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THE EFFECTS OF ASTEMIZOLE ON ANTIPYRINE CLEARANCE

Drug interactions as a result of alterations in hepatic microsomal enzyme activity are a well recognised clinical problem (Park & Breckenridge, 1981). It is important that such effects are documented, and that, in the case of new drugs in particular, information about the likelihood of such interactions be available. Antipyrine is recognised to be a suitable marker drug for investigating hepatic microsomal oxidation, since its metabolism is susceptible to induction and inhibition by other drugs (Davies *et al.*, 1973; Ohnhaus & Park, 1979; Park & Breckenridge, 1981).

This study was performed to investigate the effects of astemizole (1-(4-fluorophenylmethyl)-N-1[2-(4-methoxyphenyl) ethyl]-4-piperidinyl-1 H-benzimidazole-2-amine (Chapman & Rawlins, 1982; Nicholson & Stone, 1982), a new potent antihistamine, on antipyrine kinetics, to establish whether it had inducing or inhibitory activity on microsomal enzymes.

Twenty-eight healthy volunteers participated in this study (aged 21 to 60 years, three female). Volunteers were randomly allocated to receive astemizole 10 mg daily for 1 month or matching placebo tablets. Fifteen volunteers received astemizole and 13 received placebo. The mean age of the astemizole treated group was 30.2 ± 2.5 years (mean $\pm$ s.e. mean) and the control group 27.8 ± 2.7 years. None of the volunteers was on current medication, and three were smokers, two being in the active treatment group.

Antipyrine clearance was assessed by measure-

ment of serial salivary samples collected over a 32 h period before starting the treatment with astemizole or placebo. Antipyrine clearance was also re-assessed by the same technique on days 7–8 and 28–29 of the study. Compliance with therapy was checked by a tablet count on day 29. Samples for antipyrine clearance measurement were obtained at 3, 5, 8, 13, 24 and 32 h after a single oral dose of 600 mg antipyrine prepared without excipient in gelatine capsules (Fraser *et al.*, 1976). This method has been shown to provide reproducible accurate estimates of distribution volume, half-life and clearance of antipyrine since the partition between plasma and saliva is independent of salivary flow rate and the salivary antipyrine concentration is therefore equal to that in plasma. The antipyrine concentrations were measured by gas liquid chromatography as previously described (Fraser *et al.*, 1976). Kinetic parameters for antipyrine were calculated as previously described (Fraser *et al.*, 1976).

C_0 is the intercept of the log salivary concentration-time regression curve with the ordinate.

Volume of distribution was calculated from $V = \frac{\text{dose}}{C_0}$

and the clearance from $CL = \frac{V \times 0.693}{t_{1/2}}$

Antipyrine clearance was not significantly changed by treatment with either astemizole or placebo (Table 1) when assessed either at 1 week or 4 weeks and

Table 1 Antipyrine kinetics in control subjects and those treated with astemizole (10 mg daily) ($\pm$ s.e. mean).

		Pre-treatment	1 week	4 weeks
Clearance (l/h)	Control	3.17 $\pm$ 0.26	3.10 $\pm$ 0.21	2.87 $\pm$ 0.20
	Treated	3.56 $\pm$ 0.35	3.76 $\pm$ 0.37	3.37 $\pm$ 0.31
Half-life (h)	Control	11.44 $\pm$ 0.97	11.52 $\pm$ 0.55	12.05 $\pm$ 0.75
	Treated	10.95 $\pm$ 0.69	10.66 $\pm$ 0.93	10.81 $\pm$ 0.64
Volume of distribution (l)	Control	49.02 $\pm$ 2.30	51.06 $\pm$ 2.67	48.04 $\pm$ 2.29
	Treated	52.84 $\pm$ 3.22	49.97 $\pm$ 3.98	49.70 $\pm$ 2.59

compared to pre-treatment values. Furthermore there was no significant change in either the half-life of antipyrine, or the volume of distribution of the drug, again measured pre-treatment at 1 or 4 weeks (Table 1).

Antipyrine clearance is recognised to be a sensitive index of hepatic microsomal oxidation in man (Davies *et al.*, 1973; Ohnhaus & Park, 1979; Park & Breckenridge, 1981). Thus, Ohnhaus & Park (1979) reported a 30% increase in antipyrine clearance and a reduction in antipyrine half-life of at least 25% following administration of a number of enzyme inducing agents. In the current study, no significant change in antipyrine clearance, half-life or volume of distribution was demonstrated in the group of 15 volunteers who were receiving astemizole. Further-

more, there was no change in clearance in the group of 12 subjects receiving placebo. Thus there is no evidence that astemizole at a dose of 10 mg daily for 1 month has either an inducing or inhibitory effect on hepatic microsomal enzymes. Drug interactions during astemizole therapy via a mechanism involving change in hepatic microsomal enzyme activity are therefore unlikely.

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ON THE CLINICAL PHARMACOLOGY OF PREDNIMUSTINE

In a recent paper by Newell *et al.* (1983) the pharmacokinetics of chlorambucil and prednimustine, a chlorambucil ester of prednisolone, was reported. The authors determined the drug plasma concentrations at various times after the oral administration of 10 mg chlorambucil or 20 mg prednimustine (stoichiometrically equivalent to 10 mg chlorambucil). At no time after the administration of predni-

mustine they were able to detect either intact prednimustine, chlorambucil or its metabolite phenylacetic mustard. After chlorambucil administration, the parent compound as well as phenylacetic mustard were detected.

The presence of alkylating activity is, however, evidenced by clinical observations. Thus, in early clinical trials (Brandt *et al.*, 1975; Möller *et al.*, 1975) a