Br J Clin Pharmacol 1996; **42**: 249–252

Lack of pharmacokinetic interaction of pantoprazole with diazepam in man

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Pantoprazole, a substituted benzimidazole, is a potent and well tolerated inhibitor of the gastric H^+,K^+-ATPase with a low potential to inhibit cytochrome P450. In this randomized, placebo-controlled two-period crossover study, 12 healthy volunteers received placebo (reference) and 240 mg of pantoprazole (test) i.v. within 2 min once daily for 7 days each. On day 4 of either period, a 1 min bolus of diazepam (0.1 mg kg^{-1} body weight) was additionally injected. Pantoprazole was well tolerated and did not cause clinically relevant changes in heart rate, blood pressure, ECG and routine clinical laboratory parameters. There was no effect on diazepam clearance (0.021 l h^{-1} kg^{-1} for test and reference) and elimination half-life (36.8 h for test, 40.4 h for reference). Diazepam metabolism to desmethyldiazepam was not affected by pantoprazole. In conclusion, pantoprazole and diazepam may be administered concomitantly without dose adjustment even when high doses of pantoprazole are required.

Keywords pantoprazole proton pump inhibitor diazepam interaction

Introduction

The substituted benzimidazole pantoprazole is a selective inhibitor of the gastric H^+,K^+-ATPase with linear pharmacokinetics and a low potential to interact with the cytochrome P450 system in man. It has been shown to be a potent inhibitor of intragastric acidity. With 40 mg p.o., high healing rates and rapid pain relief have been established in patients suffering from acid related diseases. For a review of its pharmacodynamic and pharmacokinetic properties as well as its therapeutic efficacy see [1].

As omeprazole showed an apparently dose dependent interaction with diazepam in man [2, 3], the primary aim of the present study in healthy volunteers was to investigate the potential effect of pantoprazole on the disposition kinetics of diazepam. Additionally, the possible interaction of diazepam with pantoprazole was studied.

Methods

Ethics

The study was performed according to the revised Declaration of Helsinki. The study protocol was approved by the Freiburg Ethics Committee, Freiburg, Germany. Each volunteer gave his written consent after comprehensive verbal and written information on aims and possible risks of the study.

Subjects

Twelve volunteers (5 M, 7 F), assessed as healthy based on medical history, physical examination and clinical laboratory tests, were admitted to the study. Their age ranged from 20 to 29 years (median: 26 years) and their body weight from 50 to 78 kg (median: 65 kg).

Study design

In this randomized, single-blind, placebo-controlled two-period crossover study, each volunteer underwent the following treatment periods of 7 days each during which either placebo or 240 mg pantoprazole were given once daily as 2 min i.v. infusions. On day 4 of both periods, a 1 min i.v. bolus of diazepam (0.1 mg kg^{-1} body weight) was injected 1 h after placebo (reference) or pantoprazole (test), respectively. The serum concen-

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trations of diazepam and desmethyldiazepam were monitored up to 96 h post dose. For pantoprazole, serum concentrations were measured on days 3 and 4 of the test period up to 24 h. Both treatment periods were separated by a washout period of at least three weeks.

Pharmacokinetics

Diazepam and desmethyldiazepam serum concentrations were determined by a gas chromatographic method with electron capture detection (ECD) which was modified using prazepam as internal standard and a 100% dimethylpolysiloxan (0V-1; film thickness 0.3 μm) capillary column [4]. Coefficients of variation for diazepam and desmethyldiazepam at 0.03 mg l^{-1} were 7.7% and 15.7% (within-day), and 13.0% and 11.2% (day-to-day), respectively. LOQ was 0.005 mg l^{-1} for both compounds.

Serum concentrations of pantoprazole were determined by reversed phase h.p.l.c. using a gradient technique and u.v.-detection [5]; concentrations were expressed as pantoprazole-Na. The coefficient of variation at 0.5 mg l^{-1} was 2.2% (day-to-day), the limit of quantitation being 0.03 mg l^{-1}.

The following pharmacokinetic characteristics were determined for both diazepam and pantoprazole-Na: area under the concentration/time curve (AUC), terminal elimination half-life ($t_{\frac{1}{2}} = \ln 2/\lambda_z$), clearance (CL = Dose/AUC) and volume of distribution ($V_d = CL/\lambda_z$) with λ_z = estimate of the terminal rate constant.

Since the drug was administered intravenously, the AUC, which is inversely related to the clearance, was the appropriate primary characteristic for confirmative equivalence analysis; it was calculated by the trapezoidal formula and standard extrapolation to infinity.

Statistical methods

The primary aim of this randomized crossover study was the investigation of the potential influence of pantoprazole on the disposition kinetics of diazepam (test = diazepam and pantoprazole, reference = diazepam and placebo).

Of secondary interest was the potential influence of diazepam on the disposition kinetics of pantoprazole. This was investigated by a comparison of pantoprazole profiles on day 3 (without diazepam) with those on day 4 (with diazepam) of the test period.

Assuming a multiplicative model, i.e. a logarithmic transformation, equivalence between test and reference (lack-of-interaction) was concluded if the shortest 90%–confidence interval for the AUC- and hence CL-ratio test/reference of the population medians of diazepam was within the equivalence range of 0.8–1.25 (confirmative criterion) usually accepted for bioequivalence. This procedure ensures that the patient risk of erroneously accepting equivalence is at most 5% [6]. The secondary characteristics volume of distribution and half-life were analysed analogously with an explorative intention.

The sample-size consideration referred to the primary characteristic AUC. At a patient risk of 5%, the chosen sample size of 12 subjects was sufficient to achieve a power of 80% if test and reference had differed by 5% and if the within subject coefficient of variation had been 15% [7].

Results

Diazepam and desmethyldiazepam serum concentrations

The mean curves of both diazepam and desmethyldiazepam for either period (Figure 1) are virtually identical.

Equivalence, that is lack-of-interaction, was formally concluded since the 90%-confidence limits for the AUC-ratio test/reference of diazepam (confirmative criterion) were (0.87, 1.13) and thus within the equivalence range of (0.80, 1.25). The point estimate was 0.99, indicating no influence of repeated high intravenous doses of pantoprazole on the AUC of diazepam (Table 1). The corresponding results for the clearance were 1.01 (0.88, 1.15).

For the secondary characteristics volume of distribution and half-life the respective point estimates and 90%-confidence limits were 0.92 (0.78, 1.08) and 0.91 (0.78, 1.07) (Table 1). The lower limits of the confidence intervals are only negligibly below 0.8, and, hence, a relevant influence may be excluded. This is particularly so, since the sample size was calculated with regard to the primary criterion AUC and not for the secondary ones.

Pantoprazole serum concentrations

The mean concentration-time curves of pantoprazole-Na without (day 3) and with diazepam (day 4) are virtually identical. Point estimate (90%-confidence limits) of the AUC-ratio test/reference were 0.96 (0.82, 1.13). Hence, equivalence (that is no interaction) was also evident for pantoprazole. Further explorative analysis revealed point estimates and 90%-confidence limits well within the equivalence range of (0.8, 1.25) for all secondary characteristics (Table 1).

Safety and tolerability

Pantoprazole was well tolerated. There were no clinically relevant changes in heart rate, ECG and routine clinical laboratory parameters. A decrease in mean systolic blood pressure was observed 5 min after diazepam injection during both placebo and pantoprazole coadministration, however, not with pantoprazole alone. Approximately 2 h later, mean blood pressure was within the range of the respective pretreatment.

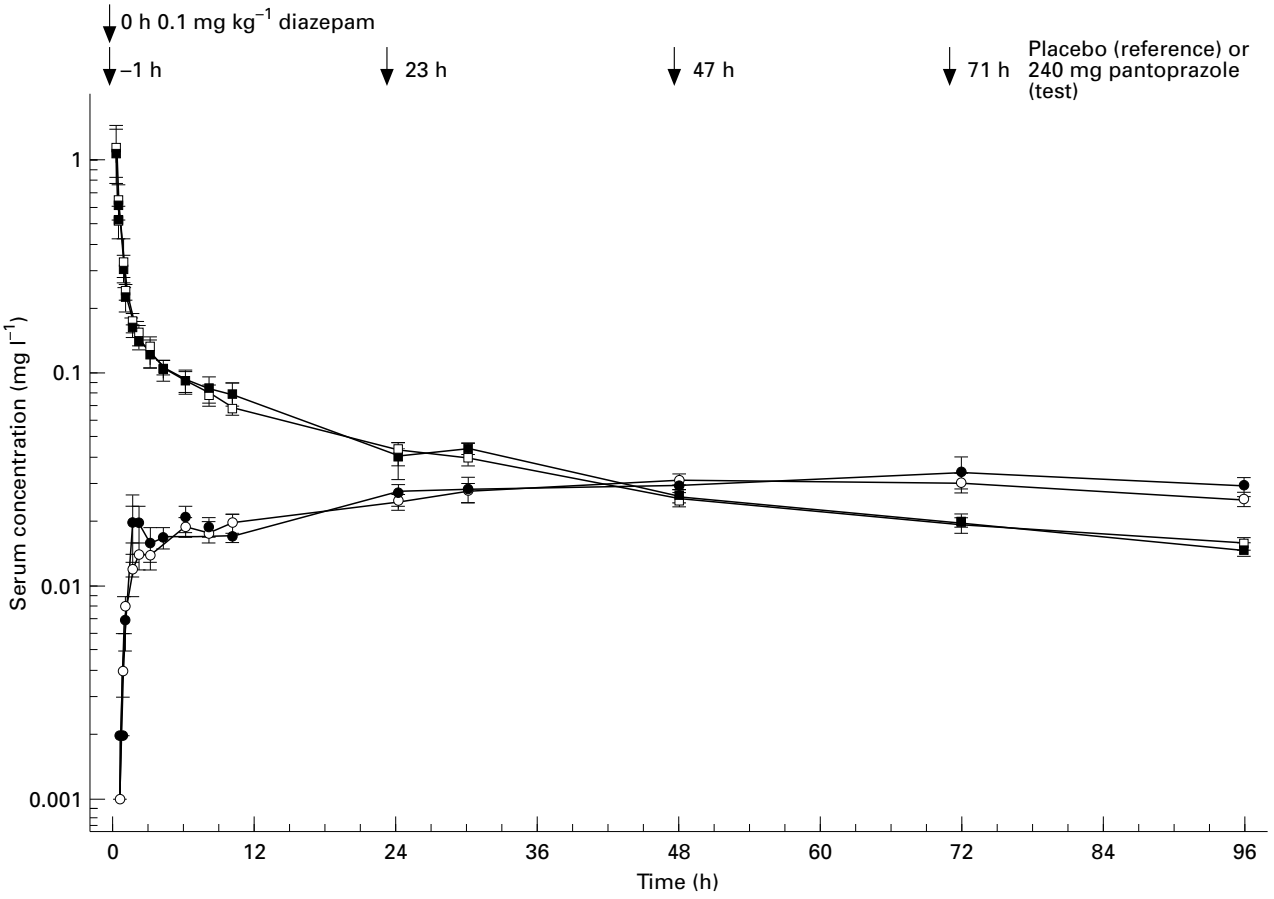

Figure 1 Mean (s.e.mean) diazepam and desmethyldiazepam serum concentrations following a single 1 min i.v. bolus of 0.1 mg kg^{-1} at 0 h on day 4 of the reference (□ = diazepam, ○ = desmethyldiazepam) and test period (■ = diazepam, ● = desmethyldiazepam), respectively. The 2 min injections of placebo or 240 mg pantoprazole are indicated by arrows, the preceding injections on days 1 to 3 are not shown.

Table 1 Summary of equivalence assessment
AUC is the confirmative criterion for concluding equivalence of diazepam with and without pantoprazole (primary aim). In the case of pantoprazole with and without diazepam (secondary aim), the AUC over one dosing interval, AUC(0, 24 h), has to be used. CL, V_d and $t_{\frac{1}{2}}$ were evaluated exploratively

	Reference without pantoprazole	*Test with pantoprazole*	*Equivalence ratio Test/Reference*	
Diazepam	*Geometric mean (68%-range), n = 12*		*Point estimate*	*90%-confidence interval*
AUC (mg l^{-1} h)	4.80 (3.59, 6.40)	4.75 (3.43, 6.58)	0.99	0.87–1.13
CL (l h^{-1} kg^{-1})	0.021 (0.016, 0.028)	0.021 (0.015, 0.029)	1.01	0.88–1.15
V_d (l kg^{-1})	1.22 (0.83, 1.78)	1.12 (0.78, 1.60)	0.92	0.78–1.08
$t_{\frac{1}{2}}$ (h)	40.4 (31.5, 51.8)	36.8 (31.4, 43.2)	0.91	0.78–1.07
	Reference without diazepam	*Test with diazepam*	*Equivalence ratio Test/Reference*	
Pantoprazole	*Geometric mean (68%-range), n = 12*		*Point estimate*	*90%-confidence interval*
AUC(0,24 h) (mg l^{-1} h)	46.63 (36.32, 59.88)	44.94 (33.92, 59.53)	0.96	0.82–1.13
CL (l h^{-1} kg^{-1})	0.081 (0.068, 0.097)	0.084 (0.068, 0.105)	1.04	0.89–1.22
V_d (l kg^{-1})	0.114 (0.123, 0.167)	0.145 (0.107, 0.195)	1.01	0.82–1.24
$t_{\frac{1}{2}}$ (h)	1.2 (1.1, 1.4)	1.2 (1.0, 1.5)	0.97	0.90–1.05

Discussion

The results demonstrate that repeated administration of high doses of pantoprazole does not affect the clearance of diazepam. Furthermore, diazepam administered as a single i.v. dose does not interact with pantoprazole. In the present study, pantoprazole was given i.v. However, due to the high dose of 240 mg (and thereby high

systemic exposure) and with regard to the low first pass-effect of pantoprazole of only 23% [8], lack of interaction may also be concluded for oral administration of pantoprazole.

Further explorative analysis of the diazepam disposition kinetics, with and without pantoprazole, showed no relevant changes for terminal half-life and volume of distribution. Consistent with the unchanged clearance of diazepam, the serum concentration-time profiles of its major metabolite, desmethyldiazepam, were comparable during test and reference. Thus, the rate of metabolism of diazepam to desmethyldiazepam is not affected by pantoprazole.

In contrast, Gugler & Jensen [2] reported a 130% prolongation of the elimination half-life and a concomitant decrease by 54% of the clearance of diazepam after repeated oral administration of 40 mg omeprazole over 6 days. The respective values obtained with 20 mg omeprazole were 36% and 27%, demonstrating an apparently dose-dependent interaction. This effect was only present in omeprazole extensive metabolizers who, however, represent the majority (approximately 95%) of the Caucasian population [9]. The clinical relevance of the above mentioned results remains to be established. The results of the present diazepam interaction study with pantoprazole and published data on lansoprazole [10] show that the interaction with cytochrome P450 isoenzymes, in the case of diazepam CYP2C19, is not a general property of the class of proton pump inhibitors, but depends on the respective substituents and route of metabolism.

In view of the linear pharmacokinetics of pantoprazole and the comparison of pantoprazole serum concentrations on day 3 (without diazepam) with those on day 4 (with diazepam), an influence of diazepam on pantoprazole may also be excluded.

In conclusion, repeated intravenous doses of 240 mg pantoprazole were well tolerated and did not cause any clinically relevant changes in cardiovascular or routine clinical laboratory tests. Diazepam and pantoprazole did not interact with each other. Thus, pantoprazole and diazepam may be administered concomitantly without dose adjustment not only in treatment of peptic ulcer disease with the recommended dose of 40 mg, but also in patients for whom high doses of pantoprazole might be appropriate (e.g. Zollinger Ellison Syndrome).

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(*Received 19 July 1995, accepted 12 February 1996*)