Pharmacokinetic and pharmacodynamic interaction trial after repeated oral doses of imidapril and digoxin in healthy volunteers

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Aims To investigate the potential pharmacokinetic and pharmacodynamic interaction between imidapril and digoxin.

Methods AUC, $C_{\max}$ and $t_{\max}$ of imidapril, imidaprilat and digoxin were calculated and evaluated in a randomized, doubleblind three-period cross-over design in 12 healthy volunteers after 8 days treatment with the following combinations: digoxin 0.25 mg day^{-1} + placebo (D + P); imidapril 10 mg day^{-1} + placebo (I + P); imidapril 10 mg day^{-1} + digoxin 0.25 mg day^{-1} (I + D).

Results Mean AUC (0, 24 h) of digoxin was $10.4 (\pm 4.9 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (D + P) and $10.7 (\pm 3.9 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (I + D), respectively (90%-confidence intervals [CI] for the ratio of (D + P) and (I + D): 0.91–1.27, point estimator [PE]: 1.06). Mean AUC (0, 24 h) of imidapril was $133 (\pm 86 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (I + P) and $108 (\pm 52 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (I + D), respectively (90%-CI: 0.76–0.94, PE 0.85). AUC (0, 24 h) of imidaprilat was $215 (\pm 91 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (I + P) and $194 (\pm 54 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h}$ (I + D), respectively (90%-CI: 0.80–1.08, PE 0.93). $C_{\max}$ was $19.9 (\pm 8.7 \text{ s.d.}) \text{ ng ml}^{-1}$ (I + P) and $15.9 (\pm 5.3 \text{ s.d.}) \text{ ng ml}^{-1}$ (I + D) (90%-CI: 0.67–1.00, PE 0.82). The results indicate a slight reduction of imidapril and imidaprilat plasma levels when coadministered with digoxin without any effect on digoxin plasma levels. Maximal ACE-inhibition was 79% (I + P) and 67% (I + D).

Conclusions Grouped data analysis of imidaprilat plasma levels *vs* ACE-activity showed that for maximal inhibition of plasma ACE activity, imidaprilat plasma levels should exceed 10 ng ml^{-1} . Under digoxin and imidapril, more plasma concentrations of imidaprilat were seen under this level as after imidapril alone, this reduces the integral of the ACE-inhibition/time curves by about 20 to 30%.

Keywords: imidapril, digoxin, pharmacokinetic–dynamic interaction

Introduction

Imidapril is a non-SH-group containing angiotensin converting enzyme (ACE) inhibitor currently under investigation for treatment of hypertension and congestive heart failure (CHF) [1, 2]. Imidapril is a prodrug, its active metabolite imidaprilat is generated in the liver after hydroxylation and eliminated via the kidneys with an elimination half-life of about 19 h. Studies with radiolabelled imidapril revealed that about 40% of the drug is absorbed after oral administration [2]. Repeated oral doses of imidapril 10 mg once daily resulted in 85 to 90% inhibition of plasma ACE [1, 2]. In patients with mild to moderate hypertension the same dose of 10 mg once daily produced sustained reduction of blood pressure in about 60% of treated patients; higher doses did not significantly increase the rate of responders [2].

Concomitant treatment of ACE-inhibitors and digoxin occurs frequently in patients with CHF. One single report describes the possibility of an interaction with captopril

leading to increased digoxin levels [3]. Although other studies investigating captopril [4] as well as several other ACE-inhibitors [5] could not confirm such an interaction, formal interaction studies with ACE-inhibitors and cardiac glycosides are demanded by registration authorities. Since digoxin and imidapril both will be given chronically and both drugs possess relatively long half-lives, an interaction should be investigated after repeated oral dosing of both drugs [6]. Furthermore, not only digoxin kinetics but also the pharmacokinetic disposition of the ACE-inhibitor might be adversely influenced. A controlled interaction study in CHF patients requiring these drugs can hardly be justified because either the ACE-inhibitor or the cardiac glycoside has to be withdrawn during the reference investigation. Therefore, studies performed in healthy volunteers can be used as surrogate [5–7].

Methods

This phase I trial was planned according to a randomised, doubleblind three-period cross-over design in 12 healthy volunteers. The study was approved by the Institutional Review Board of the Frankfurt University Hospital, and study subjects gave their written informed consent.

Dedicated to Professor Dr. N. Rietbrock on the occasion of his 65th Birthday.

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Subject selection and study protocol

The study consisted of three treatment periods of 8 days each separated by 2 weeks wash out phases. A pharmacokinetic (plasma levels of imidapril, imidaprilat and digoxin) and pharmacodynamic (ACE-activity) investigation took place on the 8th day of each treatment. The combinations given were:

(1) Imidapril 10 mg [Batch-No. G1591408, Manufacturer: Merck KGaA, Darmstadt, Germany], together with capsules containing placebo (I + P)

(2) Digoxin 0.25 mg [Batch-No. 751124404, Manufacturer: Boehringer Mannheim, Mannheim, Germany] and placebo-tablets matching to imidapril (D + P)

(3) Imidapril 10 mg together with capsules containing digoxin 0.25 mg (I + D).

In order to reach steady state digoxin plasma levels, a loading dose of digoxin was given as follows: on the 1st and the 2nd day of each treatment period subjects received 0.5 mg digoxin (i.e. 2 capsules) or 2 capsules of the matching placebo; on the 3rd to the 8th day of each treatment period subjects received digoxin 0.25 mg daily or 1 capsule of the corresponding placebo. Drugs were given together with a sufficient amount of water. Ingestion was controlled at each day by the investigators.

Investigations

Blood samples for determination of imidapril and imidaprilat were collected on the pharmacokinetic study days, at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 and 24 h. Blood samples for determination of digoxin were drawn at 0, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 h after drug intake. Blood samples for measurement of plasma ACE-activity were collected before the first drug intake of each treatment period (=baseline) and on the study days before drug administration and after 1, 2, 4, 6, 8, 12 and 24 h. On each pharmacokinetic study day, urine was collected over 24 h and 10-ml aliquots were stored.

Analytical assays

The analytical assay of imidapril and imidaprilat in plasma was performed at CEPHAC laboratories (Centre d'Etudes et de Recherche en Pharmacie Clinique, Saint-Benoit, France). A specific monoclonal antibody radioimmunoassay was used. The lower limit of quantification was 1 ng ml^{-1} for both imidapril and imidaprilat in plasma and urine. Intraday precision of imidaprilat was 3.4% and accuracy was 88% at concentrations of 1 ng ml^{-1} . Interday precision was 6.6% and accuracy was 91% (1 ng ml^{-1}). Intraday precision of imidapril was 14% and accuracy was 102% (1 ng ml^{-1}); interday precision was 15% and accuracy was 99% (1 ng ml^{-1}).

Digoxin concentrations in serum were determined using a competitive solid-phase radioimmunoassay (Digoxin-RIA ^{125}I , Coat-a-count, Biermann, Bad Nauheim, Germany). The inter-assay coefficients of variation of spiked control samples was 14% (0.7 ng ml^{-1}), 5% (1.8 ng ml^{-1}) and 4% (3.4 ng ml^{-1}). Intra-assay coefficient of variation in 10 repeated measurements was 1.7% at 0.5 ng ml^{-1} and

1.6% at 2 ng ml^{-1} . Lower limit of quantification was 0.125 ng ml^{-1} (intra-assay CV 1.1%). Cross reactivity with dihydro-digoxin was 1.2%.

Serum ACE-activity was measured by a kinetic assay (H. Biermann, Bad Nauheim, Germany). The kit is based on the cleavage of phenylalanine-glycyl-glycine to phenylalanine and glycyl-glycine. After 5 min of pre-incubation the amount of substrate cleaved by ACE was determined by the difference in u.v.-absorption at 340 nm before and 10 min after addition of the substrate. The absorption was measured on a multitec scan ELISA-reader (Fa.Labsystems, Multiscan) equipped with a 340 nm u.v.-filter. The intra-assay coefficient of variation was determined using control samples and comparing the intra-individual variation of a low (45 u.l^{-1}) and a high control sample (75 u.l^{-1}) after 12 repeated measurements (CV = 20% and 11%, respectively). The intra-subject variability of the three baseline values (i.e. ACE-activity before the start of each treatment period) was 19%. Cross-reactivity with digoxin has been ruled out.

Pharmacokinetic and pharmacodynamic parameters

All pharmacokinetic calculations were based on the plasma concentrations which were above the LLQ. For imidapril, imidaprilat and digoxin the area under the drug concentration time curve from 0 to 24 h (AUC 0, 24 h) was calculated by a model-independent method using the PC program TOPFIT® 2.0 [8]; logarithmic trapezoidal rule. $C_{\min}$ = concentration at steady state before drug intake on the study days, $C_{\max}$ = maximal concentration after drug intake at steady state, and $t_{\max}$ = time when maximal concentration occurs were read off directly from the individual concentrations measured in plasma. The urinary recovery of imidapril and imidaprilat (Ae_r) was calculated from the concentration measured in the sample and the known total volume of urine voided during the 24 h dosing interval. Percentage inhibition of ACE activity in serum at each time point $t_{(i)}$ for each individual was calculated as follows:

$$\begin{aligned} \% \text{ACE inhibition}_{t(i)} \\ = \text{ACE activity}_{t(i)} * 100 / \text{ACE activity}_{\text{baseline}} \end{aligned}$$

where day 1 of each treatment period served as baseline (= 100%). This design was chosen to consider the inherent intra-subject variability of ACE-activity over the study period. For the ACE inhibition/time profile an area under the data curve (AUD) was calculated using the linear trapezoidal rule. Assuming that digoxin has no independent effect on ACE-inhibition, phase D + P was used as a placebo-control and AUD data obtained for this phase (AUD_{D+P}) were subtracted from the AUD_{I+P} and AUD_{I+D} , respectively. Maximal ACE inhibition was depicted from the individual ACE inhibition-time curves.

Imidaprilat vs ACE-activity

Considering the sparse data situation, a grouped data analysis according to an $E_{\max}$ -Model [$E = E_0 - (E_{\max} * C / (EC_{50} + C))$], where E = ACE-activity under imidaprilat, E_0 = baseline ACE-activity, C = imidaprilat plasma concentration, $E_{\max}$ = maximal fall in ACE-activity and EC_{50} = imidaprilat plasma

concentration required to induce 50% of $E_{\max}$] was carried out. Curve parameters and their 95% confidence intervals were yielded using nonlinear regression analysis (SYSTAT®, Evanston, IL, USA). Data obtained during imidapril alone and during digoxin coadministration were fitted separately and together.

Statistical analysis

A formal sample size estimation was not performed due to a lack of information on intra-individual variability of imidapril's pharmacokinetics. Therefore 12 volunteers were arbitrarily chosen for study.

The primary pharmacokinetic target variables were the AUC (0, 24 h), $C_{\min}$ and $C_{\max}$ of imidapril, imidaprilat and digoxin. Parametric or non-parametric confidence intervals for the ratio test (i.e. combination treatment)/reference (i.e. imidapril or digoxin alone) were used after determination of the distribution of the log-transformed data [9]. It has been suggested that a clinically relevant interaction can be excluded when the 90% confidence intervals (CI) as well as the point estimator (PE) ratio test/reference for the target variables are within commonly accepted limits of bioequivalence (e.g. for the AUC 0.80–1.25, PE 0.9–1.1).

The AUD of the ACE inhibition during imidapril alone and imidapril with digoxin (corrected by AUD_{D+P}) were compared using the same bioequivalence test procedures. Furthermore, maximal ACE-inhibition was compared.

Results

All volunteers completed the study according to the protocol. A total of eight non-serious adverse events were reported, mainly headache and weakness.

Digoxin

Trough digoxin plasma levels were 0.37 ng ml^{-1} when given alone and 0.38 ng ml^{-1} when coadministered with imidapril. Mean $C_{\max}$ values of digoxin were 1.65 ng ml^{-1} when given alone and 1.62 ng ml^{-1} when coadministered with imidapril. $t_{\max}$ was reached 1 h after administration in both phases (Table 1, Figure 1). Mean AUC (0, 24 h) values were $10.4 \text{ ng ml}^{-1} \text{ h}$ (D + P) and $10.7 \text{ ng ml}^{-1} \text{ h}$ (I + D), respectively. For AUC and $C_{\max}$, the 90%-confidence intervals for the difference between (D + P) and (I + D) as well as the point estimators were within the required limits for bioequivalence, thus excluding a pharmacokinetic interaction between imidapril and digoxin affecting digoxin pharmacokinetics.

Table 1 Mean ($\pm$ s.d.) pharmacokinetic parameters of digoxin. D = digoxin, I = imidapril, P = placebo.

	D + P	I + D	90%-CI* (PE)*
$C_{\min}$ (ng ml^{-1})	0.37 ± 0.23	0.38 ± 0.15	0.68–1.53 (1.01)
$C_{\max}$ (ng ml^{-1})	1.65 ± 0.50	1.62 ± 0.48	0.86–1.15 (0.99)
$t_{\max}$ (h) (median, range)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	
AUC (0, 24 h) ($\text{ng ml}^{-1} \text{ h}$)	10.4 ± 4.9	10.7 ± 3.9	0.91–1.27 (1.06)

*90%-confidence interval (point estimator).

Figure 1 Mean plasma concentration–time course of digoxin (0.25 mg daily over 8 days) at day 8 alone ($\square$) and following administration of imidapril (10 mg over 8 days) ($\blacksquare$).

Imidapril

Mean $C_{\max}$ values of imidapril were 37.3 ng ml^{-1} (I + P) and 31.7 ng ml^{-1} when coadministered with digoxin (I + D). $t_{\max}$ was reached at 2 h at both phases (Figure 2). Mean AUC (0, 24 h) values were $133 \text{ ng ml}^{-1} \text{ h}$ (I + P) and $108 \text{ ng ml}^{-1} \text{ h}$ (I + D), respectively. Urine recovery of imidapril was 0.72 mg (mean) when imidapril was given alone and 0.55 mg (mean) during coadministration of digoxin (Table 2). For AUC and $C_{\max}$ the 90%-confidence intervals (parametric) for the difference between (I + P) and (I + D) as well as the point estimator were not entirely within the required limits for bioequivalence, suggesting a diminished bioavailability of imidapril under digoxin coadministration.

Imidaprilat

Imidaprilat plasma levels immediately before drug intake at day 8 (trough) were 3.6 ng ml^{-1} (I + P) and 3.4 ng ml^{-1} (I + D). Mean $C_{\max}$ values of imidaprilat were 19.9 ng ml^{-1} (I + P) and 15.9 ng ml^{-1} (I + D) measured about 6 hours after application on both investigations. Mean AUC (0, 24 h) values were $215 \text{ ng ml}^{-1} \text{ h}$ during imidapril alone and $194 \text{ ng ml}^{-1} \text{ h}$ during digoxin coadministration (Table 2, Figure 2). Urine recovery of imidaprilat was 0.81 mg (mean) (I + P) and 0.69 mg (mean) (I + D). For $C_{\max}$, both the parametric 90%-confidence intervals and the point estimators for the difference between (I + P) and (I + D) exceeded the required limits for bioequivalence.

Figure 2 Mean plasma concentration-time course of imidaprilat following administration of 10 mg imidapril alone (○) and together with 0.25 mg digoxin (●). Inset: Mean plasma concentration-time course of imidapril following administration of 10 mg imidapril alone (Δ) and together with 0.25 mg digoxin (▲).

Imidapril	I + P	I + D	90%-CI (PE)*
$C_{\max}$ (ng ml ⁻¹)	37.3 ± 28.5	31.7 ± 19.9	0.74–1.07 (0.89)
$t_{\max}$ (h) (median, range)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	
AUC (0, 24 h) (ng ml ⁻¹ h)	133.0 ± 86.3	108.3 ± 51.8	0.76–0.94 (0.85)
A_e (mg)	0.78 ± 0.57	0.60 ± 0.41	
<i>Imidaprilat</i>			
$C_{\min}$ (ng ml ⁻¹)	3.6 ± 1.1	3.4 ± 0.7	0.85–1.11 (0.96)
$C_{\max}$ (ng ml ⁻¹)	19.9 ± 8.7	15.9 ± 5.3	0.67–1.00 (0.82)
$t_{\max}$ (h) (median, range)	6.0 (4.0–8.0)	6.0 (4.0–9.0)	
AUC (0, 24 h) (ng ml ⁻¹ h)	215.0 ± 91.1	194.2 ± 54.4	0.80–1.08 (0.93)
A_e (mg)	0.81 ± 0.23	0.69 ± 0.19	

Table 2 Mean (±s.d.) pharmacokinetic parameters of imidapril and imidaprilat, D = digoxin, I = imidapril, P = placebo

*90%-confidence interval (point estimator).

Apparently, the reduction in imidapril bioavailability is also reflected by a slight decrease in plasma concentrations of imidaprilat. Likewise, urinary recovery of imidaprilat was slightly reduced (Table 2).

ACE-inhibition

Plasma ACE activity profiles obtained during digoxin and imidapril alone and in combination are shown in Figure 3. Maximal inhibition averaged 79% after imidapril alone and 67% when imidapril was coadministered with digoxin. Directly before drug intake on day 8 (i.e. trough), ACE-inhibition was determined to be 50% during imidapril alone and 37% under imidapril and digoxin (Table 3). The 90%-confidence intervals for the difference in the AUD between the treatment (I + P) and (I + D) were not within the required limits for bioequivalence and indicate a reduced ACE-inhibitory effect of imidapril during digoxin coadministration.

Figure 3 Plasma ACE activity (mean values) after digoxin alone (□), after imidapril alone (○) and after digoxin and imidapril (●). Baseline = baseline activity at day 1 of each treatment phase.

Table 3 Mean ($\pm$ s.d.) pharmacodynamic parameters (ACE-Activity). D = digoxin, I = imidapril, P = placebo.

	D + P	I + P	I + D	90%-CI (PE)*
ACE _{BL} (ul ⁻¹)	60.5 $\pm$ 20.1	65.5 $\pm$ 10.8	60.5 $\pm$ 14.4	
ACE _{min} (ul ⁻¹)	68.4 $\pm$ 14.7	31.9 $\pm$ 11.0	41.8 $\pm$ 20.9	
Maximal ACE-inhibition (% BL)		79 $\pm$ 10	67 $\pm$ 14	0.72–0.95 (0.83)
AUD (0, 24 h) (%inhibition)**		1181 $\pm$ 516	779 $\pm$ 522	0.47–0.89 (0.69)

*90%-confidence interval (point estimator).

**corrected by AUD_{phase 1}.

Imidaprilat vs ACE-activity

When the data (I + P) and (I + D) were fitted separately, the 95% confidence intervals of the curve parameters showed a wide intersection and did not indicate a difference in the concentration/effect-relationship of imidaprilat between the two investigations (Table 4). Therefore the data (I + P) and (I + D) were fitted together. A plot of the *C* vs *E* data, the estimated curve and the 95% confidence intervals of the parameter estimates is shown in Figure 4. Obviously maximal inhibition of ACE-activity occurs with imidaprilat plasma levels above 10 ng ml⁻¹. The distribution of data points shows that the decrease in the AUD of ACE-inhibition under digoxin coadministration is probably due to the fact that imidaprilat levels >10 ng ml⁻¹ were less frequent during digoxin coadministration.

Table 4 Imidaprilat vs ACE-activity: summary statistics (Mean [95% confidence intervals]). D = digoxin, I = imidapril, P = placebo.

	I + P	I + D	Combined fit
E ₀ (ul ⁻¹)	66 (59–72)	61 (52–69)	63 (57–68)
E _{max} (ul ⁻¹)	51 (42–61)	42 (24–52)	44 (36–53)
EC ₅₀ (ng ml ⁻¹)	2.5 (0.9–4.1)	3.2 (-0.6–5.6)	2.7 (0.9–4.4)

Discussion

Imidapril bioavailability was reduced by about 10% when given together with digoxin. The active drug imidaprilat also shows a reduction in AUC and *C*_{max}. Statistical evaluation on the basis of presence or absence of bioequivalence revealed that the lower boundary of the confidence intervals of imidaprilat's AUC and *C*_{max} as well as the AUC of imidapril fall short off the recommended limits. Furthermore, the point estimator of imidaprilat's *C*_{max} is below the required limit of 0.9 [9]. Although the reduction in the bioavailability of imidaprilat seems negligible, imidaprilat plasma concentrations causing maximal ACE-inhibition appeared to be less frequent during digoxin. Since a large proportion of imidaprilat concentrations were detected in the range of the steeper part of the concentration-response curve, even slight changes in the concentration levels may have caused pronounced changes in the response data. This constellation may be the reason for the significant reduction of the ACE-inhibition-time profile during imidapril-digoxin coadministration. However, the large intra-subject variability of the ACE-activity as well as the assay variability has to be considered.

As renal excretion of both imidapril and imidaprilat were also decreased under concomitant treatment, the most likely explanation for the reduced bioavailability of imidapril seems

Figure 4 Plasma ACE-activity vs imidaprilat plasma levels after imidapril alone (○) and after digoxin and imidapril (●). (—) Curve analysis of combined data (I + P and I + D) according: $E = E_0 - (E_{max} \cdot C / (EC_{50} + C))$ (see text). (.....) 95% confidence intervals of the parameter estimates.

a reduction in the gastrointestinal absorption of imidapril when coadministered with digoxin. This mechanism should not apply to digoxin *vice versa*, as the bioavailability of digoxin was not affected when given with imidapril. A literature search on possible drug absorption interactions [10, 11] did not reveal a comparable interaction with digoxin. Therefore, we can only speculate on the mechanism of this interaction.

Concomitant application of ACE-inhibitors and digoxin is common in patients with CHF or hypertension with coexisting CHF. In one study [3] steady state levels of digoxin determined in 20 patients with CHF rose from 1.3 to 1.7 mmol l⁻¹ when captopril was coadministered, suggesting the possibility of a pharmacokinetic interaction (e.g. affecting renal excretion). In contrast, steady state digoxin levels were not affected in a study published by Miyakawa *et al.* [4], who also investigated digoxin kinetics with and without captopril comedication in patients with CHF. The authors reported on captopril levels in this study and described $C_{\max}$ values lower (44 ng ml⁻¹) than those observed in another study in hypertensive patients (72 ng ml⁻¹) receiving the same dose. They concluded that captopril absorption might be reduced in patients with CHF, but these findings may also indicate a drug-drug interaction. In contrast, absence of an interaction between ACE-inhibitors and digoxin has been reported for lisinopril [12], trandolapril [13], ramipril [14], cilazapril [15], quinapril [16], spirapril [17], and enalapril [18]. However, all investigators focussed on digoxin plasma levels and did not consider the kinetics of the ACE-inhibitor except one study on lisinopril, where single dose pharmacokinetics of lisinopril and digoxin were not affected by each other [12].

In conclusion, the present study indicates a slight, but significant drug-drug-interaction between imidapril and digoxin, affecting imidapril and imidaprilat plasma levels and the magnitude of plasma ACE-inhibition. The pharmacokinetic parameters of digoxin remained unchanged during imidapril. The clinical relevance of this interaction for treatment of patients with CHF and/or hypertension needs to be carefully interpreted. It should be considered that plasma ACE-inhibition serves only as a surrogate marker of the clinical effects of ACE-inhibitors, which are also mediated by bradykinin potentiation and influence on tissue ACE.

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