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PHARMACOKINETICS AND DISPOSITION

U. P. Masche · K. M. Rentsch · A. von Felten
P. J. Meier · K. E. Fattinger

No clinically relevant effect of lornoxicam intake on acenocoumarol pharmacokinetics and pharmacodynamics

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Abstract *Objective*: To investigate the effect of lornoxicam co-administration on acenocoumarol pharmacokinetics and pharmacodynamics.
Methods: In an open crossover study, six healthy male volunteers received racemic acenocoumarol (10 mg) orally without/with lornoxicam co-administration (8 mg twice daily).
Results: The median (range) areas under the concentration-time curve (AUC) for (*R*)-acenocoumarol were 3458 (3035–7312) $\mu g \cdot h\ l^{-1}$ in the absence of and 3667 (2907–7741) $\mu g \cdot h\ l^{-1}$ in the presence of lornoxicam. The corresponding values for (*S*)-acenocoumarol were 479 (381–853) $\mu g \cdot h\ l^{-1}$ and 612 (425–1241) $\mu g \cdot h\ l^{-1}$. The differences were not statistically significant. Lornoxicam co-administration did not influence the free fractions or acenocoumarol's effect on factor II and VII activities. Simulations based on the results of a model-based analysis predicted that in the case of lornoxicam co-administration, the factor VII activity of a person in steady-state at 26% will remain between 14% and 32%.
Conclusion: Co-administration of lornoxicam at the upper limit of recommended doses does not alter the pharmocokinetics of the clinically relevant (*R*)-acenocoumarol or the anticoagulant activity of acenocoumarol. These data clearly differ from the results of previous studies, which showed clinically relevant influences of lornoxicam on warfarin kinetics and of piroxicam on acenocoumarol kinetics.

U.P. Masche · K.M. Rentsch · A. von Felten ·
P.J. Meier · K.E. Fattinger
University Hospital,
Zurich, Switzerland

K. Fattinger (✉)
Division of Clinical Pharmacology and Toxicology,
Department of Internal Medicine,
University Hospital,
Rämistrasse 100,
CH-8091 Zurich, Switzerland
e-mail: fattinge@kpt.unizh.ch
Tel.: +41-1-255-20-67, Fax: +41-1-255-44-11

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Introduction

Drug interactions are a major concern in patients treated with anticoagulants. Studies about these interactions have mainly been carried out with warfarin. In Europe, however, acenocoumarol is more commonly used. Because acenocoumarol and warfarin exhibit marked pharmacokinetic differences [1] and are metabolized by different cytochrome P450 isoenzymes [2], drug-warfarin interactions cannot necessarily be extrapolated to acenocoumarol.

Lornoxicam is a new non-steroidal anti-inflammatory drug (NSAID) of the oxicam class [3]. Lornoxicam co-administration increased mean racemic warfarin serum concentrations by 32% and correspondingly increased its anticoagulant effect [4]. Piroxicam co-administration substantially increased acenocoumarol serum concentrations [5]. However, the influence of lornoxicam on acenocoumarol pharmacokinetics and pharmacodynamics still needs to be characterized.

Methods

Six healthy male volunteers (aged 22–34 years, 66–80 kg) were included. The study protocol was approved by the local ethics committee. The same open crossover design and the same methods were used as in the lornoxicam phenprocoumon interaction study [6]. Ten milligrams of racemic acenocoumarol (Sintrom 2×4 mg and 2×1 mg) were given orally. Samples for acenocoumarol plasma concentration measurements were collected before (0) and 0.5, 1, 1.5, 2, 3, 6, 12, 24, 31 h and 48 hours after acenocoumarol administration. Samples for clotting factor determinations were collected at 0, 6, 12, 24, 31, 48 h and 96 h. Because of acenocoumarol's shorter half-life, the factor VII elimination rate was estimated. The half-life of factor II had to be fixed to 60 h [7].

Results

Plasma concentrations, free fractions and effect data

The median (range) areas under the concentration-time curve (AUC) for (*R*)-acenocoumarol were 3458 (3035–7312) and 3667 (2907–7741) $\mu g \cdot h\ l^{-1}$ in the absence or presence of lornoxicam. The corresponding values for (*S*)-acenocoumarol were 479 (381–853) and 612 (425–1241) $\mu g \cdot h\ l^{-1}$. Thus, (*S*)-acenocoumarol has a considerably lower AUC than (*R*)-acenocoumarol. A Wilcoxon matched-pairs signed-rank test showed no statistical significance for the effect of lornoxicam on AUC ((*R*)-isomer: $P = 0.22$, (*S*)-isomer: $P = 0.09$). The maximal concentrations were in the range of 182–320 $\mu g \cdot l^{-1}$ ((*R*)-acenocoumarol) and 76–148 $\mu g \cdot l^{-1}$ ((*S*)-acenocoumarol) and occurred at 1–6 h after administration of the dose. They were not influenced by lornoxicam co-administration.

The free fraction for (*R*)-acenocoumarol was 1.1(1.0–1.3)% and 1.0(0.9–1.2)% without and with lornoxicam co-administration, respectively. The corresponding values for (*S*)-acenocoumarol were 1.7(1.3–1.8)% and 1.4(1.2–1.6)%. Thus, lornoxicam does not change acenocoumarol plasma protein binding.

No substantial differences were present in the various pharmacodynamic data, i.e. factor II and VII activities, prothrombin time and INR values between the sessions without and with lornoxicam co-administration (Fig. 1).

Model-based pharmacokinetic/pharmacodynamic analysis

The most feasible structural and variance model was a one-compartment model with first-order absorption, absorption lag-time and interindividual variability in clearance and absorption rate. The inclusion of a parameter for relative bioavailability of (*S*)-acenocoumarol in the case of lornoxicam co-administration as compared to without lornoxicam significantly improved the fit ($\Delta OF = -6.7$, $\Delta n_{par} = 1$). Lornoxicam increases (*S*)-acenocoumarol bioavailability by 24% [95% confidence interval (95% CI) (5%, 46%]. Adding a parameter for relative bioavailability (*R*)-acenocoumarol or for an effect of lornoxicam on (*R*)-acenocoumarol or (*S*)-acenocoumarol clearance did not improve the fit.

In the analysis of the factor VII and II activity data, the fit was the same if one estimated separate effect parameters for (*S*)-acenocoumarol, assumed the same effect for both isomers or no effect for (*S*)-acenocoumarol. Thus, the (*S*)-isomer did not contribute to drug effect, because of the very high clearance for (*S*)-acenocoumarol resulting in negligible plasma concentrations. Adding a sigmoidicity factor significantly improved the fit (VII: $\Delta OF = -44.6$; II: $\Delta OF = -7.4$, $\Delta n_{par} = 1$). Adding an effect of lornoxicam co-administration on the concentration causing half-maximal effect (C_{50}) resulted in no further improvement (VII: $\Delta OF = -0.3$; II: $\Delta OF = -0.6$, $\Delta n_{par} = 1$). Table 1 gives the parameter estimates of the final model and the 95% CI for parameters describing a possible effect of lornoxicam co-administration.

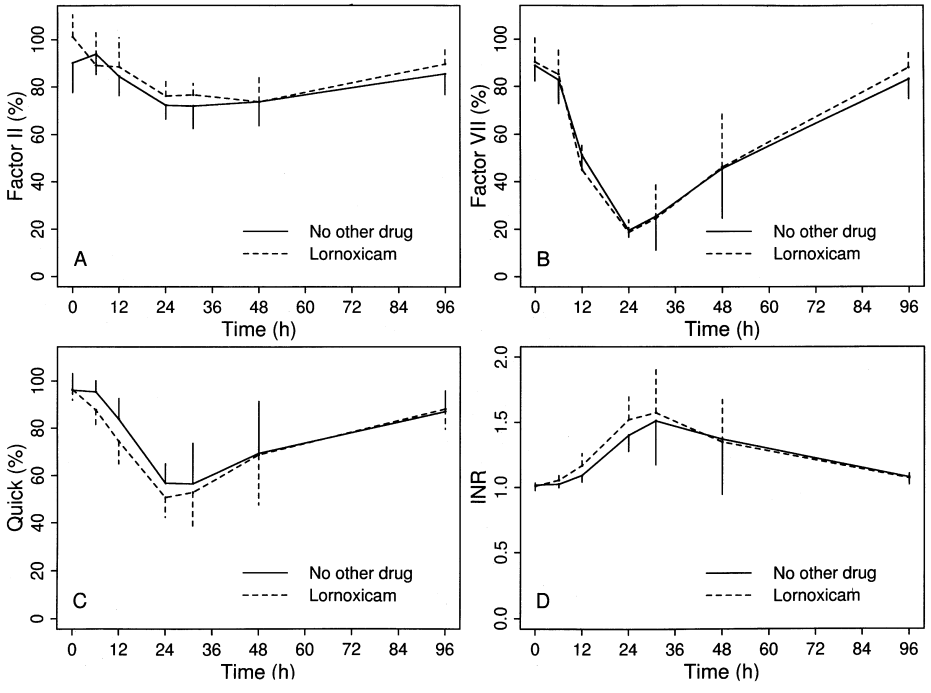

Fig. 1 Acenocoumarol pharmacodynamics: mean values and 95% CI (*vertical lines*) for factor II (A) and VII activities (B), prothrombin time (Quick; C) and INR (D) against time after administration of 10 mg racemic acenocoumarol without (*solid lines*) and with (*dashed lines*) lornoxicam co-administration

Table 1 Model-derived pharmacokinetic/pharmacodynamic parameters of acenocoumarol. *CL* clearance, *V* volume of distribution, k_a absorption rate constant, t_{lag} absorption lag time; $\sigma_{PK,prop}$ proportional part of residual intraindividual pharmacokinetic variability (expressed as coefficient of variation), $\sigma_{PK,add}$ additive part of residual intraindividual pharmacokinetic variability, K_{VII} elimination rate of factor VII, $C_{50,VII}$ and $C_{50,II}$ concentration causing half-maximal effect for factor VII and II, γ_{VII} and γ_{II} sigmodicity parameter for factor II and VII, $\sigma_{VII,add}$ and $\sigma_{II,add}$ residual intraindividual pharmacodynamic variability for factor II and VII

	Population mean estimate with (SEM)		Interindividual variability estimate with (SEM) (%)	
	(*R*)-isomer	(*S*)-isomer	(*R*)-isomer	(*S*)-isomer
CI_{NO} (l/h^{-1})	1.61 (0.20)	11.7 (1.3)	49 (35)	33 (24)
F_{Cl}[b] [95% CI][c]	1 [0.85, 1.07]	1 [0.73, 1.12]		
V (l)	19.7 (1.0)	38.2 (2.2)		
F_P[d] [95% CI][c]	1 [0.96, 1.20]	1.24 (0.12) [1.05, 1.46]		
k_a (h^{-1})	0.87 (0.13)		61 (28)	
t_{lag} (h)	0.16 (0.07)			
$\sigma_{PK,prop}$ (%)	31 (3)	37 (2)		
$\sigma_{PK,add}$ ($\mu g \cdot l^{-1}$)	8.8 (0.6)	5.4 (0.5)		
K_{VII} (h^{-1})	0.0538 (0.003)			
$C_{50,VII,NO}$ ($\mu g \cdot l^{-1}$)	21.2 (3.9)		29 (24)%	
$F_{C50,VII}$ (95% CI)[c]	1 (0.81, 1.14)			
γ_{VII}	3.85 (1.69)			
$\sigma_{VII,add}$ (%)	12.9 (1.1)			
$C_{50,II,NO}$ ($\mu g \cdot l^{-1}$)	29.1 (13.1)		86 (62)%	
$F_{C50,VII}$[c] [95% CI][c]	1 [0.68, 2.47]			
γ_{II}	2.38 (0.8)			
$\sigma_{VII,add}$ (%)	0.10 (0.01)			

[a] The estimates of interindividual variability are expressed as coefficients of variation
[b] No lornoxicam co-administration: $CL = CL_{NO}$ with lornoxicam co-administration $CL = CL_{NO}F_{CL}$
[c] 95% Confidence interval based on a likelihood ratio profile
[d] F_F Relative bioavailability in the case of lornoxicam co-administration as compared to sessions without lornoxicam
[e] No lornoxicam co-administration: $C_{50} = C_{50,NO}$, with lornoxicam co-administration $C_{50} = C_{50,NO}\ F_{C50}$

Simulations

In order to translate the 95% CI for an effect of lornoxicam co-administration on the different pharmacokinetic/pharmacodynamic parameters into clinically meaningful information, the final model was used to estimate the corresponding changes in factor VII activity. The model predicts that a patient taking 3 mg acenocoumarol daily under steady-state conditions will have a factor VII activity of 26%. If clearance were to change to the lower or upper limit of its 95% CI, the factor VII activity would change to 14% and 31%, respectively. The corresponding numbers for bioavailability were 28% and 18% and for C_{50} 32% and 17%, respectively. Thus, factor VII activity in a person in steady-state at 26% would remain in the range of 14–32%, if lornoxicam was administered concomitantly. Because at steady-state all clotting factors are decreased similarly, these predictions should also hold true for INR. Correspondingly, a person at steady-state on an INR of 2.5 would remain within the range of 2.1 and 4.1.

Discussion

Based on this study, one can exclude the possibility that lornoxicam causes a decrease of (*R*)-acenocoumarol clearance of more than 15%, an increase of (*R*)-acenocoumarol bioavailability of more than 20% or a decrease in (*S*)-acenocoumarol clearance of more than 27%. The bioavailability of (*S*)-acencoumarol was increased by 24%. However, since the concentration of (*S*)-acenocoumarol in the normal dose range is too low to contribute substantially to acenoucoumarol's anticoagulant effect [8], this increase does not have any clinical relevance.

The lornoxicam-induced increase in bioavailability of (*S*)-acenocoumarol could be explained by a decrease in the liver first-pass elimination by inhibition of (*S*)-acenocoumarol metabolism. Lornoxicam and acenocoumarol are both metabolized by the cytochrome P450 CYP2C9 [2, 9]. In contrast to the presented results, a previous drug interaction study between acenocoumarol and piroxicam, another oxicam type of NSAID, showed that piroxicam increases the AUC of (*R*)-acenocoumarol by 47%, whereas for the (*S*)-isomer the increase was less pronounced (15%) and statistically not significant [5]. These observations suggest that different mechanisms are responsible for the drug interactions of different oxicam NSAIDs with the stereoisomers of acenocoumarol.

In conclusion, co-administration of lornoxicam in high therapeutic doses did not alter the pharmacokinetics of the clinically relevant (*R*)-isomer of acenocoumarol. Only a small effect was found for the clinically not relevant (*S*)-isomer. Hence, lornoxicam should not exhibit any clinically relevant influence on acenocoumarol's anticoagulant effect.

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