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Pharmacokinetic Study of Omeprazole in Elderly Healthy Volunteers

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Summary

The pharmacokinetics of omeprazole and its metabolites were studied in 8 healthy elderly volunteers using [^{14}C]omeprazole. In another 6 healthy elderly volunteers, the pharmacokinetics of omeprazole were studied using unlabelled drug. Each volunteer received single doses of omeprazole intravenously (20mg) and orally (40mg) as solutions in a randomised crossover design. The plasma concentrations and urinary excretion of omeprazole and metabolites were followed for 24 and 96h, respectively.

The results indicate that the average metabolic capacity of omeprazole is decreased in the elderly compared with that found in earlier studies of healthy young individuals. This was reflected in an increase in bioavailability from 56 to 76%, a reduction in mean systemic clearance by approximately 50% (0.25 L/min) and a prolongation of the mean elimination half-life from 0.7 to 1.0h compared with the young.

Despite these findings, the considerable overlap in these parameters between young and old volunteers, together with data from previous pharmacodynamic studies and the wide therapeutic range of omeprazole, indicate that dosage reductions are not needed in the elderly.

Omeprazole suppresses gastric acid secretion by interacting with the gastric proton pump in the secretory membranes of the parietal cell (Fellenius et al. 1981; Wallmark et al. 1985). The drug has a pronounced effect on gastric acid secretion and despite its rapid elimination half-life ($t_{1/2} < 1\text{h}$) is still effective 24 to 72h after administration (Lind et al. 1983). The long duration of action of omeprazole might be due to slow dissociation of the inhibitory molecule from the enzyme or that recovery of acid secretion needs *de novo* synthesis of enzymes (Brändström et al. 1989; Lorentzon et al. 1985). The effective control of acid secretion by omeprazole results in very rapid healing of peptic ulcers

and erosive reflux esophagitis, and the drug is more effective than H_2 -receptor antagonists in this aspect (Bardhan et al. 1986; Hetzel et al. 1988; Klinkenberg-Knol et al. 1987; Walan et al. 1989).

Omeprazole (MW = 345.4D) is eliminated by hepatic metabolism with the major fraction ($\approx 80\%$) of its metabolites excreted by the kidneys. The rest is excreted in the faeces, primarily originating from bile secretion (Lind et al. 1987; Regårdh et al. 1990). None of the major identified metabolites appear to contribute to the pharmacological effect (Wallmark, personal communication). Previous studies indicate that impaired renal function has essentially no influence on the absorption or disposition

of omeprazole, while impaired hepatic function significantly decreases the metabolism of this drug (Andersson et al. 1993; Naesdal et al. 1986). As both hepatic (Vestal 1989) and renal (Larsson et al. 1986) function are altered with aging, the present investigation was performed to study the pharmacokinetics of omeprazole in healthy elderly volunteers for comparison with those obtained in previous studies with healthy young volunteers (Andersson et al. 1990a; Regårdh et al. 1990).

Methods

14 healthy elderly nonsmoking volunteers (8 female, 6 male) with a median age of 76 years (range 75 to 79 years) and median weight of 71 kg (range 58 to 88 kg) completed the study. They were recruited via routine health control in the Göteborg area and none was receiving regular drug therapy. The volunteers were informed of the details of the study and gave their consent to participate. The study was conducted according to the Declaration of Helsinki and approved by the Ethics and Isotope Committees, University of Göteborg, and by the Swedish National Board of Health and Welfare.

An open randomised crossover design was used. Each volunteer participated in 2 experiments, 1 with an intravenous dose of 20 mg and 1 with an oral dose of 40 mg omeprazole. The first 8 volunteers received [^{14}C]-labelled omeprazole 20 μCi per dose, while the other 6 received unlabelled drug only. The 2 doses were separated by at least 1 week. A routine clinical laboratory screen including haematology, blood chemistry and urinalysis was performed before the first and within 12 days after the second dose was administered. Alcohol and all medication, including over-the-counter drugs, were not allowed for 2 days before and during each experiment. Each experiment started at about 0800h with the volunteers having abstained from all food and liquids after 2200h the previous day. Four standardised meals were served during each experiment (2.5, 6, 8 and 10h postdose).

Both doses were dissolved in a mixture of polyethylene glycol 400, sodium bicarbonate and water

before administration. Since omeprazole is rapidly degraded in acidic media, sodium bicarbonate 8 mmol/L in solution was administered before and 10, 20 and 30 min after the oral dose. Furthermore, sodium bicarbonate 16 mmol/L was given together with the dose. To maintain identical conditions during the intravenous experiment, the oral sodium bicarbonate solution was given in amounts and at times consistent with the oral experiment. The intravenous dose was infused over 5 min.

Blood samples were taken before and 5, 7, 11, 15, 20, 25, 30 and 40 min, and 1, 1.5, 2, 4, 6, 8, 12 and 24h after the start of the intravenous infusion. In volunteers 9 to 14, an additional blood sample was taken at 10h, but since data from the first 8 volunteers showed that it was not relevant to measure plasma concentrations beyond this time point, samples at 12 and 24h were subsequently omitted. A similar blood sampling schedule was used when omeprazole was given orally, except that the blood sample after 7 min was omitted. The samples were centrifuged and the plasma stored at -20°C until analysis of omeprazole (volunteers 1 to 14), and major identified metabolites (hydroxy-omeprazole and omeprazole sulphone) and total radioactivity (volunteers 1 to 8).

Urine collection intervals (volunteers 1 to 8) were identical after oral and intravenous administrations and were as follows: 0 to 3, 3 to 6, 6 to 9, 9 to 12, 12 to 24, 24 to 48, 48 to 72 and 72 to 96h postdose. The urine portions were adjusted to $\text{pH} > 7$ with sodium bicarbonate 1 mol/L to prevent acidic degradation of omeprazole and were stored at -20°C . All samples were assayed for total radioactivity and, in the samples collected up to 24h, for omeprazole, hydroxy-omeprazole and the sulphone.

The plasma and urine concentrations of omeprazole and its 2 major metabolites were determined by an automated liquid chromatographic method which uses the Technicon 'Fully Automated Sample Treatment LC' system (Grundevik et al. 1986). The limits of determination in plasma and urine were 50 and 200 nmol/L, respectively, with a relative standard deviation of less than 10 to 15%. The assay method was linear between 50

and 100 000 nmol/L for blood and between 200 and 120 000 nmol/L for urine.

Total radioactivity was determined directly in 0.5ml of plasma or urine after the addition of 10ml of a liquid scintillator (Lumagel®). Counting was performed in a Beckman LS 3800 and correction for quenching made by external standardisation.

The pharmacokinetics of omeprazole following intravenous administration were evaluated according to a 2-compartment model using postinfusion data and model-independent methods. The equation describing the biexponential decline of the plasma concentration-time curve was derived in each individual by nonlinear regression analysis using the extended least-squares procedures in the program ELSFIT (Sheiner & Beal 1985). The area under the plasma concentration-time curve (AUC) for the intravenous dose was determined as:

$$AUC_{IV} - (C_1/\lambda_1) = (C_2/\lambda_2)$$

where C_1 and C_2 are the intercepts transformed to bolus dose administration (Loo & Reigelman 1970) and λ_1 and λ_2 are the exponents of the equation describing the plasma concentration-time curve. Total plasma clearance (CL) was calculated as:

$$CL = Dose_{IV}/AUC_{IV}$$

and the apparent volume of distribution during the terminal phase (V_z) as:

$$V_z = CL/\lambda_2$$

where the constant λ_2 is the rate constant of the terminal phase ($\lambda_2 = 0.693/t_{1/2}$).

The $t_{1/2}$ of omeprazole following the oral dose, and of the 2 identified metabolites following both intravenous and oral doses, were calculated by linear regression analysis of the terminal phase of the log plasma concentration-time curve. The corresponding AUC values were determined by the trapezoidal rule and extrapolated to infinity by dividing the last determinable plasma concentration by λ_2 .

Systemic availability of the oral dose was calculated as:

$$F = (AUC_{PO}/AUC_{IV}) \cdot (Dose_{IV}/Dose_{PO})$$

Reference values of the parameters of interest

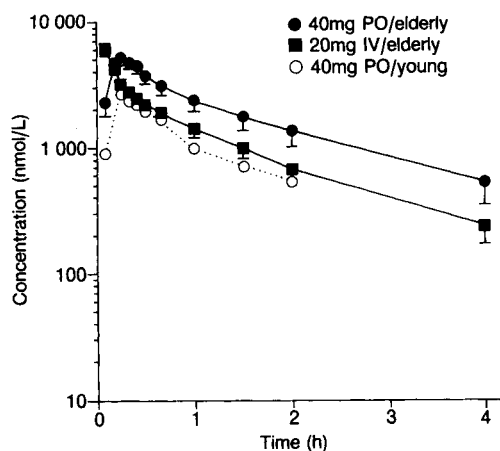


Fig. 1. Plasma concentration-time profiles (mean \pm SEM) of omeprazole following administration of the drug to 14 healthy elderly volunteers (20mg intravenously; 40mg orally) compared with mean values in 18 healthy young volunteers (40mg orally) derived from 2 separate studies (Andersson et al. 1990a; Regårdh et al. 1990).

were obtained from 2 separate studies comprising a total of 18 healthy young nonsmoking volunteers in whom omeprazole was administered in an almost identical fashion to that in the elderly volunteers (Andersson et al. 1990a; Regårdh et al. 1990). Eight of these volunteers were only given omeprazole 20mg orally and, despite a slight nonlinearity that might be expected in this dose range, the peak plasma concentration (C_{max}) and AUC values in these individuals have been adjusted to correspond to a 40mg dose. The reason for this pooling of data is that among those healthy volunteers receiving 20mg there was 1 slow metaboliser of omeprazole, who was also verified as a poor *S*-mephenytoin hydroxylator (Andersson et al. 1990b), and we therefore can present a more representative sample of the healthy young population as regards the rate of metabolism. Metabolite (hydroxy-omeprazole and omeprazole sulphone) values for comparisons are taken from Andersson et al. (1990a) and values for the total pool of metabolites are from Regårdh et al. (1990).

Statistical significance of differences between

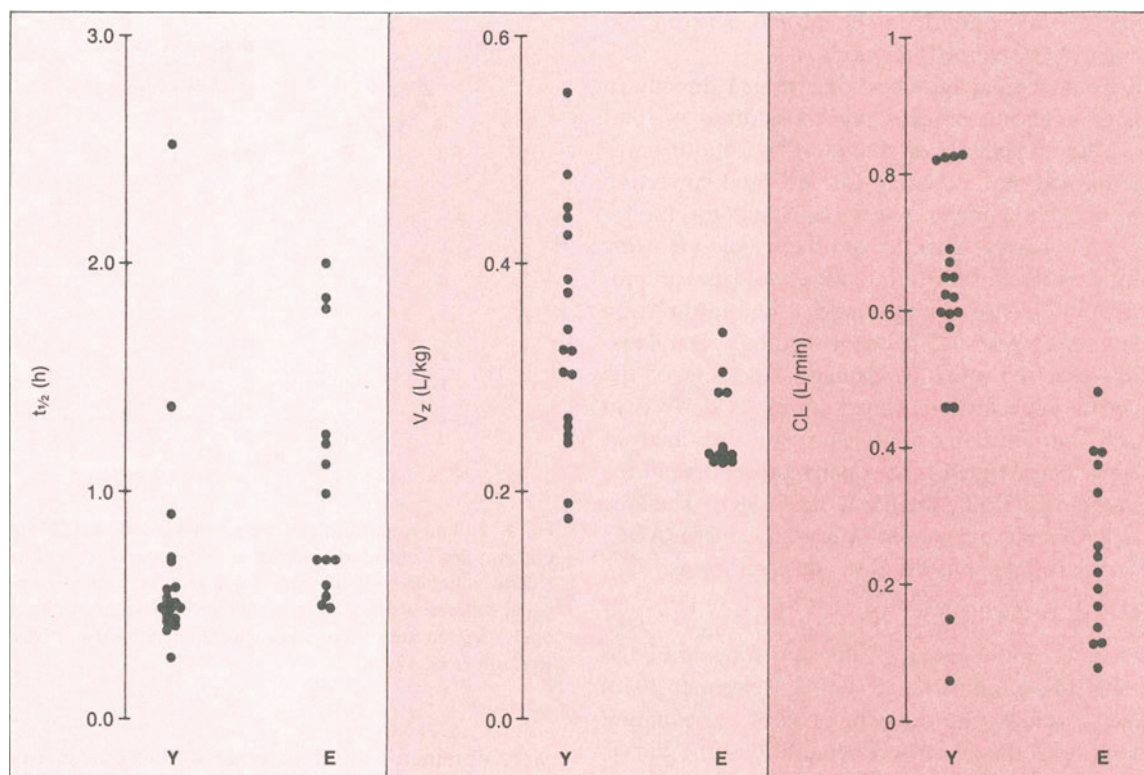


Fig. 2. Individual disposition characteristics of omeprazole 20mg following intravenous administration to 14 healthy elderly volunteers (E) and 18 healthy young volunteers (Y). $t_{1/2}$ = elimination half-life; V_z = volume of distribution; CL = total plasma clearance (Andersson et al. 1990a; Regårdh et al. 1990).

values in the elderly and the young volunteers were tested by the Mann-Whitney U-test, using $\alpha = 0.05$.

Results

The mean plasma concentration-time profile of omeprazole following a single intravenous dose of 20mg to healthy elderly volunteers is shown in figure 1. The individual pharmacokinetic parameters derived from these experiments are shown in figure 2 and mean values are presented in table I. The $t_{1/2}$ ranged from 0.5 to 2.0h with a mean value of 1.0h, compared with 0.7h in the young volunteers ($p < 0.02$). The mean V_z was significantly lower in the elderly (0.25 L/kg) compared with the young group (0.34 L/kg) [$p < 0.02$]. The mean CL in the elderly was 0.25 L/min compared with 0.59 L/min reported in the young volunteers

($p < 0.002$), i.e. CL was approximately halved in the elderly.

The mean plasma concentration-time curves of oral omeprazole for young and elderly volunteers are also given in figure 1. Omeprazole was rapidly absorbed in both the young and elderly and time to C_{max} (t_{max}) < 25 min in all volunteers. The mean C_{max} was almost doubled in the elderly (5.74 vs 3.28 $\mu\text{mol/L}$, $p < 0.02$) and mean AUC was more than doubled (8.76 vs 4.00 $\mu\text{mol/L} \cdot \text{h}$, $p < 0.002$) [fig. 3, table I]. The systemic availability showed a pronounced variation (25 to 100%) with a somewhat higher average value for the elderly (mean $F = 56\%$ in young volunteers and 76% in the elderly, $p < 0.05$). The mean $t_{1/2}$ after oral administration in the elderly was 1.24h, which was similar to that obtained after intravenous administration.

The mean plasma concentration-time curves of hydroxy-omeprazole after administration of omeprazole 20mg intravenous and 40mg oral doses to elderly volunteers are shown in figure 4. The $t_{1/2}$ of hydroxy-omeprazole (≈ 1.5 h) was somewhat longer than that of unchanged omeprazole, but no determinable concentration remained after 24h. The corresponding $t_{1/2}$ in the young individuals was 1h. The mean C_{\max} of the hydroxy-metabolite was about 20% and the mean AUC about 30% of that of omeprazole. The corresponding proportion for the AUC in the young individuals seemed to be higher ($\approx 70\%$). The mean cumulative excretion over 24h was 8.2% after the intravenous and 9.9% after the oral dose and excretion was mostly complete within 6h in all but 1 volunteer.

The mean $t_{1/2}$ of the sulphone was ≈ 4.5 h, com-

pared with almost 2h in the young individuals. The mean C_{\max} of the sulphone metabolite was 13% of that of omeprazole, while the corresponding value for the AUC was 60% following intravenous and $>100\%$ after oral doses (fig. 4). In the young individuals the C_{\max} ratio was 18% while the corresponding ratios for AUC values seemed to be lower than in the elderly. **The sulphone was not detected in urine in either group of volunteers.**

For the total pool of metabolites (including hydroxy-omeprazole and omeprazole sulphone), the mean C_{\max} was 60% and the mean AUC 2 and 3 times higher (after intravenous and oral doses, respectively) than that of intact omeprazole (fig. 4). **68% of the dose was recovered as radioactive metabolites in urine over the 96h collection period (fig. 5).**

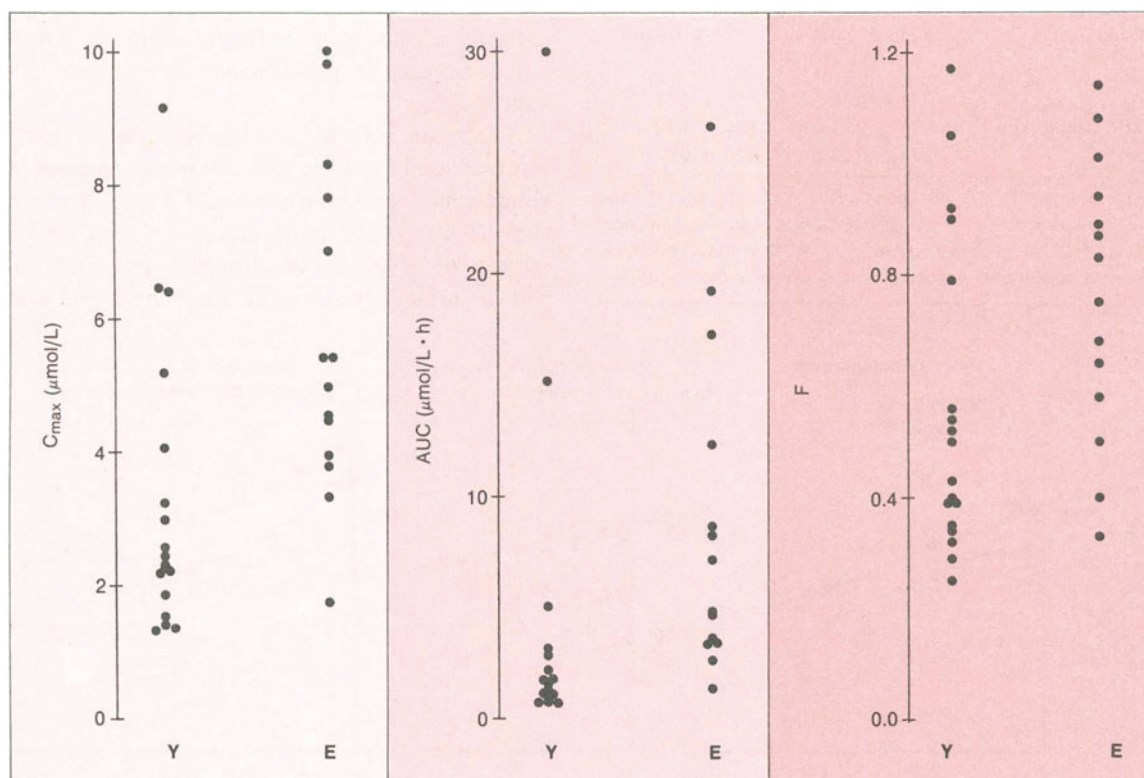


Fig. 3. Individual absorption and disposition characteristics of omeprazole following administration of oral omeprazole 40mg to 14 healthy elderly volunteers (E) and 18 healthy young volunteers (Y). C_{\max} = peak plasma concentration; AUC = area under the plasma concentration-time curve; F = bioavailability (Andersson et al. 1990a; Regårdh et al. 1990).

Discussion

Drug consumption among the elderly is high and multipharmacy is pronounced. Most physiological and biological functions change with age but the consequences of these changes for drug treatment are poorly understood. It is well known that renal function decreases with increasing age (Larsson et al. 1986), with a resultant effect on excretion ca-

Table I. Mean (\pm SEM) absorption and disposition characteristics of omeprazole after an intravenous 20mg dose and an oral 40mg dose administered to 14 healthy elderly volunteers in this study and compared with values in 18 healthy young volunteers from Regårdh et al. (1990) and Andersson et al. (1990a)

Parameter	Elderly	Young
Intravenous		
$t_{1/2}$ (h)	1.03 ± 0.14	0.68 ± 0.12
V_z (L/kg)	0.25 ± 0.01	0.34 ± 0.02
CL (L/min)	0.250 ± 0.034	0.594 ± 0.050
Oral		
C_{max} (μ mol/L)	5.74 ± 0.66	3.28 ± 0.51
AUC (μ mol/L \cdot h)	8.76 ± 2.00	4.00 ± 1.72
F	0.76 ± 0.07	0.56 ± 0.07

Abbreviations: $t_{1/2}$ = elimination half-life; V_z = apparent volume of distribution of the terminal phase; CL = total plasma clearance; C_{max} = peak plasma concentration; AUC = area under the plasma concentration-time curve; F = systemic bioavailability.

capacity. There is also a change in body composition with loss of water and muscular body cell mass and a relative increase in body fat, thus resulting in an altered volume of distribution for a number of drugs (Vestal 1978). The extent to which the metabolic capacity of the liver is affected by aging and the possible implications of such changes in drug metabolism have been previously discussed (Greenblatt et al. 1982; Lamy 1984). Impaired metabolism in the elderly, which occurs with many hepatically eliminated drugs, has been strongly suggested to primarily be a result of reduced liver mass coupled with diminished liver blood flow (Vestal 1989; Wynne et al. 1989, 1990). Recent results have also shown that there are in fact no significant age-dependent differences in the activities and contents of human liver mono-oxygenases (Schmucker et al. 1990). The volunteers in this study were all healthy nonsmokers and as such were specially selected to more clearly relate any potential differences in pharmacokinetics to their advanced age.

The mean systemic availability of omeprazole was increased from the 56% previously reported in young volunteers (Andersson et al. 1990a; Regårdh et al. 1990) to 76% in this group of elderly, i.e. an increase of 36%. Since the dose was completely absorbed (urinary recovery of intravenous and oral

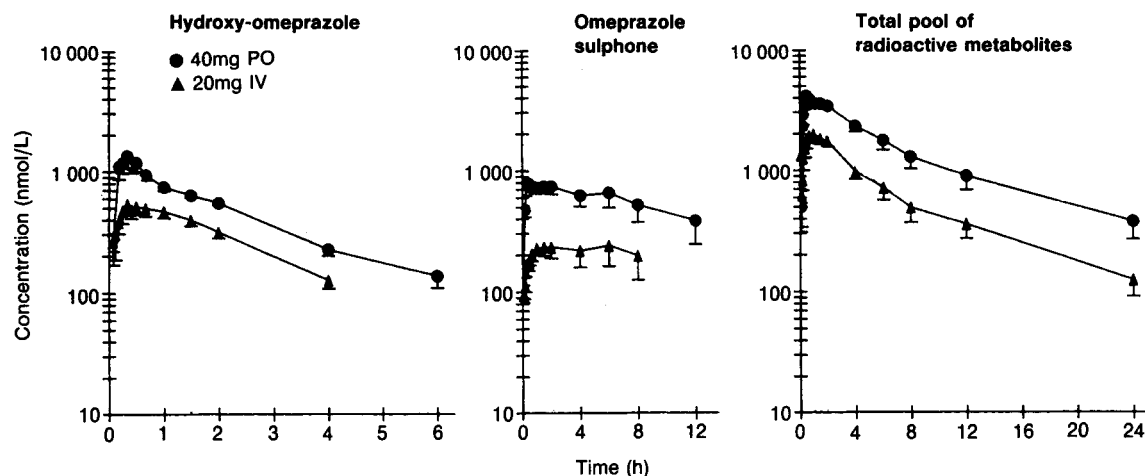


Fig. 4. Plasma concentration-time profiles (mean \pm SEM) of hydroxy-omeprazole, omeprazole sulphone and the total pool of radioactive metabolites after omeprazole 20mg intravenous or 40mg oral doses in 8 healthy elderly volunteers.

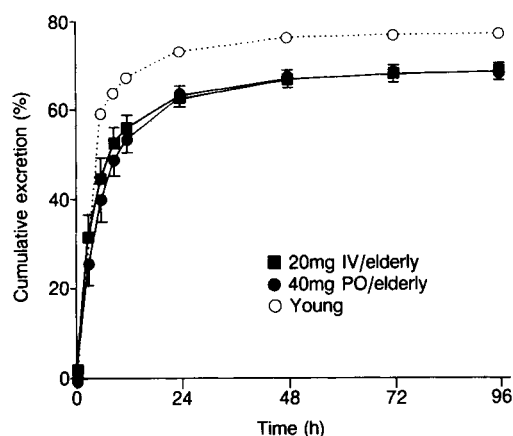


Fig. 5. Cumulative renal excretion of radioactivity, as a percentage (mean \pm SEM) of the administered dose, after administration of [14 C]omeprazole to 8 elderly healthy volunteers (20mg intravenously; 40mg orally) compared with mean values derived in a separate study of 8 healthy young volunteers (Regårdh et al. 1990).

radioactive doses was identical) the higher systemic availability displayed by the elderly is a result of reduced first-pass extraction, in this case probably primarily in the liver (Andersson et al. 1993). The increase in F in the elderly was associated with a decreased extraction ratio, from 44% in the young to 24% in the elderly, i.e. a change of 45%. The average reduction in omeprazole CL with age was 58%, which is most likely explained by a concomitant reduction in hepatic blood flow with increasing age. Since blood clearance (CL_B) equals $\dot{Q}_H \times E$, where \dot{Q}_H is liver blood flow, E is extraction ratio and CL_B is plasma clearance/0.6 (Regårdh et al. 1985), the mean values of CL_B and E yield a blood flow rate of 1.36 L/min in the young and 1.04 L/min in the old. Thus, the hepatic blood flow was approximately 25% lower in the elderly compared with that in young individuals. The combination of increased F and reduced CL resulted in an approximately 2-fold increase in C_{max} and AUC in the elderly volunteers compared with values of these parameters in young volunteers. Furthermore, the mean terminal $t_{1/2}$ was prolonged by about 50%. The individual values of AUC and $t_{1/2}$ for omeprazole suggest that among the elderly group,

2 or 3 volunteers might be slow metabolisers. However, this was not verified by mephenytoin testing. The decrease in volume of distribution might be explained by the decreased body water reported in the elderly.

The sulphone is not excreted by the kidneys. Therefore, the substantial increase in the AUC and terminal $t_{1/2}$ of this metabolite in the elderly, compared with the young, suggests that the rate of sequential metabolism of the sulphone is affected by age to at least the same extent as is the metabolism of omeprazole.

It is conceivable that the reduction in renal function with age should have some influence on the AUC and $t_{1/2}$ of hydroxy-omeprazole which is partly renally excreted. However, since the fraction of hydroxy-omeprazole undergoing further metabolism is unknown, the relative contributions of age-related reductions in renal and liver function to the observed 2-fold higher AUC and about 50% longer $t_{1/2}$ of hydroxy-omeprazole in the aged cannot be differentiated. In addition, it seems as if the amount of total radioactivity being renally excreted is somewhat lower in the elderly than in the young. This is probably compensated by increased capacity of alternative routes of elimination, preferably biliary secretion, as proposed in patients with impaired renal function (Naesdal et al. 1986).

A substantial overlap between young and elderly volunteers in several derived parameters and variables was observed. Thus, considering AUC as the most important factor for the inhibition of gastric acid secretion (Lind et al. 1983), we found that at least 7 elderly (50%) had an AUC value within the range considered normal for young individuals. A previous pharmacodynamic study in elderly patients with duodenal ulcers showed that a once-daily dose of at least omeprazole 20mg was needed to achieve significant inhibition of acid secretion in the majority of patients (Lind et al. 1991). Similar results have been obtained in young volunteers (Lind et al. 1986). Thus, despite the significant effect of age on the pharmacokinetics of omeprazole in the elderly, the results presented above, together with the fact that omeprazole has been extremely well tolerated in comprehensive clinical trials in-

cluding elderly patients, indicate that dosage reduction in the elderly is not needed.

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