

# Lack of a Pharmacokinetic Interaction between Dimebon (Latrepiridine) and Digoxin in Healthy Subjects

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## BACKGROUND

- Dimebon (latrepirdine) is an orally available, small synthetic molecule that is in Phase 3 clinical development as a potential treatment for Alzheimer's disease (AD) and Huntington disease (HD). Dimebon 20 mg 3 times daily (TID) is the dosing regimen that has been used to date in published clinical trials for the treatment of patients with AD or HD.<sup>1,2</sup>
- For medications likely to be used in older patients, such as treatments for AD, the Food and Drug Administration (FDA) recommends that drug-drug interaction studies are conducted with digoxin,<sup>3</sup> because digoxin is a narrow therapeutic index drug commonly prescribed to elderly patients for the treatment of heart failure and atrial fibrillation. Furthermore, many clinically significant drug-drug interactions occur with digoxin via inhibition of P-glycoprotein (P-gp)-mediated clearance; therefore, digoxin is also recommended by the FDA<sup>4</sup> as a probe P-gp multidrug resistance 1 (MDR1) substrate to evaluate the potential of a new chemical entity for inhibiting P-gp-mediated clearance.
- The effects of dimebon on the clinical pharmacokinetic (PK), urinary excretion, and safety of a sensitive P-gp substrate, such as digoxin, are unknown. The aim of this Phase 1 study was to evaluate the potential drug-drug interaction of dimebon with digoxin in healthy subjects. The interaction was assessed at steady-state plasma concentrations for both drugs, when P-gp inhibition was expected to be maximal. The dosing regimen for digoxin was 0.125 mg once daily (QD) for 14 days; this commercially available tablet strength was selected for safety considerations, and is a commonly prescribed dose in elderly patients.

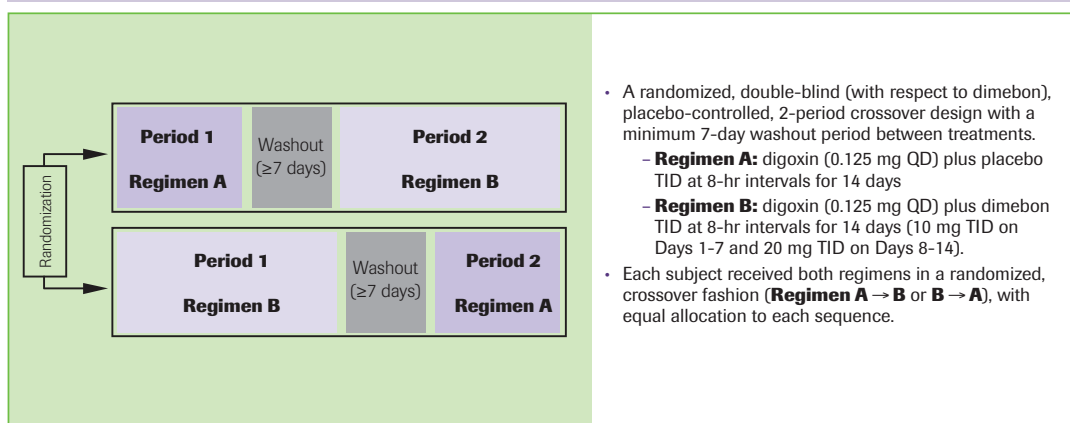
## OBJECTIVES

- To demonstrate the lack of effect of steady-state dimebon 20 mg TID on the steady-state PK of digoxin 0.125 mg QD in healthy adult subjects.
- To evaluate the safety and tolerability of digoxin 0.125 mg QD at steady-state when administered concurrently with multiple doses of dimebon 20 mg TID in healthy adult subjects.

## METHODS

### Study Design

**FIGURE 1** Study design depicting dosing schedule



- A sample size of 12 subjects was required to provide at least 90% power overall to demonstrate the lack of an interaction (i.e., equivalence in both AUC<sub>24</sub> and C<sub>min</sub>, as defined in **Table 1**).
- The study was also conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice guidelines.

### Subjects

- Healthy men or women (of non-child bearing potential), aged 18-55 years, with a body mass index of 17.5-30.5 kg/m<sup>2</sup> were eligible.
- Subjects were considered healthy if they had no clinically relevant abnormalities on physical examination, clinical laboratory evaluations, or 12-lead ECGs.
- Subjects with known sensitivity to either dimebon or digoxin were excluded.
- Because of digoxin's renal clearance, subjects with an estimated creatinine clearance (CL<sub>cr</sub>) corrected for estimated body surface area (BSA) <80 mL/min<sup>5,6</sup> were excluded.
- Other standard exclusion criteria were imposed, including presence of any clinically significant disease or condition likely to affect the properties of the drugs under investigation.

### Assessments

#### Digoxin drug concentration measurements

- Plasma PK samples were collected before the first dose on Day 1 (blank) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24-hrs post-dose on Day 14.
- Urine PK samples were collected before the first dose on Day 1 (blank) and over 3 intervals on Day 14 as follows: 0 to 8, 8 to 16, and 16 to 24-hrs post-dose.
- Digoxin plasma and urine samples were assayed using validated, sensitive, and specific HPLC-MS/MS methods. The lower limit of quantification for digoxin in plasma was 0.05 ng/mL and in urine was 0.5 ng/mL.

#### Digoxin pharmacokinetic parameters

- PK parameters (**Table 1**) were calculated for digoxin plasma and urine from the concentration-time data on Day 14 of each treatment period, using standard non-compartmental methods.

**TABLE 1** Digoxin pharmacokinetic parameters

Parameter	Definition	Method of determination
AUC <sub>24</sub>	Area under the plasma concentration-time profile from time 0 to 24 hrs on Day 14	Linear/Log trapezoidal method
C <sub>min</sub>	Lowest plasma concentration during the dosing interval on Day 14	Observed directly from data
C <sub>max</sub>	Maximum plasma concentration within the dosing interval on Day 14	Observed directly from data
T <sub>max</sub>	Time for C <sub>max</sub>	Observed directly from data as time of first occurrence
A <sub>e</sub>	Cumulative amount of drug recovered unchanged in urine on Day 14 during the 24-hr dosing interval	Sum of (urine concentration × sample volume) <sup>†</sup> for each collection interval
CL <sub>r</sub>	Renal clearance	A <sub>e</sub> /AUC <sub>24</sub>

\*C<sub>min</sub> was the lowest concentration after dosing on Day 14 (exclusive of Day 14 pre-dose).<sup>†</sup>Urine PK parameters only  
<sup>†</sup>Sample volume = (urine weight in g/1.02), where 1.02 g/mL is the approximate specific gravity of urine

### Safety and tolerability analyses

- Safety evaluations included monitoring of adverse events (AEs), vital signs, 12-lead ECGs, physical examination including blood pressure (BP) and pulse rate, and safety laboratory tests.
- Pre-dose plasma samples were collected on Days 7 and 12 for determination of digoxin concentrations, and were assayed within 2 hrs using an AxSYM. Digoxin III automatic analyzer (Abbott Laboratories, Abbott North Park, IL, USA) based on microparticle enzyme immunoassay technology. Subjects with digoxin concentrations ≥2.0 ng/mL would have been withdrawn from the study.

### Statistical Analyses

- Natural log transformed AUC<sub>24</sub> and C<sub>min</sub> for digoxin on Day 14 were analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and subject-within-sequence as random effect.
- Digoxin + placebo was the Reference treatment and digoxin + dimebon was the Test treatment.
- Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained, and were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and corresponding 90% CIs.
- Lack of an interaction was to be concluded if the estimated 90% CI for the ratios (Test/Reference) of adjusted geometric means for both AUC<sub>24</sub> and C<sub>min</sub> fell within 80% to 125%.

## RESULTS

### Subject Disposition

- Twelve male subjects (aged 24-49 years) were assigned to treatment (**Table 2**). All subjects completed the study and were included in the PK and safety analyses.

**TABLE 2** Demographic characteristics

Demographics	n (%) or mean ± standard deviation*
Male	12 (100%)
Age, years	37.8 ± 9.5
Race	
White	4 (33.3%)
Black	7 (58.3%)
Other	1 (8.3%)
Weight, kg	87.8 ± 6.4
Range	70.0-95.0
Body mass index, kg/m <sup>2</sup>	27.3 ± 2.0
Range	22.8-30.1
Height, cm	179.1 ± 3.9

\*unless otherwise specified

### Digoxin Pharmacokinetics

- When digoxin (0.125 mg QD) was administered in the presence of steady-state dimebon (20 mg TID) (**Regimen B**), median digoxin plasma concentrations over the 24-hr sampling period were similar, and nearly superimposable with those observed when digoxin was administered with placebo (**Regimen A**) (**Figure 2**).
- Digoxin was absorbed rapidly after oral administration. The median time to digoxin T<sub>max</sub> was 1.5 hrs and ranged from 1 to 3 hrs post-dose for both treatment regimens (**Table 3**).
- Individual AUC<sub>24</sub>, C<sub>max</sub>, and C<sub>min</sub> estimates were similarly variable (as judged by coefficient of variation [CV] %) following both treatment regimens (**Table 3**).
- The amount of digoxin excreted (A<sub>e</sub>) in urine and digoxin renal clearance (CL<sub>r</sub>) were similar between regimens (**Table 3**).
- Based on the ratios of the adjusted geometric means (**Regimen B/A**), when digoxin was administered in the presence of steady-state dimebon, digoxin AUC<sub>24</sub> and C<sub>min</sub> were similar to the corresponding values when digoxin was administered with placebo (**Table 4**).
- The 90% CIs of the ratios between digoxin + dimebon (Test) and digoxin + placebo (Reference) for AUC<sub>24</sub> and C<sub>min</sub> were contained within an acceptance range (80%, 125%).

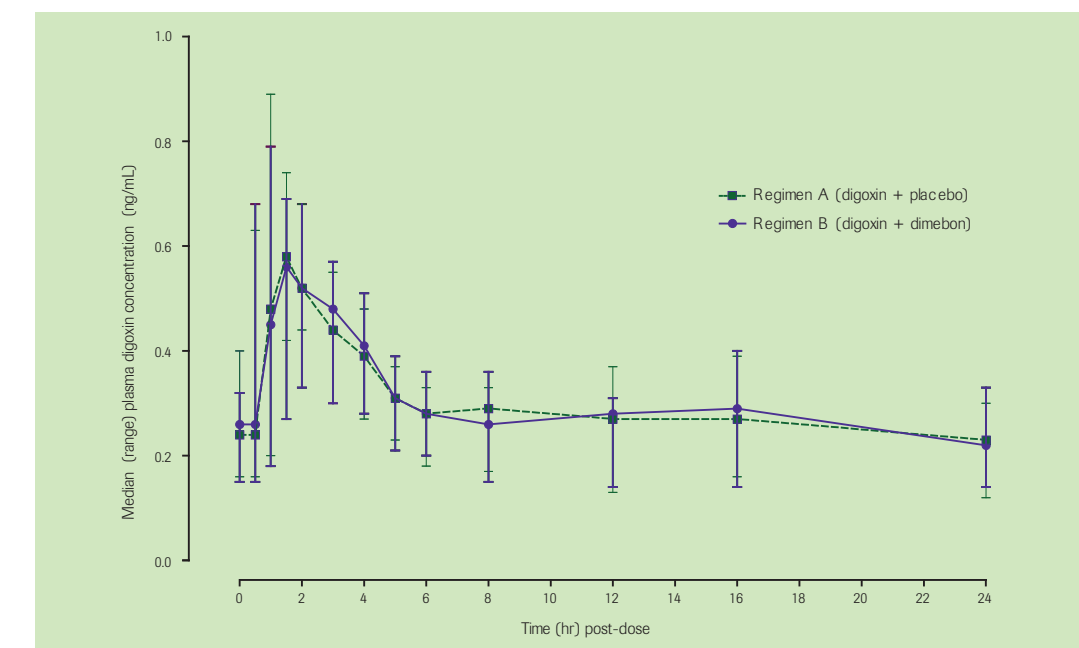
### Safety and Tolerability

- Co-administration of dimebon 20 mg TID and digoxin 0.125 mg QD was well tolerated. No subject was withdrawn due to digoxin concentrations ≥2.0 ng/mL.
- Most AEs were mild in severity in both treatment regimens, and no AE was experienced by >1 patient.
- No deaths, serious or severe AEs, or discontinuations due to AEs were reported.
- The incidence of laboratory abnormalities was comparable between treatments, and no clinically significant laboratory test results were reported.
- No clinically significant changes in vital signs or ECG parameters were recorded.

## CONCLUSIONS

- Steady-state dimebon had no effect on the steady-state PK or tolerability of digoxin in healthy male adults, suggesting the 2 agents can be co-administered without digoxin dose adjustment.
- Given that digoxin is an FDA-recommended P-gp probe substrate,<sup>4</sup> this study demonstrates that dimebon should not produce clinically meaningful effects on the PK of other P-gp (MDR1) substrates.

**FIGURE 2** Median (range) plasma digoxin concentration-time profiles for Regimen A (digoxin + placebo) and Regimen B (digoxin + dimebon) on Day 14



**TABLE 3** Geometric mean (coefficient of variation [CV] %)\* of plasma digoxin pharmacokinetic values

Parameter (units)	Regimen A (digoxin + placebo) (N = 12)	Regimen B (digoxin + dimebon) (N = 12)
T <sub>max</sub> (hrs) median (range)	1.50 (1.00-3.00)	1.50 (1.00-2.03)
AUC <sub>24</sub> (ng-hr/mL)	6.96 (18)	6.90 (20)
C <sub>max</sub> (ng/mL)	0.608 (20)	0.581 (22)
C <sub>min</sub> (ng/mL)	0.210 (22)	0.215 (23)
A <sub>e</sub> (ng) arithmetic mean (SD)	49,900 (9377)	48,900 (12,840)
CL <sub>r</sub> (L/hr)	7.06 (18)	6.79 (17)

\*Data are geometric mean (CV %) unless otherwise specified

**TABLE 4** Summary of statistical analysis of plasma digoxin exposure

Parameter	Digoxin + placebo (Test*)	Digoxin + dimebon (Reference*)	Ratio (%) <sup>†</sup>	90% CI	
				Lower	Upper
AUC <sub>24</sub> (ng-hr/mL)	6.90	6.96	99.1	93.51	105.05
C <sub>min</sub> (ng/mL)	0.22	0.21	102.2	96.22	108.62

\*Adjusted geometric mean values

<sup>†</sup>Ratio of adjusted geometric means

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**DISCLOSURE** Medivation Inc., and Pfizer Inc are developing dimebon (latrepirdine) for the treatment of AD and HD. All authors are employees of Medivation Inc., or Pfizer Inc.