Inhibition of Phenylbutazone Elimination by Its Metabolite Oxyphenbutazone (36911)

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A number of drugs which are metabolized by hydroxylation in man and animals are able to inhibit the oxidative metabolism of other drugs. For example, Dicumarol can inhibit the metabolism of diphenylhydantoin, phenobarbital and tolbutamide (1, 2), and phenylbutazone can inhibit the metabolism of tolbutamide (3) in man. It is shown in the present study that a metabolite of phenylbutazone, oxyphenbutazone or 4-butyl-1-(*p*-hydroxyphenyl)-2-phenyl-3, 5-pyrazolidinedione (4), has a similar inhibitory effect and does in fact inhibit the elimination of phenylbutazone itself in rats.

Methods. Male Sprague-Dawley rats, weighing 250–410 g, received 20 mg phenylbutazone/kg of body weight by injection into the tail vein. The drug was dissolved shortly before use in 0.2 *N* sodium hydroxide (3 ml/100 mg) which was diluted rapidly with normal saline solution and adjusted to pH 8 with phosphate buffer to yield a phenylbutazone concentration of about 10 mg/ml. Some of the rats also received oxyphenbutazone (dissolved in the same manner as phenylbutazone), 40 mg/kg 1 hr before phenylbutazone and 20 mg/kg 2, 5, and 8 hr after phenylbutazone, by intraperitoneal injection. The other rats received injections of solvent only at these times. Five 0.45 ml samples of blood were taken from the tail artery of each animal by the method of Hurwitz (5) over a period of 12 hr. Food and water were available to the animals *ad libitum*. Three weeks later, the animals that had received only phenylbutazone were given phenylbutazone with oxyphenbutazone, and vice versa. The concentration of phenylbutazone in the plasma was determined spectrophotometrically after permanganate oxidation (6) by a method which is not affected by the presence of oxyphenbutazone. Apparent plasma concentrations of phenylbutazone after repeated injection of oxyphenbutazone only were zero. Biologic half-lives, elimination rate constants, extrapolated zero-time plasma concentrations and plasma clearance values of phenylbutazone were calculated from the slope and intercept of least-squares regression lines of the logarithm of plasma-phenylbutazone concentrations versus time.

Results. Figure 1 shows the results obtained in an individual rat; the results from the entire group of 14 animals are summarized in Table I. Concurrent administration of

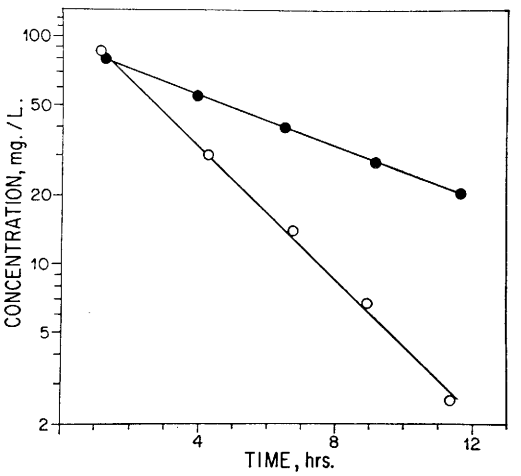

FIG. 1. Effect of oxyphenbutazone (OPB) on the elimination of phenylbutazone (PB). Shown are the plasma concentrations of PB in rat No. 2 after intravenous injection of 20 mg PB/kg in a control experiment (○), and during concurrent administration of OPB, 40 mg/kg at —1 hr and 20 mg/kg at 2, 5, and 8 hr (●).

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TABLE I. Effect of Oxyphenbutazone (OPB) on Phenylbutazone (PB) Elimination and Distribution in Male Sprague-Dawley Rats.

Rat no.	PB[b] Half-life (hr)		App. vol. of distrib. (ml/kg)		Plasma clearance (ml kg^{-1} hr^{-1})	
	Control	OPB[c]	Control	OPB	Control	OPB
1[a]	5.71	3.85	243	196	29.4	35.3
2[a]	2.04	5.32	153	212	52.0	27.6
3[a]	4.21	4.23	215	209	35.5	34.3
4[a]	3.27	4.64	212	182	44.9	27.1
5	1.97	7.09	158	311	55.6	30.5
6	3.18	4.11	159	237	34.7	40.0
7	3.31	5.14	152	213	31.8	28.8
8	1.88	4.78	156	218	57.6	31.6
9[a]	3.31	5.36	173	199	36.2	25.7
10[a]	2.77	5.04	182	209	45.5	28.8
11[a]	2.57	4.92	179	221	48.3	31.2
12[a]	2.57	5.44	197	212	53.2	25.9
13	2.31	4.60	163	289	48.9	43.6
14	2.20	4.15	163	244	51.4	40.8
Mean	2.95	4.91	179	225	44.6	32.2
SD	1.03	0.81	28	36	9.4	5.8
p value by paired t test	$<.001$		$<.01$		$<.005$	

[a] These rats received PB first; the other rats received PB and OPB in the first experiment.
[b] 20 mg/kg iv.
[c] 40 mg/kg ip 1 hr before PB, then 20 mg/kg ip every 3 hr for 3 doses.

oxyphenbutazone had a pronounced and highly statistically significant inhibitory effect on the elimination of phenylbutazone, increasing the biologic half-life from a mean of 2.95 hr to a mean of 4.91 hr and decreasing plasma clearance from 44.6 to 32.2 ml kg^{-1} hr^{-1}. The apparent volume of distribution of phenylbutazone was increased significantly from a mean of 179 ml/kg to a mean of 225 ml/kg. The intersubject variability of phenylbutazone half-lives was considerably decreased during concurrent administration of oxyphenbutazone, the coefficients of variation being 35% in the control experiments and only 16% in the experiments with oxyphenbutazone. A plot of the individual apparent first-order rate constants for phenylbutazone elimination in the control experiments versus the decrease in these constants produced by oxyphenbutazone administration (Fig. 2) shows a strong ($r = 0.98$) positive correlation. A similar plot of apparent volume of distribution data revealed a much weaker ($r = 0.83$) negative correlation; a plot of the change in apparent volume of distribution versus the change in elimination rate constant showed considerable scatter but did indicate a positive correlation ($r = 0.73$).

Discussion. Oxyphenbutazone increased the biologic half-life of phenylbutazone in rats and, to a lesser degree, increased the apparent volume of distribution of this drug. The increase in apparent volume of distribution is probably due to partial displacement of phenylbutazone from plasma proteins by oxyphenbutazone (7). The significant decrease of the plasma clearance of phenylbutazone during concurrent administration of oxyphenbutazone shows that the latter does inhibit the metabolism of the former, irrespective of any concomitant change in the distribution of phenylbutazone. The plasma clearance of phenylbutazone found in the present study (44.6 ml kg^{-1} hr^{-1}) is in very good agreement with the clearance value obtained by others (50 ml kg^{-1} hr^{-1}) in intact rats (8).

The biologic half-life of oxyphenbutazone in man is similar to that of its precursor

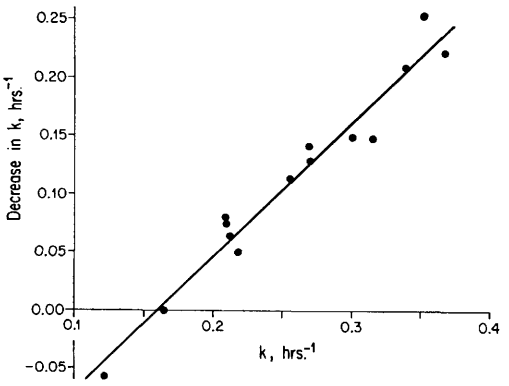

FIG. 2. Relationship between elimination rate constants for PB determined in individual rats in control experiments (k), and the changes in these constants observed during concurrent administration of OPB.

phenylbutazone, both being about 2–3 days (4). Plasma concentrations of oxyphenbutazone during repeated administration of phenylbutazone to human subjects are quite significant; the average ratio of phenylbutazone to oxyphenbutazone concentrations was about 2 in one study of 5 subjects (9). It is possible, therefore, that an inhibitory effect of phenylbutazone on the hydroxylation of other drugs may be due in part to its metabolite oxyphenbutazone. It is conceivable also that under certain conditions the elimination of phenylbutazone may be inhibited by accumulation of oxyphenbutazone. Such product inhibition by hydroxylated metabolites has already been noted in *in vitro* experiments; the metabolism of desmethylimipramine by rat liver microsomal preparations is inhibited by 2-hydroxy-desmethylimipramine (10) and that of diphenylhydantoin by 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (11). More recently it has been found that the latter has a pronounced inhibitory effect on the elimination of diphenylhydantoin in intact rats (12). A relative decrease in the elimination of phenylbutazone with increasing dose has not been found in guinea pigs, rabbits, and cats receiving 50 or 100 mg/kg and twice that dose, respectively (13). There is some indication of relatively slower elimination of phenylbutazone at higher doses in mice and rats (13); similar observations have been made in rats in this laboratory, using doses of 5 and 75 mg/kg. Phenylbutazone elimination in dogs is highly dose-dependent. The mean biologic half-life of phenylbutazone in dogs receiving 10 and 50 mg/kg intravenous doses was 2.8 ± 0.3 and 8.1 ± 2.4 hr, respectively (14); another study with 50 mg/kg and 100 mg/kg doses yielded half-lives of 8.8 and 26.0 hr, respectively (13). Whether this is due to saturation, substrate inhibition (14), product inhibition, or a combination of such effects on the biotransformation of phenylbutazone remains to be determined.

Summary. Oxyphenbutazone, a metabolite of phenylbutazone, inhibits the elimination of phenylbutazone in rats. The magnitude of this inhibitory effect is most pronounced in animals which eliminate phenylbutazone relatively rapidly in control experiments.

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