/2}$) and disappearance ($T_{1/2}$) of I in the circulation. Cumulative 96 h urinary and faecal excretions of I in normal rats were 0·4 and 26·1 % of the dose, respectively. Thus, $T_{1/2}$ represents both metabolism and excretion with the former predominating.

Following multiple dose administration of I to polyarthritic rats, $T_{1/2}$ was not related to dose or to the degree of polyarthritis inhibition but was less (mean, 5·4 h) than that for normal rats (11·3 h). These results indicate that I not only reversed the reduced drug metabolizing capabilities of polyarthritic rats due to its anti-inflammatory activity but also stimulated its own metabolism. No similar study has been reported but the present findings are consistent with the observations of Zak & others (1972) that prolonged hexobarbitone sleeping times and reduced liver microsomal benzpyrene hydroxylase in polyarthritic rats were reversed by treatment with anti-inflammatory drugs (phenylbutazone, indomethacin and flufenamic acid) or a microsomal enzyme inducer (phenobarbitone).

Research Laboratories,
The Upjohn Company,
Kalamazoo, Michigan 49001 U.S.A.

DAVID G. KAISER
ARLINGTON A. FORIST

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1-(Hexahydroazepin-1-yl)-3-*p*-carboxyphenylsulphonylurea — a metabolite of tolazamide in man

Tolazamide [1-(hexahydroazepin-1-yl)-3-*p*-tolylsulphonylurea, I] is a potent, orally-active hypoglycaemic drug. The present communication describes the identification of a major metabolite isolated from human urine.

A 24 h urine sample (695 ml) from a normal male subject following a 2 g oral dose of the drug was adjusted to pH 1 with concentrated HCl and extracted 5 times with equal volumes of methylene chloride. Combined extracts were concentrated to dryness and the residue triturated with chloroform followed by 0·1 N HCl. The insoluble fraction was twice recrystallized from 70% ethanol to yield a product (76 mg) m.p. 180–182° (uncorrected).

Found: C, 49·4; H, 5·4; N, 12·5; O, 23·0; S, 9·3. Calculated for: $C_{14}H_{19}N_3O_5S$ C, 49·25; H, 5·6; N, 12·3; 0, 23·4; S, 9·4.

Potentiometric titration in a 60% ethanol: dimethylformamide mixture give an equivalent weight of 178 (calculated :170·7) and indicated two acidic groups with pKa′ 5·64 (characteristic of –COOH) and 7·37 (assigned to $-SO_2-NH-$; pKa′ of I under the same conditions was 7·20).

The infrared spectrum showed the characteristic absorptions of I plus the following attributed to a –COOH group: 2660 and 2540 cm^{-1}, acidic–OH; 1420 and 1278 cm^{-1}, $-COO^-$; and 960 cm^{-1}, acidic –OH deformation.

The ultraviolet spectra in acidic and alkaline ethanol showed maxima at 235 ($\epsilon = 17{,}150$) and 232 ($\epsilon = 12{,}150$) nm, respectively. The absorption of the metabolite at longer wavelengths than I (maximum in acidic ethanol, 228 nm, $\epsilon = 14\,200$) is typical of an aromatic acid (Louis, Fajans & others, 1956).

From these results it is concluded that this metabolite of I is 1-(hexahydroazepin-1-yl)-3-*p*-carboxyphenylsulphonylurea analogous to the major tolbutamide metabolite, 1-butyl-3-*p*-carboxyphenylsulphonylurea (Louis & others, 1956; Thomas & Ikeda, 1966).

Research Laboratories,
The Upjohn Company,
Kalamazoo, Michigan 49001, U.S.A.

ARLINGTON A. FORIST
RAY W. JUDY

January 2, 1974

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