The effect of meloxicam on the pharmacokinetics of β -acetyl-digoxin

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The influence of multiple-dose administration of meloxicam on the pharmacokinetics of oral β -acetyl-digoxin was studied in 12 healthy male volunteers in a randomized double-blind two-way crossover study. The primary endpoint, $C_{\min ss}$, was within the accepted range for bioequivalence, as were $C_{\max ss}$ and AUC_{ss} . The 90% confidence interval and the point estimator of 98.7 for $C_{\min ss}$ were within the equivalence range of 0.8–1.25. MRT and $t_{\max}$ were also unchanged, while the elimination rate constant was decreased slightly by 12%, which is of no therapeutic relevance. It is concluded that co-treatment with meloxicam has no effect on the pharmacokinetics of oral digoxin.

Keywords meloxicam β -acetyl-digoxin pharmacokinetic interaction

Introduction

Digoxin is often used in the treatment of cardiac disease in rheumatic patients concomitantly receiving non-steroidal anti-inflammatory drugs (NSAIDs). Some NSAIDs are known to influence digoxin pharmacokinetics [1, 2]. More recently developed NSAIDs like nimesulide or lornoxicam failed to show a major interaction with digoxin [3, 4], the latter produced a modest reduction in digoxin clearance [4].

The objective of this study was to determine any pharmacokinetic interaction between β -acetyl-digoxin and the cyclooxygenase-2 inhibitor, meloxicam, with the possible consequence of increased digoxin toxicity. β -acetyl-digoxin, which is metabolized to digoxin, was chosen for this study in preference to digoxin because of its high and constant absorption rate. Meloxicam has been shown to be effective in controlled clinical trials in a dosage of 15 mg once daily, therefore this dose was selected for the study.

Methods

Subjects

Twelve healthy male volunteers (mean age 34 years, mean weight 77 kg) were enrolled. The study was performed according to the Declaration of Helsinki and Ethics Committee approval obtained. The study was of a randomized, double-blind, crossover design, with two

treatment phases of 8 days each and a washout period of 14 days. Either meloxicam 15 mg or placebo was administered once daily on days 1–8 of treatment. β -acetyl-digoxin was administered on days 1–7, in divided doses of 0.4 mg, 0.3 mg and 0.3 mg on day 1; 0.2 mg, 0.2 mg and 0.1 mg on day 2 and 0.3 mg once-daily on days 3–7. The drugs were administered within 10 min after meals. The dosing interval on days 1 and 2 was 8 h.

Blood samples for determination of plasma digoxin concentration were taken on day 7 at 0, 15, 30, 45, 60, 75 and 90 min and 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 h after drug administration. Trough concentrations of plasma digoxin were also determined on days 1–6 of treatment. Blood samples were drawn with the volunteer in the supine position. Normal daily activities and light sports were allowed during the study. Concomitant medication was forbidden.

Analytical method

Plasma and quality control samples were analysed in duplicate using a validated assay. Samples were prepared according to Enzymun-Test Kit Digoxin (Boehringer Mannheim). Cross-reactivity to dihydrodigoxin was 22%.

The lower limit of quantification was 0.3 mg ml^{-1} . The within day precision was below 9.8%, the between day precision was below 15.1%.

Figure 1 Time profile of geometric means ($\pm$ s.e. mean) of serum β -acetyl-digoxin concentration following multiple administration of β -acetyl-digoxin alone (■) and in combination with meloxicam (□).

Data analysis

The values for area under the plasma concentration time curve (AUC_{ss}), $t_{1/2,z}$ elimination rate constant (λ_z) and mean residence time (MRT) were calculated by non-compartmental methods using the TopFit programme [5]. AUC_{ss} was calculated using the linear trapezoidal method between the timepoints 144 h and 168 h. To calculate λ and its corresponding $t_{1/2}$, plasma concentrations for at least the last three time points were used for the log-linear regression procedure.

Statistical analysis

The results for the log transformed parameters C_{maxss} , C_{minss} , AUC_{ss} , $t_{1/2,z}$ and MRT are presented as the geometric mean (gMean) and geometric coefficient of variation (gCV [%]) [6, 7]. Geometric means were used because the data were log normally distributed

[8]. t_{maxss} is presented as the median with minimum and maximum values.

Comparison of mean pharmacokinetic values was made by a three factor analysis of variance (ANOVA). P values of <0.05 were considered to be statistically significant.

A multiplicative model was used for the construction of the shortest 90%-confidence interval for the ratios between the test and reference averages. Due to the narrow therapeutic window of β -acetyl-digoxin, the acceptance range of 0.8–1.25 for equivalence between the two treatments was chosen. The sample size of 12 was chosen to detect a minimum difference of $0.16 \mu\text{g l}^{-1}$ in C_{minss} between the two treatments [9].

Results

The individual plasma digoxin concentration-time curves were similar for the two treatment groups (Figure 1). The 90% confidence interval and the point estimator of 98.4 for the primary endpoint, C_{minss} , were within the equivalence range of 0.8–1.25 (Table 1). The difference in the gMean of C_{minss} between the two treatment groups was $0.03 \mu\text{g l}^{-1}$, well below the predefined clinically relevant value of $0.16 \mu\text{g l}^{-1}$ [9].

No significant differences were observed for the secondary pharmacokinetic parameters (Table 1). The largest difference of 12% was observed for $t_{1/2}$. An analysis of variance showed no interaction as an effect of treatment or period.

Discussion

The general recommendation for concomitant treatment of NSAIDs with digoxin is that frequent checks of digoxin plasma concentration and plasma creatinine should be performed in patients with a potential reduction in renal function [10]. This is due to the fact that the inhibition of renal cyclooxygenase by NSAIDs

Table 1 gMean, % gCV and mean of pharmacokinetic parameters for digoxin in both treatment groups

Parameter	Treatment	gMean	gCV (%)	Mean	90% confidence intervals
C_{minss} ($\mu\text{g l}^{-1}$)	placebo	0.71	21.3	0.73	88.2–114.6
	meloxicam	0.74	31.2	0.78	
$t_{1/2}$ (h)	placebo	55.5	32.3	58.1	72.0–106.5
	meloxicam	48.6	26.9	50.3	
AUC_{ss} ($\mu\text{g l}^{-1} \text{ h}$)	placebo	20.8	15.2	21.0	97.1–109.1
	meloxicam	21.4	13.4	21.6	
C_{maxss} ($\mu\text{g l}^{-1}$)	placebo	1.97	12.8	1.98	93.3–115.1
	meloxicam	2.04	19.6	2.08	
t_{maxss} (h)	placebo	1.3*	(0.8, 3.0)*	–	–
	meloxicam	1.5*	(0.8, 0.3)*	–	
MRT (h)	placebo	66.6	33.1	69.8	74.0–108.6
	meloxicam	59.7	26.9	61.7	

* t_{max} values are given as medians including min and max

may lead to impaired renal perfusion. For the selective cyclooxygenase-2 inhibitor, meloxicam, the risk for accumulation of digoxin seems low. The 90% confidence limits of C_{minss} , AUC_{ss} , C_{maxss} and t_{max} fell within the generally accepted equivalence interval; $t_{1/2}$ and MRT were shortened in the meloxicam-treated group. This would, if anything, lead to an increased elimination rather than to an accumulation. Considering all the pharmacokinetic parameters, it can be assumed that meloxicam does not affect the absorption, distribution and elimination of digoxin.

In summary, no pharmacokinetic interaction between meloxicam and digoxin with respect to predose digoxin plasma concentration was observed and thus concomitant administration of meloxicam would not be expected to result in an increase in digoxin toxicity.

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