

Do Therapeutic Doses of Acarbose Alter the Pharmacokinetics of Digoxin?

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Abstract

Background: Acarbose has become an important adjuvant therapy for diabetic patients. Many of these patients are also treated with digoxin for congestive heart failure or chronic atrial fibrillation.

Objective: To evaluate a possible drug interaction between acarbose and digoxin.

Methods: An open-label, analyst-blind, randomized, crossover, two-period study was conducted in 11 healthy subjects. In period I, each subject received one single oral dose of 0.75 mg digoxin. In period II, they were given acarbose tablets, 50 mg 3 times a day for 12 days. On day 8, one hour after acarbose administration, a single oral dose of 0.75 mg digoxin was administered. The study periods were separated by a 3 week washout interval. Serum digoxin levels, over time, in the two periods were compared by standard techniques.

Results: There were no differences in the pharmacokinetic parameters of digoxin in the two periods, apart from a significant increase in the mean maximum serum concentration (C_{max}) when digoxin was given with acarbose (5.97 compared to 4.67 g/L, $P = 0.02$). Simulated steady-state peak levels of digoxin ($C_{max,ss}$) achieved with a daily dose of 0.25 mg digoxin, in the presence and absence of acarbose, were 2.89 and 2.40 g/L respectively ($P = 0.05$). Simulated steady-state trough ($C_{min,ss}$) and average ($C_{ave,ss}$) concentrations were similar and within the therapeutic window.

Conclusion: There was no significant pharmacokinetic interaction between digoxin and acarbose at current therapeutic doses in the healthy volunteers. This interaction should be further studied with higher doses of acarbose and at steady-state conditions.

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Acarbose is an oral hypoglycemic agent that acts by reversible competitive inhibition of alpha-glucosidase in the intestinal mucosa [1]. The main action of acarbose is to reduce the post-prandial monosaccharide absorption and hyperglycemia [2]. Acarbose is only minimally absorbed from the gut and no systemic adverse effects have been demonstrated after long-term administration. The drug allows undigested carbohydrates to pass into the large bowel where they are fermented, causing bloating and diarrhea. These symptoms occur in 30–60% of patients, decrease with time and are dose-dependent [2].

Drug interactions with acarbose are uncommon, the most frequent being augmentation of the hypoglycemic effect of oral hypoglycemic drugs. Acarbose has not been found to interact with nifedipine, propranolol or ranitidine [Precose package insert, Bayer, West Haven, CT, USA, 1996], and did not change the pharmacokinetic profile of glibenclamide in patients with non-insulin-

dependent diabetes mellitus [3]. Acarbose has been shown to reduce the bioavailability of metformin in healthy subjects [4]. It may increase INR values in patients treated with warfarin, possibly due to the increased absorption of warfarin [5].

While an association between acarbose and low plasma levels of digoxin was suspected in four case reports [6–8], two studies in small groups of volunteers showed conflicting results [9,10]. Accordingly, we assessed the effect of co-administration of acarbose on digoxin bioavailability in normal volunteers.

Subjects and Methods

Subjects

Eleven healthy volunteers (6 women and 5 men) entered and completed the study. Their mean age was 25.5 (range 24–29 years) and mean weight 61.7 kg (range 45–75). The subjects were ascertained to be healthy by medical history, physical examination and laboratory screening. All subjects had a normal electrocardiogram. None of the subjects had received any continuous medication. Written informed consent was obtained from each subject before participation in the study, and the protocol was approved by the Helsinki Ethics Committee of the Rabin Medical Center.

Drugs

Digoxin, 0.25 mg tablets (Teva Pharmaceutical Industries Ltd., Israel) and acarbose, 50 mg tablets (Bayer, Agis Industries Ltd., Israel) were used in the study.

Study design

This was an open-label, analyst-blind, randomized, crossover, two-period study. In period I, each subject received one single oral dose of 0.75 mg digoxin (3 tablets of 0.25 mg) with 200 ml of water. In period II, the subjects were given acarbose tablets, 50 mg 3 times a day with 20 ml water for 12 days. On day 8, one hour after acarbose administration, a single oral dose of 0.75 mg digoxin (3 tablets of 0.25 mg) was administered with 200 ml of water. The study periods were separated by a 3 week washout interval. Subjects were instructed to fast for 10 hours before and 5 hours after each digoxin administration. Venous blood samples were collected before digoxin dosing and after 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120 and 168 hours. Serum was separated and stored at -20°C until assayed. Serum digoxin concentrations were measured with a fluorescence polarization immunoassay (TDx, Abbott Laboratories,

USA). All the samples from a given subject were batched and analyzed at the same time. The detection limit was 0.2 ng/ml. The inter-assay and intra-assay coefficients of variation at 2 ng/ml were 5%, respectively. Compliance to acarbose treatment was assessed by means of a form on which the subjects noted the exact time of acarbose administration and by a pill count performed on the day of digoxin administration and on the last day of digoxin serum sampling.

Pharmacokinetics and statistical analysis

Digoxin pharmacokinetic parameters were calculated using both non-compartmental and compartmental analyses. The peak digoxin concentrations (C_{max}) and the time to attain C_{max} (t_{max}) were derived directly from the experimental data. Area under the serum concentration time curve (AUC) was determined by the linear trapezoidal rule and extrapolated to infinity, with the extrapolated area accounting for less than 15% of the total AUC. The elimination rate constant (k_e) was measured by non-linear regression of the final data points (24 hours to the last quantifiable concentration after digoxin intake). Elimination half-life value ($t_{1/2 \text{ elimination}}$) was calculated as $\ln 2/k_e$. Apparent whole-body clearance was obtained with the equation: $CL/F = \text{Dose}/AUC_0$ where F is the extent of oral absorption. Apparent volume of distribution (V_d) was calculated by the formula $V_d/F = CL/k_e$. Mean residence time (MRT) was determined as $AUMC/AUC$ in which AUMC is the total area under the first moment curve.

To simulate the digoxin steady-state conditions, a two-compartment open model with first-order absorption and elimination and an absorption lag time (t_{lag}) was selected [11]. The simulation was based on a dosage regimen comprising a loading dose of 0.75 mg digoxin followed by a maintenance dose of 0.25 mg once a day for 15 days. Trough ($C_{min, ss}$) and peak ($C_{max, ss}$) serum digoxin concentrations and times to reach $C_{max, ss}$ ($t_{max, ss}$) were obtained from the simulated serum concentration-time curves. The average digoxin level ($C_{ave, ss}$) during steady-state dosing was calculated by the equation $C_{ave, ss} = \text{dose}/(CL \cdot \tau)$ where τ is the dosing interval. The calculation of the pharmacokinetic parameters for each individual subject was performed with WinNonLin software (Professional edition, version 3.0, Pharsight Corp. Mountain View, CA, USA).

Sample size ($n = 10$) was determined (SigmaStat Statistical Software) based on an expected difference in serum digoxin levels of at least 20%, a standard deviation of serum digoxin levels of 20%, $\alpha = 0.05$ and $\beta = 0.8$.

Results are reported as mean values \pm SD or, in the case of observed t_{max} , as median and range. Differences between the pharmacokinetic parameters of digoxin before and during acarbose administration were tested by the two-tailed paired Student t -test. The Wilcoxon test was used for analysis of t_{max} . An α value of 0.05 was accepted as significant.

Results

Treatments were well tolerated. The most common adverse effect was flatulence, which occurred in most of the subjects. Compliance to acarbose treatment was 97.5%.

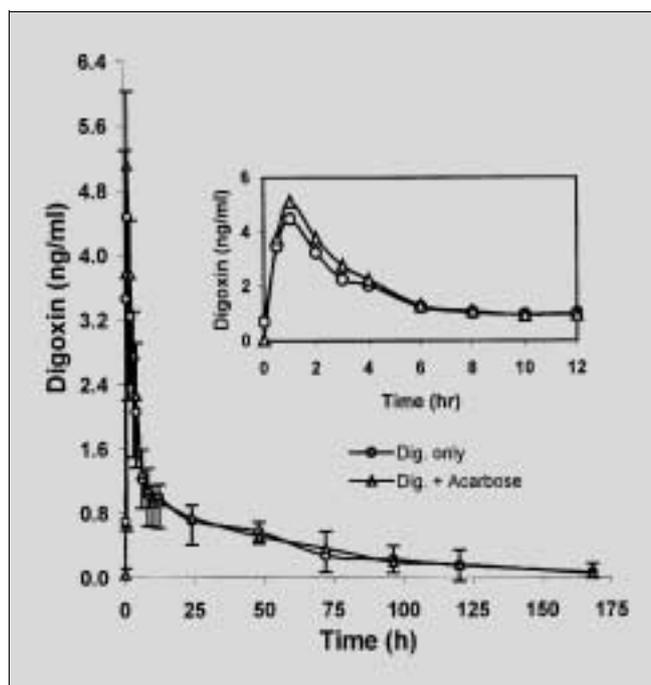


Figure 1. Serum digoxin concentrations (mean \pm SD) in 11 healthy volunteers after a single oral dose of 0.75 mg digoxin with or without acarbose. The insert focuses on the digoxin serum levels for the first 12 hours.

The mean serum digoxin concentration-time profiles with or without concomitant acarbose were very similar [Figure 1]. The mean pharmacokinetic parameters, determined by non-compartmental analysis, are presented in Table 1. In both study periods, digoxin was rapidly absorbed and peak digoxin concentrations were reached at a median time of 1.00 hour after administration. Serum digoxin concentrations decreased in an apparently bi-exponential fashion. The mean apparent volume of distribution was 9.1 L/kg, the elimination half-life was 43.2 hours, the whole-body clearance was 0.16 L/hr/kg, and the mean residence time was 62.1 hours. Co-administration of acarbose did not significantly change these kinetic parameter values of digoxin. The mean ratio for AUC was close to unity (1.02), indicating that on average the extent of

Table 1. Pharmacokinetic parameters of digoxin when administered as a single dose of 0.75 mg to 11 healthy volunteers with and without acarbose: non-compartmental analysis

Pharmacokinetic parameter	Digoxin only	Digoxin + acarbose	Ratio*	P
AUC ₀ (g hr ⁻¹ L ⁻¹)	86.2 (37.1)	87.7 (31.9)	1.02	0.88
Observed C _{max} (g/L)	4.64 (0.95)	5.97 (1.47)	1.29	0.02
Observed t _{max} (hr)*	1.0 (0.5–2.0)	1.0 (0.5–2.0)	1.00	0.79
V _d /F (L/kg)	9.1 (3.3)	9.7 (3.5)	1.06	0.70
t _{1/2 elimination} (hr)	43.2 (20.1)	44.2 (15.8)	1.02	0.87
CL/F (L/hr/kg)	0.16 (0.06)	0.16 (0.08)	1.00	0.91
MRT (hr)	62.1 (28.7)	58.4 (22.6)	0.94	0.70

Data are mean values (SD)

Ratio = mean digoxin + acarbose / mean digoxin only.

* Median; range is given in parentheses.

Table 2. Pharmacokinetic parameters of digoxin when administered as a single dose of 0.75 mg to 11 healthy volunteers with and without acarbose: compartmental analysis

Pharmacokinetic parameter	Digoxin only	Digoxin + acarbose	Ratio*	P
AUC ₀ (g · hr · L ⁻¹)	78.5 (35.8)	77.9 (33.9)	0.99	0.94
C _{max} (g/L)	4.90 (1.22)	6.55 (2.09)	1.34	0.06
t _{max} (hr)	0.90 (0.36)	0.87 (0.53)	0.97	0.88
t _{1/2} absorption(hr)	0.25 (0.27)	0.18 (0.21)	0.72	0.58
t _{lag} (hr)	0.36 (0.18)	0.37 (0.27)	1.03	0.87
t _{1/2} distribution(hr)	1.17 (0.43)	1.11 (0.69)	0.95	0.82
V _c (L/kg)	1.9 (0.9)	1.5 (0.6)	0.79	0.12
V _d (L/kg)	9.8 (2.9)	11.3 (4.3)	1.15	0.32
t _{1/2} elimination (hr)	41.8 (16.5)	44.2 (12.6)	1.06	0.55
Cl/F (L/hr/kg)	0.18 (0.07)	0.21 (0.13)	1.17	0.42
K ₁₂ (L/hr)	0.46 (0.17)	0.48 (0.30)	1.04	0.80
K ₂₁ (L/hr)	0.12 (0.04)	0.12 (0.07)	1.00	0.99
r **	0.996 (0.004)	0.993 (0.005)		

Data are mean values (SD)

* Mean digoxin + acarbose / mean digoxin only.

** Correlation coefficient between predicted and observed serum digoxin concentrations.

Table 3. Pharmacokinetic parameters of digoxin at steady state when administered as a loading dose of 0.75 mg followed by a maintenance dose of 0.25 mg once a day to 11 healthy volunteers with and without acarbose: simulation analysis

Pharmacokinetic parameter	Digoxin only	Digoxin + acarbose	Ratio*	P
C _{min, ss} (g/L)	0.78 (0.41)	0.73 (0.44)	0.93	0.63
C _{max, ss} (g/L)	2.40 (0.72)	2.89 (0.72)	1.20	0.05
t _{max, ss} (hr)	0.98 (0.35)	0.88 (0.53)	0.90	0.65
C _{average, ss} (g/L)	1.09 (0.50)	1.08 (0.47)	0.99	0.94

Data are mean values (SD)

* Mean digoxin + acarbose / mean digoxin only.

digoxin absorption did not change significantly when acarbose was co-administered with digoxin.

The pharmacokinetic parameter values determined for digoxin by compartmental analysis are shown in Table 2. There was very close agreement between predicted and measured serum digoxin levels for each subject, whether in the presence or absence of acarbose ($r = 0.993$ and 0.996 , respectively). Again, there were no substantial differences between the pharmacokinetic parameters of digoxin when given alone or with acarbose.

Simulated steady-state trough (C_{min, ss}) and average (C_{ave, ss}) concentrations achieved with a daily dose of 0.25 mg digoxin in the presence and absence of acarbose were similar (0.73 and 1.08 g/L compared to 0.78 and 1.09 g/L, respectively) [Table 3]. There was only one statistically significant difference between the results obtained during the two periods: Acarbose, when given concomitantly with digoxin, increased the observed C_{max} by 29% (from 4.64 to 5.97 g/L) [Table 1] and the estimated C_{max, ss} by 20% (from 2.40 to 2.89 g/L) [Table 3].

Discussion

Acting within the gut lumen, acarbose could reduce the bioavailability of digoxin by three different mechanisms. First, by delaying digestion of sucrose and starch, acarbose could cause a disturbance of gastrointestinal transit as well as loose stools. It is possible that this increase in intestinal motility could lead to a decrease in digoxin absorption, as has been shown with metoclopramide [6]. Second, acarbose (being an oligosaccharide, MW 645 daltons) may adhere to digoxin molecules, inhibiting absorption of the bound molecules [6]. Third, considerable metabolism of digoxin within the gastrointestinal tract may occur through reduction of the lactone double bond by intestinal bacteria. This interaction is probably of no significance since it has been reported that digoxin-metabolizing bacteria were not altered by one year of acarbose treatment [12].

Although acarbose is widely used, only four case reports have been published in which sub-therapeutic levels of digoxin were measured when acarbose was added to patients on chronic treatment with digoxin. Discontinuation of acarbose resulted in an increase in the plasma levels of digoxin to within the therapeutic range [6–8]. In one case report, re-challenge with acarbose again induced a decrease in digoxin levels [7]. Recently, Miura et al. [10] published a control study on seven healthy subjects, in which acarbose given with digoxin significantly decreased the mean AUC₀₋₄₈ and the C_{max} by 42.6% and 38.7%, respectively. The t_{max} increased by 11.8%, indicating an impairment of absorption of digoxin by acarbose. However, the doses of acarbose used in their study (300 or 600 mg/day) were beyond the therapeutic doses of this drug. At such a high dose most subjects will suffer from loose stools, which may affect the gastrointestinal transit time of any concomitant drug. Our results show no significant effect of acarbose on AUC or on parameters describing the absorption phase as well as the distribution and the elimination phases. Our results are consistent with those reported by Hillebrand et al. [9], showing no change in serum digoxin levels in six healthy volunteers after one week of acarbose treatment. Moreover, the effects of digoxin on blood pressure, heart rate and ECG were not influenced by acarbose, nor were the metabolic effects of acarbose (lowering of post-prandial blood glucose and serum insulin) altered by digoxin.

Diabetic patients have autonomic neuropathy that affects gastrointestinal motility; this may affect absorption of drugs. Hence, this is one limitation of our study, which was performed in healthy subjects.

In our study, as well as in those reported by Miura et al. [10] and Hillebrand et al. [11], a single oral dose of digoxin was used to assess a possible interaction between digoxin and acarbose. A concern persists as to whether a single-dose study can predict the steady-state condition during long-term use. Further studies of a possible interaction should be carried out under steady-state conditions in patients treated chronically with digoxin. The simulation performed in our study can only partly replace real conditions. In this respect, our simulations of multiple dosing of digoxin showed no significant differences in C_{min, ss}, C_{ave, ss} and t_{max}. The 20% increase in C_{max, ss} is clinically unimportant since the trough and the average serum digoxin concentrations at steady state, with and without acarbose, were similar and within the

therapeutic window [Table 3]. These simulation tests are based on the assumption that the pharmacokinetic parameters of digoxin do not change between single- and multiple-dose regimens. This assumption is supported by the common practice in patients on long-term digoxin therapy where no change in dosage regimen is needed to maintain the plasma digoxin level within the therapeutic window under stable pathophysiologic conditions [13]. Moreover, despite the large number of pharmacokinetic studies published, no evidence of any time-dependent effect of digoxin on its absorption or disposition in the body has been reported.

In our study, the pharmacokinetic parameters of digoxin were characterized by high inter-individual variability [Tables 1–3]. This finding is consistent with many reports in the literature as reviewed by Reuning et al. [13]. Several factors contribute to the intervariability among healthy subjects, including body weight, enterohepatic cycling, physical exercise and high fiber meals [13]. This variability is even greater in patients where pathologic factors are involved, such as impaired renal function, impaired thyroid function and co-administration of interacting drugs such as antacids, cyclosporine, verapamil, quinidine and amiodarone [13]. Our results show that between-individual variability in some pharmacokinetic parameters of digoxin is even higher when digoxin is co-administered with acarbose. Whether this element of increased between-individual or between-dose variability is of significance [14,15] requires further study.

In conclusion, our results do not support a clinically significant pharmacokinetic interaction between digoxin and acarbose in healthy subjects. Further study of a possible interaction may be justified, under steady-state conditions, in patients on chronic digoxin treatment. Such a study should also include subjects taking higher doses of acarbose.

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