Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects

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Plasma concentrations of lansoprazole and of its sulphone, sulphide and 5-hydroxylated metabolites were determined after oral administration of a single 30 mg dose and after 7 days of treatment with a daily 30 mg dose in 12 elderly subjects (mean age 83 years). Results after a single dose were compared with those from a historical control group of 18 young subjects (mean age 23 years). Mean values of AUC after single dose were 2668 ng ml⁻¹ h in the young subjects and 5216 ng ml⁻¹ h in the elderly ($P < 0.05$). Mean $t_{1/2}$ values in young and elderly subjects were 1.4 h and 2.9 h, respectively ($P < 0.001$). Plasma concentrations of the metabolites were similar in both groups. However, the hydroxylated metabolite of the sulphone was detected only in elderly subjects. Steady state plasma concentrations of lansoprazole were reached after 3 days of dosing with lansoprazole. The accumulation ratio was 1.31 in the elderly subjects.

Keywords lansoprazole pharmacokinetics elderly subjects multiple dose

Introduction

Lansoprazole, a substituted benzimidazole, is a proton pump inhibitor acting on the membrane H⁺/K⁺ ATPase of the gastric parietal cell, [1–3]. It is acid-labile and is formulated as enteric-coated granules in a capsule. In man, lansoprazole is extensively metabolized after oral administration, urinary recovery of unchanged drug being less than 1% of the dose. Sulphone and sulphide metabolites as well as 5-hydroxylated metabolites of lansoprazole have been detected in the blood. The hydroxylated metabolite of the sulphone has been found only after a dose of 60 mg lansoprazole [4, 5]. The aim of this study was to evaluate the influence of age on the pharmacokinetics of lansoprazole.

Methods

Study design

The study was approved by the Ethics Review Board of the C.H.U. Paris-Quest. Twelve elderly subjects (1 man and 11 women) with a mean age of 83 ± 3 years (range: 68–92 years) and a mean weight of 58 ± 3 kg (range: 48–85 kg), were studied. All had clinical and laboratory examinations including ECG and measurement of creatinine clearance. None of the subjects had patho-

logical renal or hepatic impairment; four had a history of hypertension (subjects 2, 5, 6, 8). Medications, with the exception of antacids, which could not be stopped during the study, were continued, but were administered 3 h after dosing with lansoprazole on the 1st and 7th days of treatment. All subjects signed a consent form. Each subject was dosed for 7 consecutive days with one 30 mg capsule lansoprazole taken with 150 ml water in the morning on an empty stomach, 30 min before breakfast on the 2nd to the 6th day of the study and 2 h before on days 1 and 7. The subjects were admitted to hospital throughout the study period.

Blood samples were drawn before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12 and 24 h after the first and final administration of lansoprazole. A blood sample was also drawn before administration on the 5th and 6th days of the study. Blood was taken into heparinized tubes and the plasma separated immediately and stored at -20°C until analysed. A historical control group of young subjects consisted of 18 healthy volunteers (nine men and nine women) with a mean age of 23 years (range: 20–32 years) and a mean weight of 61 kg (range: 48–80), given a single oral dose of 30 mg of lansoprazole when fasting. Six of them had participated as controls for a pharmacokinetic study in hepatic failure [6] and the other 12 in a study of the influence of food [4].

Assay methods

Plasma concentrations of lansoprazole and of its sulphone, sulphide and hydroxylated metabolites as well as of the hydroxylated metabolite of the sulphone were assayed by h.p.l.c. as described by Delhotal *et al.* [7]. The limit of quantification was 2 ng ml⁻¹ for lansoprazole and 3 ng ml⁻¹ for the metabolites. Between-run coefficients of variation were < 10% between 8 to 1500 ng ml⁻¹.

Pharmacokinetic analysis

The terminal elimination rate constant (λ_z) was determined by linear regression of the last 4–6 plasma lansoprazole concentrations (log values). The single dose AUC values were estimated by the linear trapezoidal method with extrapolation to infinity by addition of the ratio of the final quantifiable plasma lansoprazole concentration divided by the terminal elimination rate constant. The half-life was calculated for each subject after the first dose and on the 7th day after the final dose. Lansoprazole C_{max} and t_{max} values were noted directly from the data.

The average steady state plasma drug concentration (C_{av}) was calculated from $AUC(\tau)/\tau$ where $AUC(\tau)$ is the AUC in a dosing interval at steady state and τ is the dosing interval (24 h).

The accumulation ratio (Rac) was calculated from $AUC(\tau)/AUC(24)$ where $AUC(24)$ is the AUC calculated from 0 to 24 h after dosing.

Molar metabolite/lansoprazole AUC(24) ratios (Rm) were calculated.

Statistical analysis

Results were expressed as mean and standard deviation. Differences in pharmacokinetic data were analysed for statistical difference by paired and unpaired *t*-test. Values of t_{max} were compared using the non-parametric Kruskal-Wallis test. Statistical significance was assumed when $P < 0.05$.

Results

Single dose

Mean plasma concentrations of lansoprazole and its metabolites following administration of the first dose

Figure 1 Mean plasma lansoprazole (□) and metabolite concentrations (sulphide (○) sulphone (●) hydroxylated lansoprazole (△) and hydroxylated sulphone (▲)) after oral administration of a single 30 mg oral dose of lansoprazole to elderly subjects ($n = 12$).

in the elderly subjects are shown in Figure 1. The hydroxylated metabolite of the sulphone was detected in the elderly subjects but was not quantifiable in young subjects. The mean elimination half-life of lansoprazole in the elderly subjects (2.9 h) was significantly longer than in young subjects (1.4 h, $P < 0.001$, 95% CI -2.16–0.70) and the mean AUC value (5216 ng ml⁻¹ h) was significantly greater (Table 1) than that observed in young subjects (2668 ng ml⁻¹ h, $P < 0.005$, 95% CI -4662–434). Plasma concentrations of the detectable metabolites in young subjects were similar to those in the elderly. Rm values in young and elderly subjects were, respectively, 0.082 ± 0.137 vs 0.089 ± 0.106 for sulphone, 0.018 ± 0.032 vs 0.023 ± 0.026 for sulphide and 0.065 ± 0.057 vs 0.078 ± 0.042 for hydroxylated lansoprazole metabolite (NS).

Multiple dose study

Administration of 30 mg lansoprazole once a day to the elderly subjects resulted in mean trough plasma lansoprazole concentrations of 10.1, 13.9 and 10.7 ng ml⁻¹ on days 5, 6 and 7 of treatment, respectively. Steady state was reached on day 5. The mean terminal elimination half-life of lansoprazole (2.7 h) did not differ

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) of lansoprazole in elderly ($n = 12$) subjects after the first and the last 30 mg oral daily dose

Parameters	First dose	Last dose	95% confidence interval of difference
t_{max} (h)*	1.5 (1–4 h)	1.5 (0.5–2.5)	-0.26, 0.82
C_{max} (ng ml ⁻¹)	1148 $\pm$ 536	1284 $\pm$ 541	-539, 267
AUC (ng ml ⁻¹ h)	5216 $\pm$ 3855	5701 $\pm$ 4128**	-2201, 1231
$t_{1/2}$ (h)	2.9 $\pm$ 1.2	2.7 $\pm$ 1.2	-0.40, 0.21
C_{av} (ng ml ⁻¹)		238 $\pm$ 172	
Rac		1.31 $\pm$ 0.52	
$t_{1/2}$ sulphone (h)	2.4 $\pm$ 2.9	2.5 $\pm$ 2.9	-0.51, 0.39
$t_{1/2}$ hydroxylated lansoprazole (h)	3.8 $\pm$ 3.2	3.2 $\pm$ 1.3	-1.13, 2.19
Rm sulphone	0.089 $\pm$ 0.106	0.094 $\pm$ 0.124	-0.021, 0.017
Rm hydroxylated lansoprazole	0.078 $\pm$ 0.048	0.078 $\pm$ 0.042	-0.014, 0.024

* median (range).

**AUC (τ).

significantly from that after the first dose. The mean accumulation ratio (Rac) was 1.31 (Table 1).

Values of the pharmacokinetic parameters of metabolites following the first and final dose in elderly subjects did not differ significantly (Table 1).

Discussion

Differences in body weight between the elderly and young subjects were not significant, suggesting that body weight was not responsible for the age-linked differences in the pharmacokinetics of lansoprazole. The elderly subjects were all female except one whereas the control group of young subjects included nine men and nine women. However, pharmacokinetic parameters were unrelated to the sex of the young subjects.

The decreased clearance seen in elderly subjects may

have resulted from a decrease in other metabolic pathways in relation to age, as possibly reflected by the presence in elderly subjects of the hydroxylated metabolite of the sulphone, a metabolite which has never been found in healthy young subjects following administration of a dose of 30 mg, but only after administration of doses of 60 mg. In common with other hydroxylated metabolites, this metabolite is eliminated by the liver or kidney after conjugation. In hepatic failure, a large decrease in the clearance of lansoprazole, accompanied by an increase in the sulphone Rm and a decrease in the hydroxylated lansoprazole metabolite Rm, was observed [6].

The plasma accumulation ratio of lansoprazole was 1.32 in the elderly subjects, a value similar to that (1.16) observed in young subjects (Tolman *et al.*, unpublished data).

We conclude that, although the clearance of lansoprazole is lower in elderly subjects, its accumulation on daily dosing is similar to that in young subjects.

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