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Carvedilol increases the systemic bioavailability of oral digoxin

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The effects of a single oral dose of 25 mg carvedilol on the plasma and urinary kinetics of digoxin after an oral and intravenous 0.5 mg dose, were investigated in two separate double-blind, placebo-controlled, period-balanced cross-over studies in healthy male subjects. Carvedilol increased the mean maximum plasma concentration and the area under the plasma concentration time-curve of digoxin when administered orally. The effects were virtually confined to the first 4 h after dosing, and the apparent terminal disposition rate constant was not changed. Carvedilol did not alter the plasma and urinary kinetics of intravenously administered digoxin.

Keywords carvedilol digoxin interaction bioavailability

Introduction

Carvedilol (SK & F 105517, BM 14190) is a vasodilator with β-adrenoceptor blocking properties, under development for the treatment of hypertension and angina pectoris (Cubeddu *et al.*, 1987; Sponer *et al.*, 1987). The concomitant administration of carvedilol with digoxin is therefore possible. Digoxin is known to have a low therapeutic index, and to be susceptible to pharmacokinetic interactions. The present study was conducted to assess whether a single oral dose (25 mg) of carvedilol influences the pharmacokinetics of digoxin, and to elucidate the mechanisms of any such interaction.

Methods

Two separate studies were conducted with essentially similar design and procedures but using different subjects. In the first study the potential for interaction between carvedilol and orally administered digoxin was assessed. In the second that between carvedilol and intravenously administered digoxin was assessed. In each phase eight healthy male volunteers (ages 23–27 years) were studied on two occasions separated by at least 1 week.

The studies were conducted in accordance with the Declaration of Helsinki (Venice Amendment, 1983), and the study protocols were approved by an independent Ethics Committee.

Commercially available digoxin preparations were used (Lenoxin®, Wellcome, FRG).

In the first study the subjects received a single oral dose of 0.5 mg digoxin concomitantly with either 25 mg carvedilol or matched placebo. In the second study the subjects received a single intravenous dose of 0.5 mg digoxin by constant rate infusion over 10 min preceded by the administration of either a single oral dose of 25 mg carvedilol or matched placebo. The treatments (carvedilol, placebo) were investigated in a double-blind, period-balanced, within-subject cross-over design with randomly allocated sequences.

On the day preceding each study, the subjects abstained from alcohol, and foods or beverages containing methylxanthine or tyramine. They were fasted from 22.00 h on the night prior to each study and up to 5 h after dosing. The subjects reported to the study room at approximately 07.30 h, emptied their bladders and were positioned supine in bed. An i.v. cannula was placed in a forearm vein for blood sampling.

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In the second study a further i.v. cannula was placed in a contralateral forearm vein for infusion of digoxin. After a supine rest of 60 min the treatments (carvedilol or placebo) were administered with 150 ml water, immediately followed by administration of digoxin (orally in study 1, intravenously in study 2: 10 ml solution/10 min in a side-line to a main line of 100 ml h^{-1} isotonic saline).

A one-lead ECG was monitored for 8 h after dosing. Blood pressure (Korotkoff sounds I and V) was measured non-invasively by an automated device, every 10 min for the first 4 h and every 15 min for the following 4 h. A full 12-lead ECG was recorded prior to dosing, and at 4 and 8 h after dosing. The subjects remained supine in bed, in a relaxed recumbent position up to 8 h after dosing. At 5 h after dosing a light lunch was served, with the subjects sitting upright in bed. From 8 h after dosing, the subjects were ambulatory but under further surveillance until 12 h after dosing. At 12 h after dosing the subjects were allowed to leave the Study Unit after an assessment of their fitness.

In the first study, venous blood (5 ml) was sampled prior to dosing, and then at 15, 30, 45, 60, 90, 120, 180 min and 4, 6, 8, 12, 34, 36 and 48 h after dosing. In the second study blood was sampled prior to dosing, and then at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180 min and at 4, 6, 8, 12, 24, 36, 48 and 72 h after the start of the infusion. In each study urine was collected in five fractions: a pre-dosing blank, and then 0–8, 8–24, 24–36 and 36–48 h after dosing.

Plasma concentrations of digoxin were measured by radio-immuno-assay (Amerlex-digoxin, Amersham, UK). The calibration range extended from 0.09 to 5.40 ng ml^{-1}. The coefficients of variation at these concentrations were 0.7 and 6.1%, respectively. Urinary digoxin concentrations were measured by h.p.l.c. with u.v. detection. The calibration range extended from 10 to 400 ng ml^{-1}, with coefficients of variation of 15.6 and 3.0%, respectively. The following pharmacokinetic variables were calculated using a standard non-compartmental approach: maximum observed plasma drug concentration (C_{max}, ng ml^{-1}), time to reach C_{max} (t_{max}, min), the concentration at 24 h after dosing ($C(24)$, ng ml^{-1}), AUC up to the last measurable plasma concentration ($AUC(0,t)$, ng ml^{-1} h). AUC extrapolated to infinity (AUC, ng ml^{-1} h), the apparent terminal disposition rate constant (k, h^{-1}), and 48 h urinary recovery ($Ae(48)$, ng).

The treatments were contrasted by analysis of variance according to a general linear model with effects for subject, period, treatment, group and sequence. The residuals after fitting both untransformed and log-transformed data by this model were assessed for normality by the Frank-Shapiro W'test (Royston, 1983) and by inspection of their normality plots. Log-transformation was chosen when this substantially improved agreement with the assumption of normality. Homogeneity of the variances was assessed by inspecting plots of the residuals *vs* the fitted values. Assuming constancy of variance, conventional 2-sided 95% confidence intervals were calculated for the estimate of the true difference (for untransformed data), e.g. ratio (back-transformed from the log-transformed data, i.e. geometric mean of the individual ratios) of the treatment means. Because of the discrete sampling, t_{max} was contrasted by distribution-free point and interval estimates (Meineke, 1987; Steinijans & Diletti, 1985).

Results

Clinical findings

Both treatments were equally well tolerated. No adverse events occurred. The concomitant administration of carvedilol with digoxin had little influence on supine resting mean heart rate and diastolic blood pressure, relative to the administration of digoxin alone. The mean supine systolic blood pressure was decreased by the administration of carvedilol relative to placebo, in the first study by an average of 5 mm Hg (95% CI: −10 to −1 mm Hg) and by 6 mm Hg (95% CI: −11 to −1 mm Hg) in the second study. This effect was evident by the second hour after dosing and lasted up to at least 7 h after administration of carvedilol. No treatment effects were observed for the ECG variables.

Pharmacokinetic effects: orally administered digoxin

The time courses of the median plasma concentrations of digoxin are shown in Figure 1. The treatment means (R: [digoxin + placebo], T: [digoxin + carvedilol]), and the point and interval estimates of their contrasts are listed in Table 1.

Pharmacokinetic effects: intravenously administered digoxin

The time courses of the median plasma concentrations of digoxin were almost superimposable. The treatment means (R: [digoxin +

Table 1 Treatment means ($n = 8$) and ranges, and treatment contrasts for the observed maximum plasma digoxin concentration (C_{max}), time to reach C_{max} (t_{max}), plasma digoxin at 24 h after dosing ($C(24)$), AUC(0,48,72) and AUC, apparent terminal disposition rate constant (k), and 48 h urinary digoxin excretion ($Ae(48)$). Treatment comparisons are presented as point estimates and their 95% confidence intervals for the difference of the means (T–R, untransformed data) or the ratio of the treatment means (for log-transformed data, i.e. geometric mean of the individual ratios T/R). For t_{max}, the median was reported, and the contrasts are based on distribution-free analysis

	Digoxin + placebo (R)		*Digoxin + carvedilol (T)*		*Treatment contrast*	
	mean	*range*	*mean*	*range*	*point estimate*	*95% confidence interval*
Orally administered digoxin						
C_{max} [ng ml^{-1}]	1.62	(0.89, 2.56)	2.59	(1.54, 4.17)	T–R : 0.97	(0.20 to 1.73)*
t_{max} [min]	84	(45, 180)	96	(45, 180)	T/R : 1.00	(0.58 to 2.00)
$C(24)$ [ng ml^{-1}]	0.23	(0.19, 0.30)	0.28	(0.19, 0.38)	T/R : 1.19	(1.10 to 1.27)*
AUC(0,48) [ng ml^{-1} h]	15.0	(10.80, 18.32)	17.9	(11.59, 19.83)	T/R : 1.19	(1.10 to 1.30)*
AUC [ng ml^{-1} h]	25.6	(14.30, 38.23)	30.7	(14.89, 45.30)	T/R : 1.19	(0.97 to 1.46)
k [h^{-1}]	.0166	(.0112, .0265)	.0170	(.0088, .0272)	T/R : 1.00	(0.76 to 1.31)
$Ae(48)$ [ng]	216	(127, 391)	188	(100, 259)	T–R : −28	(−113 to 57)
Intravenously administered digoxin						
C_{max} [ng ml^{-1}]	16.7	(9.42, 22.00)	17.6	(11.30, 24.80)	T–R : 0.86	(−1.35 to 3.07)
$C(24)$ [ng ml^{-1}]	0.29	(0.18, 0.40)	0.27	(0.14, 0.36)	T/R : 0.91	(0.80 to 1.03)
AUC(0,72) [ng ml^{-1} h]	27.9	(20.99, 34.26)	26.7	(19.66, 32.99)	T/R : 0.96	(0.90 to 1.02)
AUC [ng ml^{-1} h]	36.3	(24.85, 47.83)	35.7	(27.97, 44.64)	T/R : 0.99	(0.90 to 1.09)
k [h^{-1}]	.0169	(.0123, .0224)	.0152	(.0109, .0237)	T/R : 0.89	(0.72 to 1.10)
$Ae(48)$ [ng]	258	(233, 282)	246	(196, 281)	T–R : −13	(−47 to 21)

* Statistically significant at the 5% level.

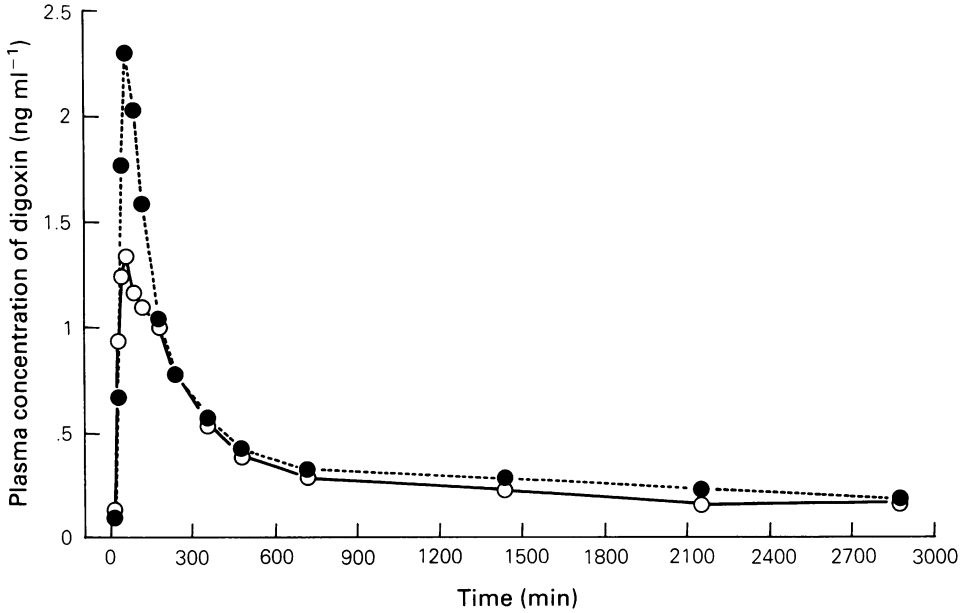

Figure 1 Time courses of the median plasma concentrations of digoxin after administration of a single oral dose of 0.5 mg digoxin either concomitantly with 25 mg oral carvedilol (T,●), or with carvedilol matched placebo (R,○).

placebo], T: [digoxin + carvedilol]), and the point and interval estimates of their contrast are listed in Table 1.

Discussion

The administration of a single oral dose of 25 mg carvedilol with an oral dose of 0.5 mg digoxin, caused a significant increase in the C_{max}, C(24) and AUC of digoxin. C_{max} was increased on average by 0.97 ng ml^{-1} (95% CI: 0.20 to 1.73), but the potentially more relevant $C(24)$ level, i.e. the trough on once daily dosing, was increased to a lesser extent: T/R was 1.19, with a 95% CI of 1.10 to 1.27, i.e. an increase similar to that observed for the AUC(0,48). The apparent terminal disposition rate constant k was not affected. The observed effects were not confirmed by the urinary findings. This might have been due to the fact that only urinary concentrations of digoxin were measured and not those of its main metabolites, i.e. digoxigenin, and digoxigenin mono- and bisdigitoxosides.

Extensive *in vitro* testing excluded assay interference as a possible cause of this finding. The lack of effect of carvedilol on the pharmacokinetics of intravenously administered digoxin suggested that the observed effects were not related to changes in the clearance of digoxin. It is therefore concluded that carvedilol augmented the systemic bioavailability of digoxin after oral administration, possibly as a consequence of intestinal vasodilatation.

The clinical relevance of these effects after oral administration of digoxin is likely to be small. Similar or greater differences in C_{max} values were observed when digoxin was given in different oral formulations or by different routes of administration, without major shifts in trough concentration and without ill effects (Bertler *et al.*, 1974; Bodem & Dengler, 1978; Rodin & Johnson, 1988).

Acute interaction studies with concomitant administration of the treatments, especially when performed in healthy subjects, do not necessarily reflect the outcome in clinical practice. Thus, early vasodilatory responses (as suspected here) may be pronounced on first administration but may become attenuated on chronic treatment. Also, our data suggest a time-limited interaction which might not occur if the drugs are not taken simultaneously. The present preliminary data indicate a need to monitor digoxin therapy more carefully when carvedilol is added to the treatment.

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