Pharmacokinetic and pharmacodynamic drug interactions between digoxin and macrogol 4000, a laxative polymer, in healthy volunteers

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Aims The aim of this study was to examine the bioequivalence between a single oral dose of digoxin administered alone and with a coadministration of macrogol 4000 (a laxative polymer) in 18 healthy volunteers.

Methods This was an open, randomised, two-way cross-over study, with a single dose oral administration of 0.5 mg digoxin administered alone or in combination with macrogol 4000, 20 g day^{-1} during 8 days. Pharmacokinetics of digoxin, heart rate and PR ECG interval at rest were assessed.

Results Macrogol 4000 coadministration was associated with a 30% decrease of digoxin AUC and a 40% decrease in its C_{max} ($P<0.05$). Digoxin t_{max} and $t_{1/2,z}$ were not significantly altered. Heart rate and PR interval did not differ during the two therapeutic sequences, digoxin alone and digoxin in combination.

Conclusions Macrogol 4000 coadministration interacts with single-dose digoxin pharmacokinetics. This is most likely due to a reduction of the intestinal absorption of digoxin. However, there was no consequence of this interaction on heart rate and AV conduction.

Keywords: digoxin, drug interaction, healthy volunteers, macrogol 4000, pharmacodynamics, pharmacokinetics

Introduction

Macrogol 4000 (Forlax®), a laxative polymer, has been registered for the symptomatic treatment of functional constipation at the dosage of 10–20 g daily. Macrogol 4000 is not absorbed; it increases the osmotic pressure in the gut. These osmotic effects could induce modifications in intestinal resorption of drugs.

Digoxin is a cardiac glycoside commonly used in the treatment of congestive heart failure and atrial dysrhythmias, mainly eliminated by kidneys as unchanged drug with a long elimination half-life of approximately 36 h (range: 30–40 h) [1]. The intestinal absorption of digoxin is incomplete, dependent upon formulation characteristics and highly variable between individuals [2]. The therapeutic range of plasma concentrations of digoxin is 0.8 ng ml^{-1} to 2.0 ng ml^{-1} [2–5].

Since an alteration in absorption of concomitantly administered drugs is theoretically possible with macrogol 4000, and because digoxin is a widely prescribed drug with a narrow therapeutic index, the objective of the study was to assess a possible influence of macrogol 4000 on the pharmacokinetic profile of digoxin.

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Methods

Study design

Eighteen healthy volunteers (10 males and 8 females) aged 22 years (19–36) were included in a double-blind, 2-period cross-over trial after giving their written informed consent to participate. Local Ethics Committee approval for the study was obtained. The two therapeutic sequences were performed in a randomised order and were separated by 11–25 days of washout. During one period, subjects received a single oral dose of 0.5 mg digoxin (2 tablets of Digoxin Nativelle®). During the other period, they received the same dose of digoxin coadministered with 20 g macrogol 4000, preceded (4 days) and followed (3 days) by single administrations of macrogol 4000, at the dosage of 20 g day^{-1}.

Blood samples for digoxin level determination were taken before digoxin administration ($t0$), 15, 30, 45, 60, 90, 120, 150, 180 min and 4, 6, 9, 12, 16, 24, 32, 48,

58, 72, 82, 96, and 120 h after drug administration. The day of digoxin administration, 12-lead ECG were recorded at the same evaluation times as plasma samples for determination of heart rate (RR interval) and PR interval at rest. Subjects were hospitalized during the first 24 h following oral administration of digoxin.

Drug assay

Plasma digoxin concentrations were measured with the use of a modified enzyme multiplied digoxin immunoassay. The detection and quantification limits were 0.02 and 0.08 ng ml^{-1}, respectively [6].

Pharmacokinetic analysis

Model independent methods were used to estimate the pharmacokinetic parameters of digoxin, using WinNonlin software, version 1.5 (Scientific Consulting Inc, USA). The following parameters were calculated for each period: time of plasma peak appearance (t_{max}, h), maximum plasma concentration (C_{max}, ng ml^{-1}), area under plasma concentration time curve calculated from time 0 to the last sampling time (t) and from 0 to infinity (AUC(0,t) and AUC(0, ∞) ng ml^{-1} h) by the linear trapezoidal method, and apparent elimination half-life ($t_{1/2,z}$, h).

Pharmacodynamic parameters

Heart rate and PR interval at rest were calculated, for each ECG recording at 50 mm s^{-1}, from three consecutive QRS intervals, using a digitizing table (SummaSketch Professional MM II 1812, Summagraphics, Seymour, CT USA).

Statistical analysis

The pharmacokinetic parameters of digoxin with and without coadministration of macrogol 4000 were compared by using an analysis of variance (ANOVA) for a two-period crossover design and a Dunnett-test (at the 0.05 significance level). Two one-sided tests bioequivalence decision rule for log-transformed data was applied to compare the magnitude of the differences observed in C_{max} and AUC. The accepted bioequivalence limits of the 90% confidence interval of the geometric mean ratio were 0.80–1.25. Experimental t_{max} were compared by using the sign test. The maximal effects on heart rate and AV conduction observed under treatment were compared using a paired Student's t-test. Differences were considered to be statistically significant at $P<0.05$.

Results

Pharmacokinetics

Figure 1 shows the time course profile of mean plasma concentrations of digoxin obtained with and without macrogol 4000. The pharmacokinetic parameters are summarized in Table 1.

The coadministration of macrogol 4000 resulted in a 40% decrease ($P<0.05$) in mean C_{max} values (2.5 ± 0.7 and 1.4 ± 0.4 ng ml^{-1}) with a 90% confidence interval of the ratio of 0.49–0.70, outside the bioequivalence limits.

Similarly, the AUC(0,t) and AUC(0, ∞) mean values decreased by 30% ($P<0.05$) with a 90% confidence interval of the ratio of, respectively, 0.61–0.80 and 0.62–0.79, both outside of the bioequivalence limits.

However, the t_{max} values were unaffected by macrogol 4000 with respective mean values of 1.5[0.8–2.3] h (alone) and 1.5[1.0–2.0] h (combination) (NS). The digoxin elimination half-life was not significantly different in the absence and the presence of macrogol 4000 (33.8 ± 8.8 h and 30.7 ± 10.2 h, respectively).

Pharmacodynamic parameters

No modification of AV conduction under treatment was observed over the 24 h hospitalization between the two therapeutic sequences. We observed a bradycardic effect during the first 6 h following the digoxin administration, with a maximal decrease of 18.9 ± 8.1% alone and 16.9 ± 8.6% in combination (NS).

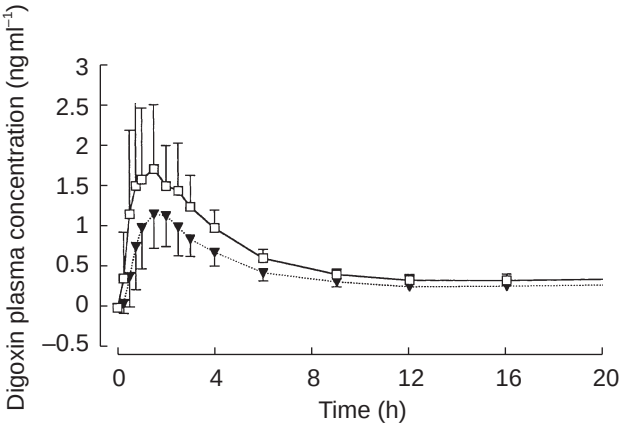

Figure 1 Digoxin plasma concentration over time. Mean values $\pm$ s.d. ($n=18$). □ digoxin alone, ▼ digoxin + macrogol 4000.

Table 1 Digoxin pharmacokinetic parameters (mean ± s.d.).

Parameters	*Alone*	*In combination*	*Ratio % (90% CI)*	P
C_{max} (ng ml^{-1})	2.5 ± 0.7	1.4 ± 0.4	58.6 [49 to 70]	< 0.05
t_{max} (h)†	1.5 (0.8–2.3)	1.5 (1.0–2.0)		NS
$t_{1/2,z}$ (h)	33.8 ± 8.8	30.7 ± 10.2		NS
AUC $(0,t)$ (ng ml^{-1} h)	23.2 ± 5.2	15.8 ± 3.9	70.0 [61 to 80]	< 0.05
AUC $(0,\infty)$ (ng ml^{-1} h)	28.3 ± 6.3	19.9 ± 4.8	70.3 [62 to 79]	< 0.05

†Median (95% CI).

Discussion

Pharmacokinetics

The digoxin pharmacokinetic parameters observed in our study are in accordance with those found in the literature in healthy volunteers with comparable doses [7, 8]. We observed a statistically significant difference between the two therapeutic sequences for the C_{max} and AUC values, without any difference for t_{max}, suggesting that macrogol 4000 coadministration interacts with single-dose digoxin pharmacokinetics by reducing the absorption of the drug. These data are in accordance with the results of Padoin *et al.* who previously showed a decreased amoxicillin absorption with a coadministration of saline-macrogol in healthy volunteers [9].

Macrogol 4000 is not absorbed and has a local osmotic intestinal action. Thus, the decreased absorption rate of digoxin observed in our study could be explained by a decreased concentration at the absorption site, resulting from an increased volume of liquid in the intestinal lumen caused by macrogol 4000, or by local changes in pH or electrolytes. However, no effect on stool hydratation, stool electrolytes output and pH has been found in healthy volunteers treated by low doses of macrogol 4000 [10]. Another hypothesis could be a direct physicochemical interaction between macrogol 4000 and digoxin. In fact, it is well known that such an interaction is observed with liquid antacids, which coat digoxin tablets and thus interfere with their dissolution [3], with kaolin and pectin which adsorb digoxin [2] and with cholestyramine known to bind cardiac glycosides [3].

12-lead ECG

Digoxin is well known to have a depressor effect on the sinusal function and the AV nodal conduction at rest [1, 11]. In this single-dose digoxin study, we observed a bradycardia during the first hours after the digoxin administration, with no consequence of macrogol 4000 coadministration. However, as there was no placebo period, this mild bradycardia cannot be clearly related to digoxin administration. No significant changes in AV conduction were observed in the subjects. Similar results on PR interval were observed recently by Chaufour *et al.* in healthy volunteers, at the dose of 0.25 mg of digoxin per day during 7 days [12]. These results could be explained by the low dose of digoxin tested, which is below the loading dose required to achieve a full therapeutic effect.

Clinical implications

Although there is considerable debate on the plasma concentration-effect relationships during digoxin acute and chronic treatment [1, 5], a decrease in digoxin digestive absorption could result in loss of therapeutic effect. We did not observe any reduction in the pharmacodynamic response following a single dose administration of 0.5 mg digoxin in normal subjects. The pharmacokinetic interaction observed in this study has to be evaluated in patients during chronic digoxin treatment in order to assess the therapeutic consequences of this drug–drug interaction.

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