Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers

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Aims To study the effect of eprosartan, a nonbiphenyl tetrazole angiotensin II receptor antagonist, on digoxin pharmacokinetics in a randomized, open-label, two period, period balanced crossover study in 12 healthy men.

Methods Each subject received a single 0.6 mg oral dose of digoxin (Lanoxicaps® 0.2 mg/capsule, Glaxo Wellcome) alone or following 4 days of dosing with eprosartan 200 mg orally every 12 h. Each study period was separated by a 14 day washout interval. Serial blood samples were obtained for up to 96 h after each digoxin dose for determination of digoxin pharmacokinetics. The effect of eprosartan on digoxin pharmacokinetics was assessed through an equivalence-type approach using AUC(0, t') as the primary endpoint.

Results For AUC(0, t'), the ratio of digoxin + eprosartan : digoxin alone was 0.99 with a 90% confidence interval (CI) of [0.90, 1.09]. For C_{max}, the ratio was 1.00 with a 90% CI of [0.86, 1.17]. t_{max} was similar for both regimens. Both regimens were safe and well tolerated.

Conclusions Based on AUC and C_{max} data, it can be concluded that eprosartan has no effect on the pharmacokinetics of a single oral dose of digoxin.

Keywords: eprosartan, digoxin, pharmacokinetics, angiotensin II, receptor antagonist, drug-interaction

Introduction

The renin-angiotensin system plays a vital role in the normal homeostatic regulation of cardiovascular and renal function. It is often activated in diseases such as hypertension, congestive heart failure and chronic renal failure and plays a central role in the pathophysiology of these disorders. A number of non-peptide angiotensin II antagonists have recently been described [1, 2] that differ from the angiotensin converting enzyme inhibitors in that they inhibit angiotensin II action directly at the receptor level rather than blocking angiotensin II synthesis. Eprosartan is a new nonbiphenyl tetrazole angiotensin II receptor antagonist currently in clinical development for essential hypertension. In the rat and dog, eprosartan has been shown to be a potent and highly selective competitive antagonist of angiotensin II at the AT1 receptor [2–4].

Identifying and characterizing drug interactions with digoxin are important because digoxin is widely used in cardiovascular disorders and has a narrow therapeutic index. Numerous pharmacological agents have been shown to produce clinically significant interactions with digoxin. Drugs which reduce digoxin absorption include antacids (aluminium hydroxide, magnesium hydroxide and magnesium trisilicate), antidiarrheals (kaolin and pectin), cholestyramine, and several chemotherapeutic agents (cyclophosphamide, vincristine and bleomycin) [5]. Certain antibiotics including sulphasalazine, neomycin and aminosalicylic acid reduce digoxin absorption while others, including erythromycin and tetracycline, increase the bioavailability of digoxin [5]. Antiarrhythmic drugs, such as quinidine and amiodarone, and certain calcium channel blockers, particularly verapamil, can markedly increase steady-state serum digoxin levels [6].

The usual therapeutic plasma concentration range for digoxin is 0.9–2 ng ml^{-1}, with the maximum tolerable concentration usually around 2 ng ml^{-1} [7]. However, the optimal therapeutic concentration of digoxin shows great inter–individual variation, as does the toxic concentration. Any change in this concentration, as a consequence of a pharmacokinetic interaction with other drugs used concurrently, may therefore lead either to a clinically significant reduction in the pharmacologic response or to an increase in the incidence of unwanted toxic effects. Since a considerable number of patients requiring therapy with eprosartan are expected to be on concurrent digitalis therapy, it is desirable to investigate any potential effect of eprosartan on plasma digoxin concentrations.

The objectives of this study were to evaluate the effect of steady state oral dosing of eprosartan on the pharmacokinetics of a single oral dose of digoxin. The study design is similar to that proposed by Antman and colleagues to use for screening potential drug interactions with digoxin [8].

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Methods

The study was conducted at the FOCUS Clinical Drug Development GmbH, Clinical Pharmacology Unit in Neuss, Germany. The protocol and statement of informed consent were approved by the Freiburg Ethics Committee prior to the start of the study, and the study was conducted in accordance with the Declaration of Helsinki. Subjects gave written informed consent prior to enrolling in the study.

This was a randomized, open-label, two period, period balanced crossover study. Subjects were randomly assigned to receive digoxin alone or digoxin plus eprosartan during period 1. Then, after a dose-free interval of at least 14 days following completion of period 1, subjects received the alternate regimen in period 2. For the digoxin alone regimen, digoxin (Lanoxicaps® 0.2 mg/capsule, Glaxo Wellcome) was given as a single oral dose of 0.6 mg. For the digoxin plus eprosartan regimen, eprosartan 200 mg was given twice daily for 7 days, with digoxin 0.6 mg given as a single oral dose on the morning of day 4.

Twelve healthy, non-smoking, male subjects between 18 and 45 years of age, inclusive, were selected for study participation. All subjects had a medical history, complete physical examination, 12-lead electrocardiogram (ECG), haematology, sitting blood pressure and pulse rate, and clinical laboratory tests within 15 days prior to the start of the study. In addition, subjects underwent screening for drugs of abuse and were tested for hepatitis B and C and HIV; negative results were required for inclusion in the study. Subjects had a negative urine drug screen and were without any clinically relevant abnormalities on screening history, physical or laboratory examinations.

For each study session, blood samples for pharmacokinetic analysis of digoxin were drawn into heparinized tubes prior to digoxin dosing, and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84 and 96 h following digoxin dosing. A follow-up medical examination and clinical laboratory tests were performed within 7 to 10 days following the last pharmacokinetic sampling period.

Plasma concentrations of digoxin were determined by radioimmunoassay using a I^{125}-labeled digoxin derivative. The concentration range of the assay was 0.10 to 3.63 ng ml^{-1} based on a 50 µl plasma sample. The lower limit of quantification was 0.10 ng ml^{-1}. A three-run validation was performed to verify the precision and accuracy of the assay. The within-run precision for the assay at nominal concentrations of 0.10, 0.25, 1.01, and 3.63 ng ml^{-1} was 8.4, 3.7, 1.7, and 2.6%, respectively. The between-run precision of the assay at these concentrations was 3.2, 3.2, 2.1, and 2.1%, respectively. The mean accuracy of the assay at concentrations of 0.10, 0.25, 1.01, and 3.63 ng ml^{-1} was 103, 99, 101, and 101%, respectively.

Pharmacokinetic analysis of the individual digoxin plasma concentration-time data was conducted using non-compartmental analysis. The following pharmacokinetic parameters were derived: maximum observed digoxin plasma concentration (C_{max}), time at which C_{max} occurred (t_{max}), terminal phase rate constant (λ_z) and the corresponding half-life ($t_{\frac{1}{2},z}$). λ_z was determined using unweighted linear regression analysis of at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal slope. The area under the plasma concentration versus time curve from time zero to infinity, and the area under the plasma concentration time curves up to the last common time point, within an individual, for which digoxin could be quantified [AUC(0, t')] were also determined. Lack of an interaction of eprosartan on the pharmacokinetics of digoxin was assessed through an equivalence-type approach which used a two one-sided tests procedure [9]. Eprosartan would be considered to have no effect on the pharmacokinetics of digoxin if the 90% confidence interval (CI) for the ratio of the AUC values was completely contained within the range [0.70, 1.43]. The parameters AUC(0, t'), AUC and C_{max} were ln-transformed prior to separate analysis of variance (ANOVA) with the effects of sequence, subject, period and regimen included in the model [10]. t_{max} was analysed using a non-parametric method which took into account possible period effects [11].

Results

The mean age of the 12 subjects was 31 years (range 24–39 years) and mean weight was 78.8 kg (range 60–102 kg). A total of six adverse experiences (AE) were reported for four subjects following treatment with study medication. Of these, two AEs (hypertonia and hyperbilirubinemia) occurred following administration of digoxin alone and four AEs (headache, fatigue, eye pain and abdominal pain) occurred following digoxin plus eprosartan. All AEs were considered mild to moderate in nature. Except for the occurrence of hypertonia which was assessed as not related to digoxin administration, all AEs were considered to be possibly related to study medication.

Pharmacokinetic data were available for all 12 subjects following oral administration of digoxin alone and digoxin co-administered with eprosartan. However, $t_{\frac{1}{2}}$ could not be accurately determined for three subjects on one of their two dosing occasions because a non-quantifiable concentration was reported in the terminal phase followed by a quantifiable concentration. Following a single oral dose of digoxin either alone or with steady state eprosartan, maximum plasma concentrations of digoxin occurred at approximately 1.5 h following dosing. Thereafter plasma concentrations of digoxin declined in an apparent biexponential manner. Mean (s.d.) pharmacokinetic parameters of digoxin following oral administration of digoxin alone or with eprosartan at steady–state are presented in Table 1. The mean digoxin plasma concentration-time profiles for each regimen are presented in Figure 1.

In the majority of subjects, $t_{\frac{1}{2},z}$ could be determined on each study day and was approximately 40 h for digoxin alone and 47 h for digoxin plus eprosartan. However, the time period over which $t_{\frac{1}{2},z}$ was calculated was less than three half-lives. AUC values generally had extrapolated areas of greater than 20% but less than 40%. Therefore, both $t_{\frac{1}{2},z}$ and AUC estimates should be viewed with caution. Since AUC values based on a large extrapolated area may be inaccurate [12], AUC(0, t') was used as the primary endpoint for statistical analysis and AUC was used as a secondary endpoint.

The results of the statistical analysis are also presented in Table 1. The 90% CI for the ratios of the geometric means

Table 1 Summary [mean (s.d.)] pharmacokinetic parameters of digoxin determined in the presence and absence of eprosartan and associated point estimates and 90% confidence intervals*.

Parameter	*Digoxin alone*	*Digoxin + eprosartan*	*Comparison*	*Point estimate*	*90% CI*
AUC(0, t') (ng ml^{-1} h)	24.3 (5.9)	24.2 (5.9)	B: A	0.99	[0.90, 1.09]
AUC (ng ml^{-1} h)	32.6 (9.0)	33.0 (7.5)	B: A	1.01	[0.81, 1.26]
C_{max} (ng ml^{-1})	2.53 (0.76)	2.57 (0.81)	B: A	1.00	[0.86, 1.17]
t_{max} (h)***	1.5 (1.0–2.0)	1.5 (1.0–4.0)	B-A	0.25 h	[−0.25, 0.50 h]
$t_{\frac{1}{2}}$ (h)**	39.8 (7.2)	46.9 (15.7)	B-A	5.95 h	[−4.38, 16.28 h]

*Point estimates and 90% confidence intervals for: 1) the ratios of the geometric means for AUC(0, t'), AUC, and C_{max}; 2) the mean difference for $t_{\frac{1}{2}, z}$, and 3) the median difference for t_{max}. **$n = 9$. ***Presented as median and range.
A = digoxin alone, B = digoxin plus eprosartan.

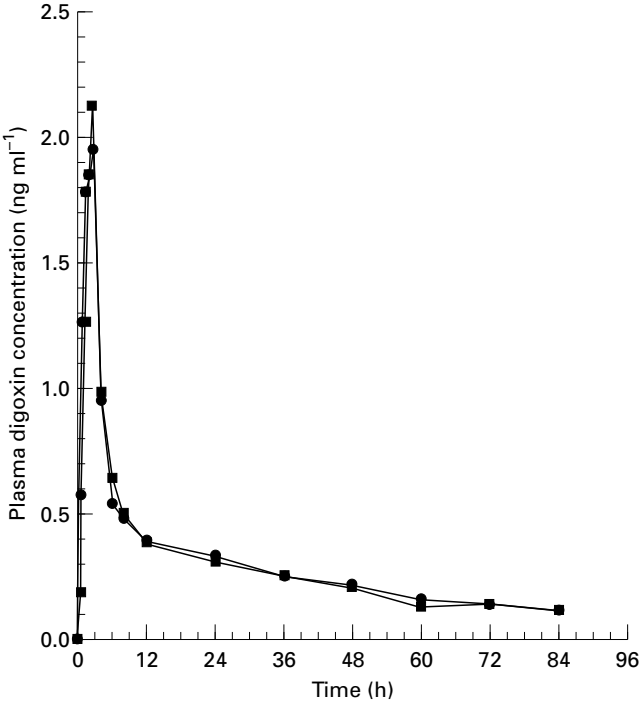

Figure 1 Mean plasma concentrations (ng ml^{-1}) of digoxin following oral administration alone (●) or with 200 mg (twice daily) eprosartan (■) at steady state to healthy male volunteers ($n = 12$).

for digoxin + eprosartan : digoxin alone for AUC(0, t'), AUC and C_{max} were completely contained within the equivalence range [0.70, 1.43]. Hence, eprosartan can be considered to have had no effect on the pharmacokinetics of digoxin.

Discussion

Eprosartan is being developed for the treatment of mild to severe essential hypertension. It is likely that eprosartan will be prescribed concomitantly with digoxin, and thus the potential effect of eprosartan on digoxin pharmacokinetics was the focus of this study.

The present study was designed with these considerations in mind and evaluated the effect of eprosartan on the pharmacokinetics of a single oral dose of digoxin using an equivalence-type approach. Based on AUC and C_{max} data, eprosartan had no effect on the pharmacokinetics of single-dose digoxin.

In a recent review and appraisal of the study methodology associated with digoxin interaction studies, Antman and colleagues discussed the merits and limitations of four study designs [8]. These designs encompassed single and multiple doses of digoxin in cardiac patients and normal volunteers. The authors noted that a single dose digoxin pharmacokinetic study in healthy volunteers serves as a valuable screen for potential digoxin drug interactions. If a potential drug interaction is observed with this screening study or if a clinically relevant pharmacokinetic interaction is expected (e.g., based on other drugs within the class or previous experience with the compound in question), further testing with multiple doses in healthy volunteers or single and multiple dose studies in cardiac patients may then be warranted. Conversely, if no drug interaction is noted with this screening study and if no clinically relevant pharmacokinetic drug interactions are anticipated, then no further pharmacokinetic studies may be needed beyond the initial screen.

Eprosartan is primarily eliminated via the faeces as unchanged drug, with renal clearance representing approximately 30% of total clearance (data on file, SmithKline Beecham Pharmaceuticals). Based on the pharmacokinetics of eprosartan and the considerations noted by Antman and colleagues, the likelihood of an interaction between eprosartan and digoxin was considered to be remote, and so the single dose digoxin design in healthy volunteers was selected as the most appropriate initial study design.

Eprosartan was safe and well tolerated when co-administered with a single oral dose of digoxin. The adverse experiences that occurred were mild to moderate in nature and did not require any corrective therapy. The results of the pharmacokinetic analysis indicate that a clinically relevant interaction between eprosartan and digoxin is unlikely at the doses evaluated in this study.

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