DISPOSITION OF PROMETHAZINE IN RABBIT: INFLUENCE OF ROUTE OF ADMINISTRATION

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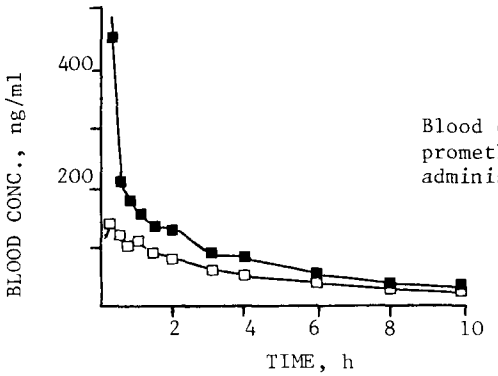
Despite many years of widespread use there is very little information available on the metabolism or pharmacokinetics of promethazine in man or animal species. The purpose of this investigation was to compare the blood concentration-time profile of this drug and its metabolites following different routes of administration.

The disposition of [^{35}S] promethazine (5 mg/kg) was investigated in 6 rabbits (New Zealand White, 3.2±0.5 kg) following an intravenous bolus injection (IV) and oral administration of an aqueous solution (PO). A balanced crossover design was used allowing one week between studies in each rabbit. Blood samples were collected over a 10 hour period following dosing. Promethazine and two of its primary metabolites, monodesmethyl-promethazine and promethazine sulphoxide were assayed in whole blood after basifying and solvent extraction. A reverse phase high performance liquid chromatographic system with prochlorperazine as an internal standard was used to simultaneously quantify the three compounds.

The clearance of promethazine, calculated from the IV studies, averaged 52.2 ± 13.2 ml/min/kg. Clearance is essentially totally metabolic since less than 1% of dose is excreted unchanged in the urine. The volume of distribution, calculated by the area under curve (AUC) method, was 22.9 ± 6.8 L/kg and the terminal half-life was 316 ± 103 minutes. Both metabolites had blood concentrations approximately one third of promethazine and showed similar half-lives to the parent drug. Following PO administration the AUC for promethazine was statistically significantly reduced ($p < 0.01$ by paired t test); systemic availability averaged 0.50 ± 0.24. A set of blood concentration-time curves for a typical rabbit is shown in figure.



Blood concentration-time profiles for promethazine after IV (■) and PO (□) administration.

Systemic availability after oral administration is the product of the fraction of the dose absorbed (f_A) and the fraction of the dose lost by first pass metabolism (f_M). Urinary recovery of [^{35}S] showed that f_A averaged 0.80 ± 0.08. Thus f_M may be calculated to be 0.61 ± 0.27.

Four rabbits also received a third promethazine dose directly into the hepatic portal vein (HPV). This route of administration gave a systemic availability of 0.59 ± 0.19. The excellent agreement between this value and f_M from the oral studies strongly suggests that metabolism of promethazine during the first pass is limited to the liver and the contribution from the gastrointestinal mucosa is minimal.