PHARMACOKINETICS OF SALICYLATE AFTER CHRONIC DOSING IN MAN

L.J. Aarons, F. Bochner, D.M. Johns and M. Rowland, Department of Pharmacy, University of Manchester, Manchester, M13 9PL, U.K.; Department of Medicine, Royal Brisbane Hospital, Brisbane 4029, Australia

Salicylate dosage is empirical; often it involves increasing the dose until side effects develop and then decreasing the dosage slightly. Prediction of individual salicylate dosage is hampered by its well recognised dose dependent kinetics (Levy, 1965). Most detailed kinetic studies have been based on single dose urine data. The present study emphasises chronic administration and unbound drug in plasma.

Two healthy male volunteers who gave their informed consent, each ingested 300 mg aspirin, in solution, every eight hours until steady state was reached. Blood, urine and saliva was then collected. The procedure was repeated, raising the dose by increments of 300 mg, until side effects, gastro-intestinal discomfort and tinnitus, occurred. At that time, one subject was taking 1200 mg and the other 1500 mg every eight hours. On a separate occasion, each subject ingested 2.4 g aspirin in solution.

Salicylic acid in plasma was measured by fluorimetry. Salicylic acid, salicyluric acid and gentisic was measured by hplc. Total urinary salicylate was determined colourimetrically (Levy and Procknal, 1968). Plasma binding was measured by ultracentrifugation.

The mean steady state plasma and unbound concentration increased disproportionally with dose. Salicyluric acid was the major urinary metabolite; but due to saturation of this pathway the percent excreted decreased from 80% to 60% upon increasing from the lowest to highest dose. The binding of salicylate also decreased with increasing plasma concentration.

All the data - unbound salicylate in plasma and the cumulative salicylurate excreted in urine at steady state at each dose level - were fitted simultaneously using a nonlinear regression programme, to a pharmacokinetic model which is based on unbound drug in plasma and two pathways of elimination, one saturable (salicylurate formation) and one non-saturable (other pathways). Attempts to fit the plasma data alone failed. Simulation from the fits of the single dose data overpredicted the steady state salicylate plasma concentration data. Likely explanations include, decreases in plasma binding and stimulation of salicylurate metabolism.

Tinnitus was noted at plasma salicylate concentration above 100 mg/L. Both subjects experienced some hearing loss at the highest dosing rate; hearing recovered upon withdrawing aspirin.

Levy, G. (1965). J. Pharm. Sci., 54, 959.

Levy, G. and Procknal, J.A. (1968). J. Pharm.Sci., 57, 1330.