PHARMACOKINETICS OF PROMETHAZINE FOLLOWING MULTIPLE DOSING IN THE RABBIT

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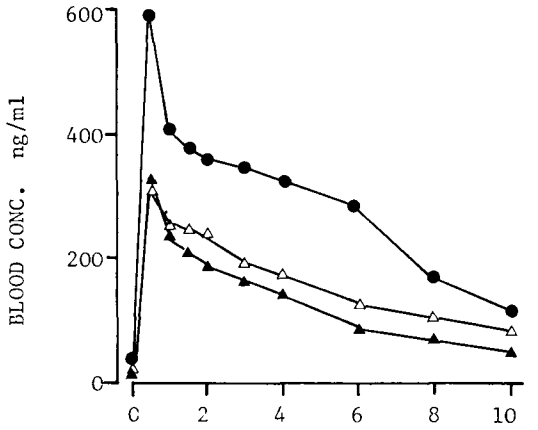
Promethazine is widely prescribed for its sedative and antihistamine properties and therapy frequently involves multiple dosing. The consequences of prolonged administration of promethazine on drug metabolism status has only been studied under in vitro conditions (Fernandez & Castro 1977). We have investigated the effects of subchronic dosing with promethazine upon its own disposition and that of antipyrine (a commonly used model compound for assessing drug metabolising capacity) in the rabbit.

Six rabbits (New Zealand White, 2.94 $\pm$ 0.20 kg) received single daily doses of promethazine (10mg/kg) by intramuscular injection for fourteen days. During the second, eighth and fourteenth day of the dosing regimen, blood samples were collected prior to, and for ten hours following dosing. Whole blood concentrations of promethazine and monodesmethylpromethazine were determined using a reverse-phase HPLC system following solvent extraction. In four rabbits antipyrine (10mg/kg) was administered intravenously prior to, and immediately following the promethazine dosing regimen. After protein precipitation using acetonitrile plasma levels of antipyrine were determined directly using a reverse-phase HPLC system.

The clearance of promethazine increased from 59.9 $\pm$ 15.2 ml min^{-1} kg^{-1} on the second day, to 65.0 $\pm$ 7.8 on the eighth day and 78.0 $\pm$ 16.4 ml min^{-1} kg^{-1} on the fourteenth day of treatment. The analogous clearance term for monodesmethylpromethazine similarly increased from 229 $\pm$ 72.6 on the second day to 269.6 $\pm$ 69.8 and 379.9 ml min^{-1} kg^{-1}. The clearances of promethazine and monodesmethylpromethazine were statistically significantly higher ($p<0.05$ by paired t test) on the fourteenth day than their clearances on the second day of treatment. The terminal half-life for promethazine did not change during multiple dosing. A set of blood concentration time curves for a typical rabbit is shown in figure.



Blood concentration-time profiles for promethazine during multiple dosing- (●) day 2, (Δ) day 8 and (▲) day 14

Antipyrine clearance was statistically significantly increased ($p<0.01$ by paired t test) from 8.44 $\pm$ 1.16 before treatment to 9.60 $\pm$ 1.38 ml min^{-1} kg^{-1} after treatment with promethazine. Therefore prolonged administration of promethazine results not only in auto-induction of its own metabolism but also may influence the pharmacokinetics of other co-administered drugs as exemplified by antipyrine.

Fernandez, G. and Castro, J.A. (1977) Drug Metab. Dispos. 5: 91