Effect of multiple doses of losartan on the pharmacokinetics of single doses of digoxin in healthy volunteers

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- 1 Losartan (DuP 753, MK-954) is a novel, potent and highly selective AT₁ angiotensin II receptor antagonist. The effect of multiple oral doses of losartan on digoxin pharmacokinetics was evaluated in healthy male subjects.
- 2 In a double-blind and randomized fashion, subjects received 50 mg losartan or placebo once daily for 15 days in each period. At least 7 days elapsed between the two treatment periods. On days 4 and 11 of each period, subjects also received a single 0.5 mg dose of digoxin intravenously and orally respectively.
- 3 Eleven of 13 subjects completed the study. Side effects were mild and transient (12 out of 13 subjects reported at least one adverse experience). During the study, no laboratory abnormalities were noted.
- 4 Multiple oral doses of losartan (50 mg daily) did not affect the pharmacokinetic parameters of 0.5 mg of digoxin i.v. AUC(0,48h) of immunoreactive digoxin during losartan 28.8 ± 2.9 vs 28.5 ± 3.9 ng ml⁻¹ h during placebo; not significant, and 96 h urinary excretion [% dose] during losartan 54.0 ± 7.2 vs $51.9 \pm 6.5\%$ during placebo; not significant). Geometric mean ratios (90% confidence interval) for AUC and urinary excretion were respectively, 1.03 (0.98, 1.08) and 1.09 (0.98, 1.21).
- 5 Multiple oral doses of losartan did not affect the pharmacokinetic parameters of oral digoxin AUC(0,48 h) during losartan 23.6 ± 3.7 ng ml⁻¹ h vs 22.4 ± 2.6 ng ml⁻¹ h during placebo; not significant, C_{max} 3.5 ± 0.7 ng ml⁻¹ with vs 3.1 ± 0.5 ng ml⁻¹ without losartan; not significant and t_{max} 0.6 ± 0.2 h with vs 0.9 ± 0.7 h without losartan; not significant, and 96 h urinary excretion [% dose] during losartan 51.2 ± 6.3 vs $46.3 \pm 2.4\%$ during placebo; not significant). Geometric mean ratios (90% confidence interval) for AUC and urinary excretion were respectively, 1.06 (0.98, 1.14) and 1.12 (0.97, 1.28).
- 6 We conclude that multiple oral doses of losartan (50 mg daily) do not alter the pharmacokinetics of immunoreactive digoxin, following either intravenous or oral digoxin. Furthermore, the co-administration of digoxin with losartan is well tolerated by healthy male volunteers.

Keywords losartan DuP 753 MK-954 AT₁ angiotensin II receptors digoxin pharmacokinetics

Introduction

Losartan (DuP 753, MK-954) is a highly selective AT₁ angiotensin II receptor antagonist which has been

shown to be effective in the treatment of hypertension and haemodynamically active in patients with congestive heart failure [1, 2]. In these groups of patients, multiple drug therapy is frequent. Digoxin is likely to be

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co-administered with losartan in patients with congestive heart failure and in hypertensive patients with atrial fibrillation. Since the therapeutic index of digoxin is narrow, it is important to determine whether losartan administration alters plasma concentrations of immunoreactive digoxin in a fashion similar to other drugs (e.g. quinidine, amiodarone and verapamil) [3–7].

To allow the concomitant use of losartan and digoxin, the co-administration of these two drugs should be safe and the presence or absence of a clinically relevant pharmacokinetic interaction between these two drugs should be defined. Therefore, the objective of this study was to determine whether losartan treatment (50 mg once daily) affects the pharmacokinetics of intravenous and oral digoxin. The 50 mg dose of losartan was chosen based on its safety in subjects in several multiple dose studies [8] and the efficacy of the 50 mg dose in patients with hypertension [9]. *A priori*, we postulated that losartan would not increase the plasma AUC of digoxin immunoreactivity by more than 30%.

Methods

Thirteen young, healthy male volunteers (19–32 years old, mean weight 74 kg) participated in the study. All were non-smokers for at least 3 months. Any medication and alcohol were withheld during the study. Subjects had to be in good health on the basis of their history, physical examination and routine lab examination. Recruitment of healthy individuals preceded the start of the study by 2 weeks. The study was performed according to the provisions of the Declaration of Helsinki. Written informed consent was obtained from each volunteer and the study was approved by the local hospital ethics committee.

Study design

This was a double-blind, randomized, two-period cross-over study in which the subjects received 50 mg losartan or placebo daily for 15 days in each period. For each subject, the order of treatment (placebo or losartan) was determined by a random allocation schedule. Both treatment periods were separated by at least 7 days of washout. On days 4 and 11 of each period, subjects also received single intravenous (Lanoxin, Wellcome) and oral (Lanoxin Elixir, Wellcome) doses of digoxin. The digoxin dose by either route was 0.5 mg. The order of digoxin route was the same in each period: the i.v. dose on day 4 and the oral dose on day 11. The complete study design is outlined in Figure 1. The 15-day treatment period with losartan is supported by available data on losartan which shows an approximate 2 h half life for losartan, a 6–9 h half-life for its active metabolite and once-a-day efficacy in the treatment of hypertension [Data on file, and 8].

On days 2, 3, 5 to 10 and 12 to 15 of both study periods, subjects reported to the Clinical Research Unit (CRU) after having fasted from midnight, for measure-

ment of vital signs and to receive study medication (losartan or placebo) between 07.00 and 09.00 h, i.e. within 60 min of the digoxin dosing time planned on day 4 and day 11. No food was allowed until 1 h postdose. On day 1, subjects remained in the CRU for observation until 8 h postdose and vital signs (blood pressure and heart rate) were frequently measured. A 12-lead ECG was taken predose, 30 min, 4, 8 and 24 h postdose. A blood sample (5 ml) was taken 3 h postdose to test the possible interference of losartan and its active metabolite, E-3174, with the digoxin radioimmunoassay. A pooled 0–6 h urine collection from which a 20 ml aliquot was frozen, was also performed for a similar purpose.

On day 4, 30 min after losartan or placebo intake, 0.5 mg digoxin was administered intravenously over 10 min. Vital signs were frequently recorded during the day and ECGs were taken predose, 30 min, 4, 8 and 24 h after the administration of the digoxin dose. Serum samples for digoxin assays were obtained prior to and at regular time intervals (16 samples over 96 h) after dosing according to a fixed blood collection schedule until 96 h post digoxin administration. Urine for digoxin assays was collected predose, 0–6 h, 6–12 h, 12–24 h, 24–36 h, 36–48 h, 48–72 h and 72–96 h post digoxin administration. Trough losartan measurements were taken prior to dosing with losartan and digoxin and 24 h postdose. The subjects remained in the CRU for 24 h after administration of the digoxin infusion. On day 11 the same procedures were carried out as on day 4 but digoxin was administered orally, as an elixir, 30 min post losartan.

Safety assessment included physical examination, vital signs, 12-lead ECG and routine laboratory tests. A complete physical examination was done predose and within 1 week after the last dose of period 2 for each subject. Vital signs including blood pressure and heart rate, and a 12-lead ECG were done as described earlier. Blood and urine for laboratory safety studies were collected from each subject predose on day 1 of each period and within 1 week after period 2. On days 4 and 11 of each period a laboratory safety test (including electrolytes) was performed at least 60 min before digoxin administration.

Analytical data

Immunoreactive digoxin levels in plasma and urine were determined using a commercially available radioimmunoassay (Amerlex Digoxin RIA kit; Amersham, United Kingdom). For the determination of digoxin in plasma the included instructions for the kit were followed exactly as described. For urine analysis, however, stock solutions of digoxin in blank urine were prepared and further diluted with phosphate buffer pH 7.4 for construction of calibration curves in urine over a larger concentration range than in plasma. In plasma and urine, respectively, linearity was found in the range of 0.18–5 ng ml⁻¹ and 0.25 ng ml⁻¹ to 8 ng ml⁻¹. Intra-assay precision and inter-assay precision and accuracy were lower than 10%, using

Figure 1 Outline of the study design. On day 4: 0.5 mg digoxin i.v., on day 11: 0.5 mg digoxin orally. PK = Pharmacokinetics of digoxin.

determinations in duplicate. Plasma concentrations of losartan and its active carboxylic acid metabolite (E-3174, also known as EXP 3174 [9]) were analysed by h.p.l.c. [10]. The limit of detection was 5 ng ml⁻¹ for both losartan and E-3174.

Analysis of pharmacokinetic data

Mean differences between losartan and placebo for pharmacokinetic parameters of digoxin immunoreactivity were calculated using a general linear model (SAS Institute, Cary, North Carolina, USA) adjusting for period, treatment, sequence, and subject within sequence effects, using a significance level of $\alpha=0.05$. The area under the curve AUC(0,48 h), the urinary excretion of digoxin (0, 96 h, AU) and the peak concentration ($C_{\max}$) were analysed. From the general linear model, least square means (lsmean) were used to calculate the mean treatment differences. AUC data were ln-transformed for statistical analysis of the geometric mean ratio for digoxin (with losartan/without losartan [i.e. placebo]) as the principal measure of drug interaction. The 90% confidence interval for the ratio of geometric lsmeans was calculated using the standard error for the lsmean treatment differences. A confidence interval for this ratio falling within (0.77, 1.30) was defined as indicating a clinically insignificant effect, with emphasis on a 30% increase. The times to peak plasma concentration ($t_{\max}$) are the observed individual values from the plasma concentration *vs* time curves. Statistical analysis of $t_{\max}$ was performed by a nonparametric, signed rank test. All data are presented as mean $\pm$ s.d.

All available data were included in the statistical analysis. However, in two subjects after intravenous digoxin and two subjects after oral digoxin, limits of assay sensitivity precluded calculation of 48 h AUCs. Similarly, incomplete or erroneous urine collection precluded analysis of urinary excretion of digoxin in four subjects after intravenous digoxin and in three subjects after oral digoxin. However, individual review of these excluded results showed them to be consistent with the analysis of the evaluable results.

Results

Clinical results

Eleven of the 13 volunteers completed the study as per protocol. One subject was discontinued on the 4th day of period 1 (prior to the administration of losartan and digoxin) due to an increase in AST and ALT which began before initiation of losartan treatment. Another subject was withdrawn from the study on day 5 of the first period due to non-compliance. In the 11 other subjects there were no clinically significant laboratory changes noted.

Twelve of the 13 subjects had at least one adverse event. Side effects were mild, self-limiting, and required no treatment. A total of six adverse events, considered possibly or probably related to drug, were recorded in four subjects. These included single episodes of nausea ($n=3$ during losartan and $n=1$ with placebo) and palpitations ($n=1$ during losartan alone and $n=1$ during losartan and digoxin). Electrocardiographic measurements were limited to PR interval, QRS duration and QTc interval predose, at 0.5, 4, 8 and 24 h postdose digoxin administration. No effect of digoxin on these parameters was apparent, either during placebo or during losartan. Cardiac rhythm did not change following digoxin in any subject.

Digoxin pharmacokinetics

The mean values of immunoreactive digoxin AUC(0,48 h), cumulative urinary excretion (AU), $C_{\max}$ and $t_{\max}$ are listed in Table 1. Figure 2 summarizes the ratio analysis of plasma AUC and urinary excretion of immunoreactive digoxin.

Levels of immunoreactive digoxin after intravenous digoxin were not detectable in plasma in most subjects after 48 h making it appropriate to focus only on 48 h AUC for the primary pharmacokinetic analysis. The pharmacokinetics of intravenous digoxin did not differ significantly when digoxin was administered during treatment with losartan compared with placebo, as

Table 1 Mean values of AUC(0,48h) AU, $C_{\max}$ and $t_{\max}$ of either i.v. or oral digoxin in healthy males receiving continuous oral doses of 50 mg losartan or placebo. Data are mean values $\pm$ s.d. (n =number of subjects with evaluable results for each parameter, see text)

Parameter	i.v. digoxin		Oral digoxin	
	Placebo	Losartan	Placebo	Losartan
AUC(0,48h) (ng ml ⁻¹ h)	28.45 $\pm$ 3.92	28.76 $\pm$ 2.93	22.43 $\pm$ 2.57	23.63 $\pm$ 3.67
	$n=9$	$n=10$	$n=9$	$n=11$
AU (%dose)	51.89 $\pm$ 6.48	54.01 $\pm$ 7.20	46.26 $\pm$ 2.44	51.16 $\pm$ 6.30
	$n=7$	$n=7$	$n=8$	$n=8$
$C_{\max}$ (ng ml ⁻¹)			3.07 $\pm$ 0.53	3.46 $\pm$ 0.70
			$n=11$	$n=11$
$t_{\max}$ (h)			0.86 $\pm$ 0.74	0.64 $\pm$ 0.23
			$n=11$	$n=11$

Figure 2 Ratio (losartan/placebo) analysis of plasma AUC (0,48 h) and urinary excretion (AU, 0,96 h) of digoxin given intravenously and orally. Open circles indicate the individual AUC and AU ratios, arrowheads indicate the geometric lsmean ratio, and the brackets indicate the boundaries of the 90% confidence intervals about the geometric lsmean ratios.

measured by the area under the curve and the urinary excretion of digoxin over 96 h. The geometric mean (90% confidence interval) was 1.03 (0.98, 1.08) for digoxin AUC and 1.09 (0.98, 1.21) for AU. Thus, the ratios of geometric lsmeans for these critical pharmacokinetic parameters were well within the interval (0.77, 1.30).

Also, the pharmacokinetics of immunoreactive digoxin after oral dosing did not differ significantly when digoxin was administered during treatment with losartan compared with placebo, as measured by the AUC(0,48 h), $C_{\max}$, $t_{\max}$ and the amount of urinary excretion of digoxin over 96 h (AU). The geometric mean (90% confidence interval) for digoxin AUC was 1.06 (0.98,

1.14), for $C_{\max}$ was 1.12 (0.97, 1.28) and for AU was 1.08 (0.98, 1.18). These ratios of geometric lsmeans were all within the interval (0.77, 1.3). Mean concentration vs time profiles for digoxin, following intravenous and oral administration of 0.5 mg digoxin were superimposable during both losartan and placebo (not shown).

Immunoreactive digoxin $t_{\max}$ during oral losartan treatment (0.64 h) was not significantly different from that obtained during placebo treatment (0.86 h). Six of the 11 subjects had the same $t_{\max}$ on both losartan and placebo.

The steady state trough concentration of losartan was below 5 ng ml⁻¹ (i.e. below the detection limit). The steady state trough concentration of E-3174 was about

12–15 ng ml⁻¹. Mean values of trough (24 h postdose) concentration of E-3174 on the 4th day did not differ from those on the 11th day (13.4 ± 4.5 vs 12.3 ± 3.2 ng ml⁻¹).

Discussion

A variety of mechanisms can contribute to drug interactions with digoxin, including alterations in renal and nonrenal clearance, absorption and distribution volume [3–6]. For example, captopril increases serum digoxin by about 25% and the mechanism involved appeared to be a reduction of renal clearance of digoxin [11]. In contrast, neither ramipril nor lisinopril altered digoxin levels in volunteers [12, 13].

Losartan, a highly selective AT₁ angiotensin II receptor antagonist, has been developed for treatment of hypertension and, possibly, congestive heart failure. This study was designed to permit an assessment of whether losartan influences the pharmacokinetics of digoxin to a clinically significant degree.

The pharmacokinetics of digoxin, administered either intravenously or orally, were not affected by losartan administration, suggesting that a clinically significant interaction would not be expected in practice. In particular, the AUC(0,48 h) and cumulative urinary excretion of digoxin after i.v. injection of digoxin did not differ significantly when digoxin was administered with losartan compared to placebo. Similarly, the pharmacokinetics of oral digoxin did not appear to be affected by losartan.

These results should be interpreted conservatively as only digoxin immunoreactivity was measured and an interaction affecting a cross-reacting metabolite of digoxin might not be detectable. However, after intravenous administration of digoxin, most circulating immunoreactivity is due to intact digoxin [7]. Therefore, based on the same radioimmunoassay methods with which other interactions with digoxin have been detected [3–6, 11–13], the present study strongly suggests that losartan does not affect the pharmacokinetics of digoxin.

The authors want to thank Drs Man Wai Lo and John Gilbert of Merck Research Laboratories, Drug Metabolism, for guidance in assay validation and pharmacokinetic analysis of the data and Mr Edward J McWilliams for assistance in administration of the study. Ms Hannah Lu is acknowledged for performance of the assay of losartan and E-3174.

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(Received 23 January 1995,
accepted 9 August 1995)