Pharmacokinetics in the Elderly

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Summary. The pharmacokinetics of sulphamethizole, paracetamol and phenylbutazone were investigated and compared in young and geriatric subjects. The rate and extent of absorption of the drugs did not appear to be affected by increasing subject age. However, the mean half-lives for sulphamethizole and paracetamol were significantly increased in the geriatric subjects. A number of correlations are presented between the elimination rate constants of the drugs and certain subject parameters and variables. The elimination of phenylbutazone was found not to be influenced significantly by subject age. The apparent volumes of distribution of the three drugs were not age-dependent.

Key words: Sulphamethizole, paracetamol, phenylbutazone, single-dose kinetics, plasma/blood concentrations, metabolites, absorption, disposition, geriatrics.

A number of authors (for example Mawer et al., 1972; Dettli et al., 1971) have examined the influence of disease on pharmacokinetics in man. However, relatively few studies have appeared in the literature with regard to the possibility that the aging process may significantly alter human pharmacokinetics (Ewy et al., 1968; Mölholm Hansen et al., 1970; Jori et al., 1972; Simon et al., 1972). One of the most detailed of these studies was that conducted by O'Malley and co-workers (O'Malley et al., 1971) who examined the influence of age and sex on the pharmacokinetics of antipyrine and phenylbutazone in man. The elimination of these drugs is almost solely dependent on drug metabolism.

We chose to develop a similar study to that of O'Malley and co-workers but to include drugs that are eliminated by renal excretion. We also intended to ascertain whether drug absorption was different in the elderly. With this aim the drugs sulphamethizole, paracetamol and phenylbutazone were chosen for study and were administered as single oral doses in a cross-over design to young and geriatric subjects. Sulphamethizole and paracetamol are drugs with relatively short biological half-lives, the former being eliminated mainly by renal excretion and the latter largely by metabolism. Phenylbutazone usually exhibits a long and variable half-life and is eliminated by metabolism.

Subjects and Methods

Six young subjects acting as controls, aged 22-30 (mean 24.0) years, and seven geriatric subjects, aged 73-91 (mean 80.9) years, were selected in order to maximise homogeneity within and between the groups. In an attempt to obviate any potential sex-linked differences (O'Malley et al., 1971; Kato and Gillette, 1965) in the elimination of the drugs only male subjects were used. Since it is well known that human subjects suffering from functional pathology of the liver or kidney may exhibit an increase in the elimination half-life of some drugs, an attempt was made to reduce the differences between the two groups to those due to age alone by selecting apparently healthy subjects. A number of biochemical and haematological variables were therefore measured in blood samples collected from the subjects prior to their selection for the study. Only those subjects whose serum urea, creatinine, bilirubin, alkaline phosphatase, GOT, GPT, and plasma proteins were within normal limits were included. In addition the geriatric subjects underwent a physical examination. All the young subjects received no other medication for 48 hours before and during the course of the study. However, three of the geriatric subjects were receiving other drugs; subjects O.W. and E.W. were undergoing maintenance digoxin therapy, while L.F. was receiving methyldopa. Informed consent was given by all the subjects.

Each of the subjects was given the three drugs by oral administration in the order sulphamethizole, paracetamol and phenylbutazone. A period of no less than six days was allowed to elapse between administration of each successive drug to any one subject. The drugs were administered mid-morning. All subjects, with the exception of one of the control group had eaten a light breakfast at least two hours prior to dosage.

Sulphamethizole and paracetamol were administered at a dose level of 14.3 mg/kg, the former as a
suspension (2.0 percent) and the latter in solution (0.8 percent). Phenylbutazone dosage was 5 mg/kg, the drug being packed in two hard gelatin capsules.

In the sulphasalazine and paracetamol studies, venous blood samples were taken from the control subjects at approximately 0.25, 0.5, 0.75, 1, 1.5, 2.5, 4, and 6 hours after administration. Additional samples were taken from the geriatric subjects at 2, 3, 5, and 7 hours. The blood sampling protocol for phenylbutazone in the two age groups consisted of the collection of a number (between two and ten) of samples on the first day of the study, followed by at least one sample on the second, third, fourth, and fifth days. In all studies the blood was taken into heparinised tubes, and the exact time of sampling noted. Urine samples were collected for 24 hours after administration of sulphasalazine and paracetamol. No urine was collected after administration of phenylbutazone.

Unchanged sulphasalazine in blood and urine and acetylated sulphasalazine in urine were estimated by the method of Bratton and Marshall (1939). Paracetamol in plasma and urine and conjugated paracetamol in urine were quantitated using a procedure developed by Heirwegh and Favery (1967). Unchanged phenylbutazone in plasma was assayed by the method of Jähnenchen and Levy (1972).

The Mann-Whitney U-test was used for comparisons between the two groups (Goldstein, 1964).

Results

Sulphasalazine

The time interval between drug administration and achievement of the maximum observed blood level of sulphasalazine was used as a measure of the rate of drug absorption from the gastrointestinal tract. The mean values (with their standard errors) for this parameter for the young and geriatric subjects were 1.2 ± 0.2 hours and 2.1 ± 0.5 hours respectively. The difference between the groups was not significant (P > 0.05).

Fig. 1 shows the resulting blood concentration of sulphasalazine after oral administration to a typical young subject and a typical geriatric subject. The elimination rate constant (k_1) for the drug was calculated in each case from the slope of the least squares line through the linear terminal portion of the log blood level against time plot (Equation 1):

\[
\text{Slope} = -\frac{k_{el}}{2.303}
\]

The biological half-life (t_1/2) was then calculated by use of equation (2):

\[
t_{1/2} = \frac{0.693}{k_{el}}
\]

The mean half-life of sulphasalazine and the mean creatinine clearance adjusted for body surface area were significantly different between the groups (P < 0.01; Table I). The mean concentration of sulphasalazine in blood six hours after administration was almost three times greater for the geriatric subjects than for the young controls, and this difference was significant (P < 0.01; Table I).

The mean percentage of the dose of sulphasalazine excreted in urine as unchanged drug and metabolite in 24 hours and the percentage of the excreted drug that was acetylated were not significantly different between the groups (P > 0.05; Table I).

The blood clearance (V_D k_1 el) of sulphasalazine was calculated using equation (3) (Portmann, 1970):

\[
\text{AUC}^\infty = \frac{F D}{V_D k_{el}}
\]

where \text{AUC}^\infty = area under the blood level-time curve from time zero to infinity
\text{F} = fraction of the dose absorbed
(assumed to be 1)
\text{D} = dose
\text{V}_D = apparent volume of distribution of the drug
\text{k}_{el} = elimination rate constant

The renal clearance could then be found from equation (4):

\[
\text{Renal Clearance} = f \times \text{Blood Clearance}
\]

where \text{f} = fraction of the absorbed dose excreted unchanged in the urine

Both the blood and renal clearance values were adjusted for body surface area.

The mean values for the blood clearance were 167 ± 17 ml/min/1.73 sq m for the young controls and 90 ± 11 ml/min/1.73 sq m for the geriatric subjects, and the corresponding means of the renal clearances were 145 ± 18 ml/min/1.73 sq m and