EFFECTS OF PHENYLBUTAZONE AND OXYPHENBUTAZONE ON HEPATIC DRUG METABOLISM IN THE RAT

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Two widely used approaches for the assessment of drug metabolising status in animals and man are the direct *in vitro* measurement of hepatic enzyme activity and the use of a drug metabolism marker compound *in vivo*. The use of the antipyrine breath test as a non-invasive assessment of enzyme induction and inhibition in experimental animals has proved successful (Rhodes and Houston, 1983; Rhodes et al, 1984) and the determination of ethoxycoumarin-O-deethylase (ECOD) activity as an *in vitro* index is well established (Prough et al, 1978). We therefore decided to investigate the effects of two drugs, phenylbutazone (P) and oxyphenbutazone (Ox) on these two test systems.

For the antipyrine breath test, six male Sprague-Dawley rats (wt 200-260g) were used. Each rat received control (corn oil, 2ml/kg), P (50mg/kg in corn oil) or Ox (50g/kg in corn oil) in a randomised Latin square experimental design, half an hour prior to a dose of |N-methyl ^{14}C| antipyrine (25mg/kg; 10uCi/kg; i.p.). All rats received all three treatments by intra-peritoneal injection. All administrations were separated by a period of one week, serial collections of exhaled $^{14}CO_2$ were performed and the CER (^{14}C exhalation rate)-time profiles constructed. The CER data (Table 1) demonstrate significant inhibition of antipyrine metabolism after a single dose of Ox with a 36% increase in half-life and a 17% decrease in the CER max - the maximum rate of $^{14}CO_2$ exhalation achieved. The increase in total $^{14}CO_2$ exhaled (Cum $^{14}CO_2$) caused by Ox administration indicates a more pronounced inhibition of the other pathways of antipyrine metabolism than that yielding norantipyrine by N-demethylation. No changes in CER parameters were noted after P administration.

ECOD acivity in liver microsomes from untreated male Sprague-Dawley rats was measured in control incubations and in those to which varying concentrations of Ox and P had been added. The percentage inhibition of ECOD activity caused by these two compounds was then determined, enabling the calculation of an IC50 value (Table 1) - concentration giving rise to a 50% inhibition of control activity - for each compound.

Table 1. CER and IC50 data for oxyphenbutazone (Ox) and phenylbutazone (P) in rats.

	Half-life (min)	CER max	Cum $^{14}CO_2$	IC50 (mM)
Control	129 ± 21	0.104 ± 0.014	25.2 ± 1.7	-
P	148 ± 50	0.100 ± 0.012	25.0 ± 1.1	0.3
O	176 ± 31*	0.086 ± 0.009*	29.0 ± 4.0*	0.14

Data are presented as means ± s.d. for 6 animals (not IC50)
* indicates significant difference from control $p<.05$ by 2-way analysis of variance.

The *in vivo* data on the inhibitory effects of these two compounds demonstrate significant changes in antipyrine half-life, CER max and Cum $^{14}CO_2$ following Ox administration, but not after a single dose of P. The *in vitro* results however show similar inhibitory activities of both Ox and P.

Prough, R.A.,et al (1978) Meth.Enz.52(C): 372-377.
Rhodes, J.C., Houston, J.B. (1983) Drug.Met.Dispos. 11 : 131-136.
Rhodes, J.C., et al (1984) Xenobiotica 14 : 677-686.