Clin. Pharmacokinet. 23 (6): 469-476, 1992
0312-5963/92/0012-0469/$04.00/0

CPK1 241

# Pharmacokinetic Study of Omeprazole in Elderly Healthy Volunteers

*Sten Landahl, Tommy Andersson, Mayethel Larsson, Bodil Lernfeldt, Per Lundborg, Carl-Gunnar Regårdh, Eva Sixt* and *Inger Skånberg*
Department of Geriatric and Longterm Care Medicine, Clinic IV, Vasa Hospital, Göteborg, and Astra Hässle AB, Mölndal, Sweden

***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 ($t_{1/2}$ < 1h) 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 (≈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 71kg (range 58 to 88kg) 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 20mg and 1 with an oral dose of 40mg omeprazole. The first 8 volunteers received [$^{14}$C]-labelled omeprazole 20 $\mu$Ci 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 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 $\lambda_1$ and $\lambda_2$ 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 $\lambda_2$ 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 $\lambda_2$.

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 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

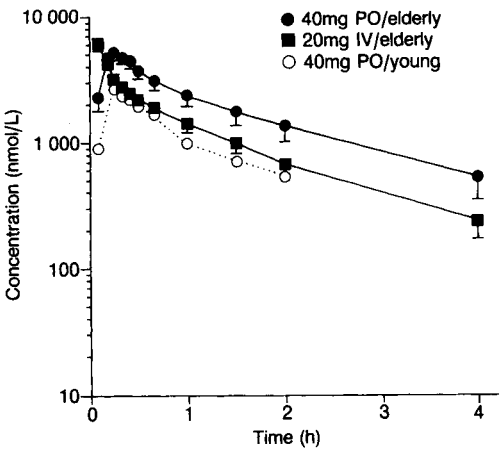


**Fig. 1.** Plasma concentration-time profiles (mean ± SEM) of omeprazole following administration of the drug to 14 healthy elderly volunteers (20mg intravenously; 40mg orally) compared with mean values in 18 healthy young volunteers (40mg orally) derived from 2 separate studies (Andersson et al. 1990a;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

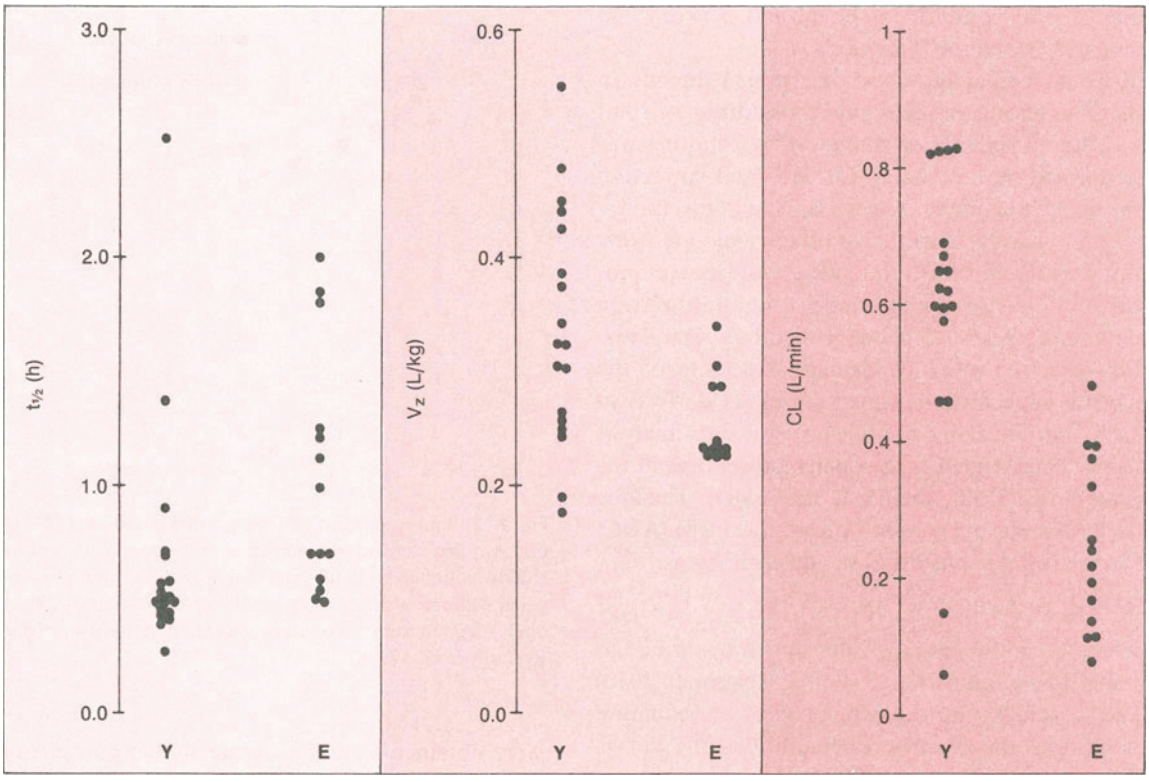


**Fig. 2.** Individual disposition characteristics of omeprazole 20mg following intravenous administration to 14 healthy elderly volunteers (E) and 18 healthy young volunteers (Y). $t_{½}$ = elimination half-life; $V_z$ = volume of distribution; CL = total plasma clearance (Andersson et al. 1990a; Regårdh 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 $t_{½}$ 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 μmol/L, $p < 0.02$) and mean AUC was more than doubled (8.76 *vs* 4.00 μmol/L • 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 $t_{½}$ 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 (≈1.5h) 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 (≈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 ≈4.5h, compared 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).

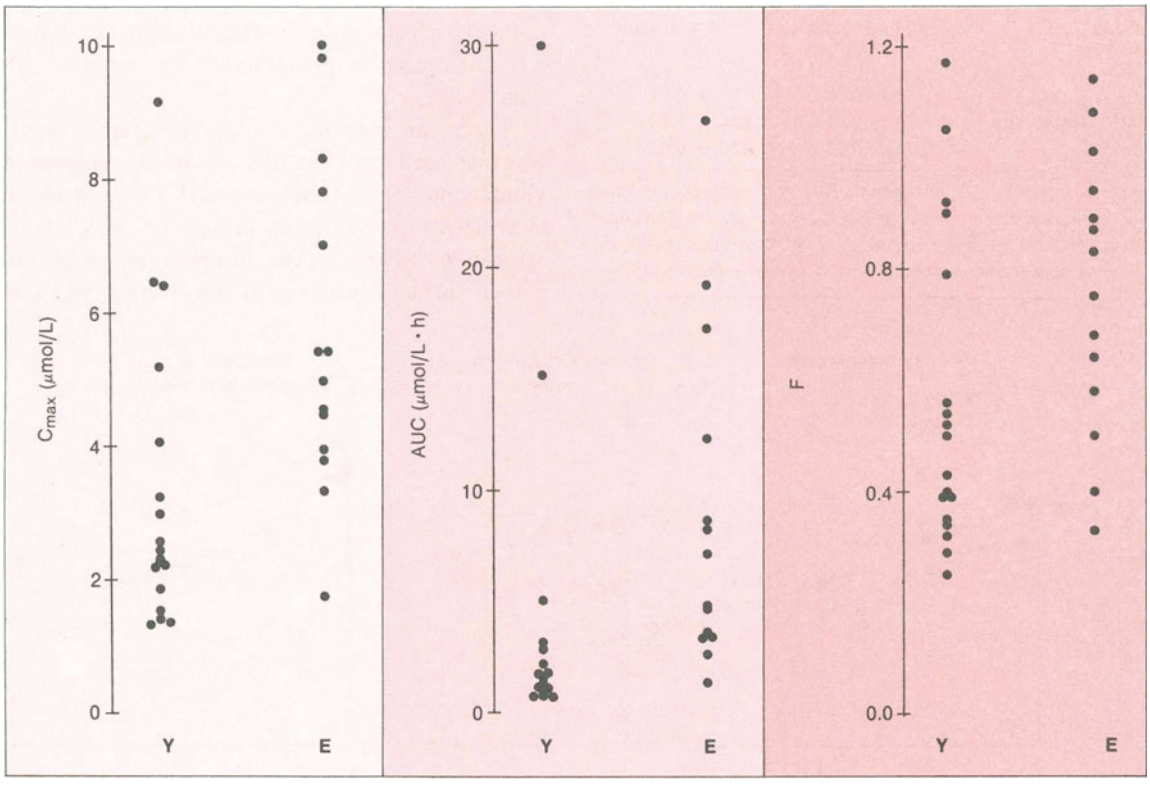


**Fig. 3.** Individual absorption and disposition characteristics of omeprazole following administration of oral omeprazole 40mg to 14 healthy elderly volunteers (E) and 18 healthy young volunteers (Y). $C_{max}$ = peak plasma concentration; AUC = area under the plasma concentration-time curve; F = bioavailability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

**Table I.** Mean (± 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** | | |
| $t_{½}$ (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** | | |
| $C_{max}$ (μmol/L) | 5.74 ± 0.66 | 3.28 ± 0.51 |
| AUC (μmol/L · h) | 8.76 ± 2.00 | 4.00 ± 1.72 |
| F | 0.76 ± 0.07 | 0.56 ± 0.07 |

*Abbreviations:* $t_{½}$ = 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.

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

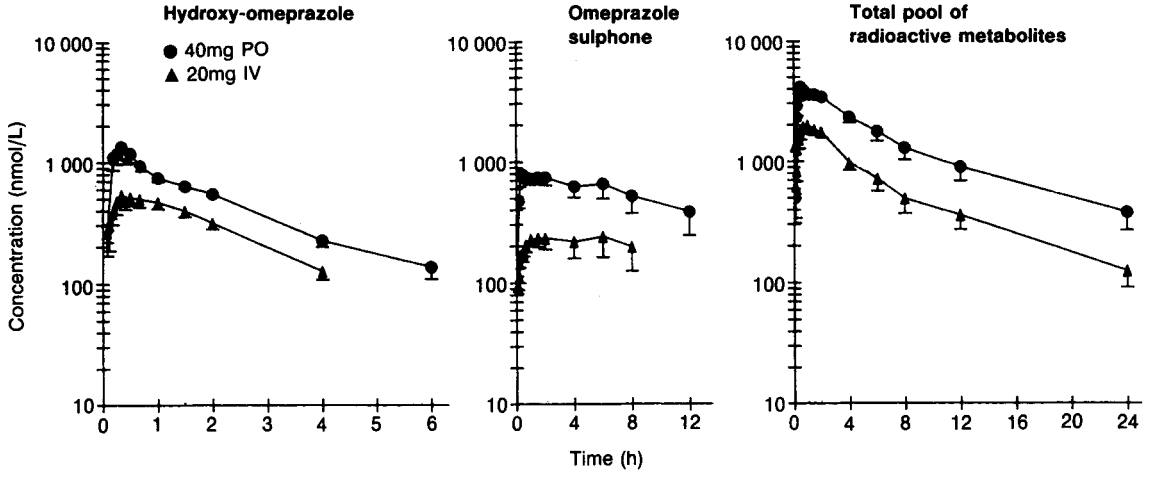


**Fig. 4.** Plasma concentration-time profiles (mean ± SEM) of hydroxy-omeprazole, omeprazole sulphone and the total pool of radioactive metabolites after omeprazole 20mg intravenous or 40mg oral doses in 8 healthy elderly volunteers.

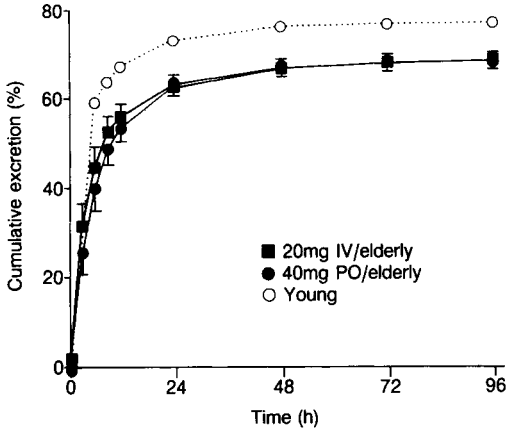


**Fig. 5.** Cumulative renal excretion of radioactivity, as a percentage (mean ± SEM) of the administered dose, after administration of [$^{14}$C]omeprazole to 8 elderly healthy volunteers (20mg intravenously; 40mg orally) compared with mean values derived in a separate study of 8 healthy young volunteers (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 $t_{½}$ was prolonged by about 50%. The individual values of AUC and $t_{½}$ 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 $t_{½}$ 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 $t_{½}$ 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 $t_{½}$ 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.

## *Acknowledgement*

We thank Inger Grundevik, Bioanalytical Chemistry, Astra Hässle AB, Mölndal, for assays of plasma samples.

## *References*

Andersson T, Cederberg C, Regårdh CG, Skånberg I. Pharmacokinetics of various single intravenous and oral doses of omeprazole. European Journal of Clinical Pharmacology 39: 195-197, 1990a

Andersson T, Regårdh CG, Dahl-Puustinen ML, Bertilsson L. Slow omeprazole metabolizers are also poor *S*-mephenytoin hydroxylators. Therapeutic Drug Monitoring 12: 415-416, 1990b

Andersson T, Olsson R, Regårdh CG, Skånberg I. Pharmacokinetics of [$^{14}$C]omeprazole in patients with liver cirrhosis. Clinical Pharmacokinetics, in press, 1993

Bardhan KD, Bianchi Porro G, Bose K, Daly M, Hinchliffe RFC, et al. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. Journal of Clinical Gastroenterology 8: 408-413, 1986

Brändström A, Lindberg P, Bergman NÅ, Alminger T, Ankner K, et al. Chemical reactions of omeprazole and omeprazole analogues. Acta Chemica Scandinavica 43: 536-611, 1989

Fellenius E, Berglindh T, Sachs G, Olbe L, Elander B, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking ($H^+$, $K^+$)ATPase. Nature 290: 159-161, 1981

Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. New England Journal of Medicine 306: 1081-1088, 1982

Grundevik I, Jerndal G, Balmér K, Persson BA. Fully automated gradient elution liquid chromatographic assay of omeprazole and 2 metabolites. Journal of Pharmacology and Biomedical Analysis 4: 389-398, 1986

Hetzel DJ, Dent J, Reed WD, Narielvala FM, Mackinnon M, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 95: 903-912, 1988

Klinkenberg-Knol EC, Jansen JMBJ, Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. Lancet 1: 349-351, 1987

Lamy P. Modifying drug dosage in elderly patients. In Covington & Walker (Eds) Current Geriatric Therapy, pp. 35-72, Saunders Company, Philadelphia, 1984

Larsson M, Jagenburg R, Landahl S. Renal function in an elderly population. A study of S-creatinine, $^{51}$Cr-EDTA clearance, endogenous creatinine clearance and maximal tubular water reabsorption. Scandinavian Journal of Clinical and Laboratory Investigation 46: 593-598, 1986

Lind T, Andersson T, Skånberg I, Olbe L. Biliary excretion of intravenous [$^{14}$C]omeprazole in humans. Clinical Pharmacology and Therapeutics 42: 504-508, 1987

Lind T, Cederberg C, Axelson M, Olbe L. Long-term acid inhibitory effect of different daily doses of omeprazole 24 hours after dosing. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 137-138, 1986

Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin stimulated acid secretion in man. Gut 24: 270- 276, 1983

Lind T, Cederberg C, Olausson M, Olbe L. Omeprazole in elderly duodenal ulcer patients: relationship between reduction in gastric acid secretion and fasting plasma gastrin. European Journal of Clinical Pharmacology 40: 557- 560, 1991

Loo JCK, Riegelman S. Assessments of pharmacokinetic constants from post infusion blood curve obtained after iv infusion. Journal of Pharmaceutical Sciences 59: 53-57, 1970

Lorentzon P, Eklundh B, Brändström A, Wallmark B. The mechanism for inhibition of gastric ($H^+$+$K^+$)-ATPase by omeprazole. Biochimica et Biophysica Acta 817: 25-32, 1985

Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, et al. Pharmacokinetics of [$^{14}$C]omeprazole in patients with impaired renal function. Clinical Pharmacology and Therapeutics 40: 344-351, 1986

Regårdh CG, Andersson T, Lagerström PO, Lundborg P, Skånberg I. The pharmacokinetics of omeprazole in humans – a study of single intravenous and oral doses. Therapeutic Drug Monitoring 12: 163-172, 1990

Regårdh CG, Gabrielsson M, Hoffman KJ, Löfberg I, Skånberg I. Pharmacokinetics and metabolism of omeprazole in animals and man – an overview. Scandinavian Journal of Gastroenterology 20 (Suppl. 108): 79-94, 1985)

Sheiner LB, Beal SL. Pharmacokinetic parameter estimates from several least squares procedures: superiority of extended least squares. Journal of Pharmacokinetics and Biopharmaceutics 13: 185-201, 1985

Schmucker DL, Woodhouse KW, Wang RK, Wynne H, James OF, et al. Effects of age and gender on in vitro properties of human liver microsomal monooxygenases. Clinical Pharmacology and Therapeutics 48: 365-374, 1990

Vestal RE. Drug use in the elderly: a review of problems and special considerations. Drugs 16: 358-382, 1978

Vestal RE. Aging and determinants of hepatic drug clearance. Hepatology 9: 331-334, 1989

Walan A, Bader JP, Classen M, Lamers CBHW, Piper DW, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. New England Journal of Medicine 320: 69-75, 1989

Wallmark B, Lorentzon P, Larsson H. The mechanism of action of omeprazole – a survey of its inhibitory actions in vitro. Scandinavian Journal of Gastroenterology 20 (Suppl. 108): 37-51, 1985

Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 9: 297-301, 1989

Wynne HA, Goudevenos J, Rawlins MD, James OFW, Adams PC, et al. Hepatic drug clearance: the effect of age using indocyanine green as a model compound. British Journal of Clinical Pharmacology 30:634-637, 1990

Correspondence and reprints: *Tommy Andersson*, Clinical Pharmacology, Astra Hässle AB, S-431 83 Mölndal, Sweden.