Voriconazole does not affect the steady-state pharmacokinetics of digoxin

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Aims Voriconazole is a triazole antifungal agent with potent fungicidal activity against Aspergillus species. Digoxin is a commonly prescribed cardiac glycoside with a narrow therapeutic index. This aim of this study was to investigate the effect of multiple-dose voriconazole on the steady-state pharmacokinetics of digoxin in healthy male volunteers.

Methods This was a double-blind, randomized, placebo-controlled, parallel-group study. All subjects received daily administration of oral digoxin for a total of 22 days (0.5 mg twice daily on day 1, 0.25 mg twice daily on day 2 and 0.25 mg once daily on days 3–22). In addition, on days 11–22 the subjects were randomized to receive either voriconazole (200 mg twice daily) or matching placebo.

Results Concomitant administration with voriconazole did not significantly alter the C_{max}, AUC_{t}, t_{max} or CL_R of digoxin at steady state. The ratios between groups for C_{max} and AUC_{t} at day 22, corrected for baseline (day 10) were 109.8% [90% confidence interval (CI) 97.1, 124.1] and 100.5% (90% CI 91.4, 110.5), respectively. In addition, group mean C_{min} values were similar in both treatment groups throughout the study. There were no significant differences between treatments with respect to the incidence of adverse events, all of which were classified as mild and transient in nature.

Conclusions The steady-state pharmacokinetics of digoxin are not affected in a clinically relevant manner by the concomitant administration of voriconazole.

Keywords: cytochrome P450, digoxin, pharmacokinetics, voriconazole

Introduction

Voriconazole is a triazole antifungal agent, available as oral and intravenous formulations, with potent activity against a broad spectrum of clinically significant pathogens, including Aspergillus and Candida species [1–3], and emerging fungal pathogens, such as Scedosporium and Fusarium species [4, 5].

The pharmacokinetics of voriconazole have been investigated following single and multiple (10–30 days) doses in both healthy volunteers and patients [6–8]. Voriconazole is extensively metabolized by the cytochrome (CYP) P450 system, mainly by the polymorphically expressed CYP2C19 isoenzyme, by CYP2C9, and to a lesser extent by CYP3A4 [9].

Digoxin is a commonly prescribed cardiac glycoside used predominantly by the elderly for the treatment of cardiac arrhythmias and heart failure. Satisfactory clinical responses are rare at plasma concentrations below 0.8 ng ml^{-1}, whereas the risk of toxicity increases markedly above 2.0 ng ml^{-1} [10]. This narrow therapeutic index means that the clinical use of digoxin is complicated by possible drug interactions, which may lead to severe toxicity [11–13].

There are several case reports in the literature of drug interactions between digoxin and theazole antifungal agents itraconazole or ketoconazole resulting in significant elevations in plasma digoxin concentrations, and subsequent toxicity (nausea, diarrhoea and arrhythmia), in previously stabilized patients [14–20]. The precise mechanism of the interaction is unknown, but is considered likely to be related to inhibition of the ATP-dependent plasma membrane transporter P-glycoprotein (P-gp). Effects of other drugs on the transporter within the cellular membranes of the gastrointestinal tract, liver and kidneys are all considered to be P-gp-mediated processes affecting the pharmacokinetics of digoxin [21–24].
Although voriconazole belongs to the same class of antifungal agents as itraconazole and ketoconazole, in vitro data indicate that it is neither a substrate nor an inhibitor of P-gp (Pfizer data on file). Based on these data, it is not anticipated that there would be a drug–drug interaction between voriconazole and digoxin. The present study was therefore conducted to investigate the effects of voriconazole oral maintenance therapy (200 mg twice daily), on the steady-state pharmacokinetics of digoxin, and to evaluate the safety and tolerability of these drugs when coadministered.

Methods

Study subjects

Healthy male volunteers, aged 18–45 years, weighing 60–100 kg, and with a body mass index within a permitted range of 18–28 using Quetelet’s Index [weight (kg)/height² (m)], were randomized to receive study treatment following the provision of written informed consent. The study protocol was approved in writing by the Clinical Research Ethics Committee, Anatole France Street, Brussels, Belgium.

Volunteers with any evidence of clinically significant disease, allergy, drug sensitivity, or laboratory test results outside the normal range were excluded. In addition, volunteers with clinically significant abnormalities in resting electrocardiogram (ECG) or 24-h ambulatory ECG were excluded. In addition, on days 10 and 22, blood samples were collected predose on days 2–22 for rapid assay of digoxin concentrations using a commercial radioimmunoassay (Amberlex radioimmunoassay kit; Kodak Clinical Diagnostics Ltd, Raritan, New Jersey, USA). Subjects with digoxin concentrations of ≥2.5 ng ml⁻¹ were to be withdrawn.

Pharmacokinetic sampling

Blood samples (5 ml) were taken predose on the morning of days 2–22 for digoxin assay and on days 11–22 for voriconazole assay to assess trough plasma concentrations of the drugs. In addition, on days 10 and 22, blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h postdose for the determination of plasma digoxin concentrations. Blood was collected in heparinized tubes, centrifuged at 1500 g at 4 °C for 10 min within 1 h of collection, and stored upright in screw-capped polypropylene tubes at −20 °C, pending assay.

Twenty-four-hour urine collections were initiated immediately before digoxin dosage on days 10 and 22. The total volume of urine was recorded and two 20-ml aliquots were stored at −20 °C for subsequent digoxin determinations.

Assays

Digoxin concentrations in plasma and urine samples were determined by radioimmunoassay using a commercially available kit (BCO Analytical Services, Bergschot, the Netherlands). The interbatch precision and inaccuracy of the plasma assay were 4.5–7.3% and 5.5–15.8%, respectively, over the concentration range 0.62–3.10 ng ml⁻¹. For the urine assay, interbatch precision and inaccuracy were 4.2–7.4% and 5.0–20.2%, respectively, over the concentration range 24.8–124 ng ml⁻¹. The limit of quantification for both sample types was set at 0.15 ng ml⁻¹, the lower limit of the calibration curve. Tests for interference by voriconazole were conducted prior to the analysis of subject samples.

Plasma voriconazole samples were assayed using a previously validated high-performance liquid chromatogra-
Statistical analysis were clinically reviewed and tabulated, but not subjected to formal statistical analysis. Similarly, laboratory and other safety data were analyzed visually but not subjected to formal statistical analysis. All analyses and tabulations were performed using SAS/STAT software. The lower limit of quantification was set at 10 ng ml⁻¹, corresponding to the lower limit of the calibration curve.

Safety assessments

All adverse events that occurred during treatment, or up to 30 days post final dose, were documented, together with their severity, time of onset and duration, and the investigator’s assessment of their relationship to treatment. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing conditions were recorded. Objective test findings that resulted in dosage change or discontinuation were also recorded as adverse events. All adverse events were followed up until their sequelae had resolved or stabilized satisfactorily.

Parameter calculations

The maximum observed plasma concentration (C_max) and the time to the first occurrence of C_max (t_max) were obtained directly from the plasma concentration–time curves. The area under the plasma digoxin concentration–time curve over a dosing interval at steady state (AUC_t) was determined using the linear trapezoidal method. Renal clearance (CL_R) was calculated as Ae/AUC_t, where Ae was the total amount of digoxin excreted in the urine during the dosing interval. Attainment of steady-state concentration was confirmed by visual inspection of the predose concentrations (C_min) of digoxin on days 2–10 and predose concentrations of both digoxin and voriconazole on days 11–22.

Statistical analysis

Log-transformed AUC_t and C_max, and untransformed t_max and CL_R were subject to an analysis of variance (ANOVA) with repeated measures appropriate for the parallel-group design. Mean changes and 90% confidence intervals (CI) were calculated from the day 22 vs. day 10 (baseline) pharmacokinetic data for the digoxin + voriconazole and digoxin + placebo groups. C_min data were analysed visually but not subjected to formal statistical analysis. Similarly, laboratory and other safety data were clinically reviewed and tabulated, but not subjected to formal statistical analysis. All analyses and tabulations were performed using SAS/STAT® software [26].

A sample size of 24 subjects (12 subjects per group) was considered sufficient to detect a difference of 20% in AUC_t or CL_R of digoxin at steady state with a probability of 0.8. The calculations were based on placebo data from a previous study (Pfizer Inc., data on file), where baseline mean AUC_t was 15.5 ng·h ml⁻¹ with the variance of the intrasubject change in AUC_t of 6.6 ng·h ml⁻¹.

Results

Subjects

A total of 25 subjects were screened and randomized to either the digoxin + voriconazole (n = 12) or digoxin + placebo (n = 13) groups. One subject in the digoxin + placebo group withdrew consent after 2 days’ administration of digoxin for reasons unrelated to treatment and was assessed for adverse events only. All of the remaining 24 subjects were assessed for pharmacokinetics, laboratory safety data and adverse events. There were no significant differences between the digoxin + voriconazole and digoxin + placebo groups with respect to mean age, weight, or height (Table 1).

Digoxin pharmacokinetics

No subjects were withdrawn from the study due to plasma digoxin concentrations being ≥2.5 ng ml⁻¹. Visual inspection of C_min data for digoxin indicated that most subjects achieved steady state by day 5. In addition, mean C_min values were similar for both treatment groups throughout the 22-day study period (Figure 1). The steady-state pharmacokinetics of digoxin were unaffected by concomitant administration of voriconazole. There were no significant differences between the mean plasma digoxin concentrations on days 10 and 22 for the digoxin + voriconazole and digoxin + placebo groups (Figure 2).

The mean C_max was similar on days 22 and 10 for both treatment groups. The ratio between day 22 and day 10 C_max (day 22/day 10 ratio) was 95.6% (90% CI 87.6, 104.3) for the digoxin + voriconazole group and 87.1% (90% CI 79.8, 95.0) for the digoxin + placebo group.

Table 1 Baseline demographic characteristics of all randomized subjects.

<table>
<thead>
<tr>
<th></th>
<th>Digoxin + voriconazole</th>
<th>Digoxin + placebo</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>25 (19–28)</td>
<td>26 (19–36)</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>77 (63–97)</td>
<td>75 (60–94)</td>
</tr>
<tr>
<td>Mean height, cm (range)</td>
<td>181 (169–191)</td>
<td>179 (169–192)</td>
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<tr>
<td>Mean body mass index* (range)</td>
<td>24 (20–28)</td>
<td>23 (20–28)</td>
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* Determined according to Quetelet’s Index [weight(㎏)/height²(ｍ)].
After correction for the change observed in the digoxin + placebo group, the day 22/day 10 ratio for $C_{\text{max}}$ was 109.8% (90% CI 97.0, 124.1) for the digoxin + voriconazole group. The day 22/day 10 ratio for AUC$_t$ was 93.2% (90% CI 87.2, 99.7) for the digoxin + voriconazole group and 92.8% (90% CI 86.8, 99.2) for the digoxin + placebo group. After correcting for placebo, the day 22/day 10 ratio for the digoxin + voriconazole group was 100.5% (90% CI 91.4, 110.5) (Table 2).

There was no significant difference in $t_{\text{max}}$ between days 10 and 22 for either the digoxin + voriconazole or digoxin + placebo groups. Renal clearance was higher on day 22 compared with day 10 for both groups. The differences in mean CL$_R$ between day 22 and day 10 for the digoxin + voriconazole and the digoxin + placebo groups were 16.8 (90% CI −0.4, 33.9) and 15.8 (90% CI −1.3, 33.0) ml min$^{-1}$, respectively. Comparison across the two treatment groups resulted in a mean difference of 1.0 (90% CI −23.3, 25.2) ml min$^{-1}$ (Table 2).

Voriconazole pharmacokinetics

Visual inspection of voriconazole $C_{\text{min}}$ data obtained on days 11–22 indicated that most subjects attained steady state by day 16 (after 5 days of voriconazole treatment). By day 22, all subjects were at steady state.
Safety

There were no serious adverse events, discontinuations or dose reductions due to either adverse events or safety tests. Adverse events were reported in a similar number of subjects in each group: nine subjects reported 23 events in the digoxin + voriconazole group compared with 10 subjects reporting 24 events in the digoxin + placebo group. Headache was the only event reported by more than two subjects in any one group (five voriconazole, six placebo). The majority of adverse events occurred during days 11–22, when digoxin was coadministered with either voriconazole or placebo. In total, only seven events were considered to be drug-related (three voriconazole, four placebo).

Three subjects reported three treatment-related visual adverse events. One subject in the digoxin + voriconazole group experienced enhanced visual perception, which was first experienced when receiving digoxin alone, and did not worsen following the initiation of voriconazole treatment. In the digoxin + placebo group, one subject experienced enhanced visual perception and one subject experienced intermittent retro-ocular pain. All visual events were classified as mild, and resolved without intervention.

Discussion

The present study demonstrated that concomitant administration of voriconazole 200 mg twice daily does not clinically alter the steady-state pharmacokinetics of digoxin with respect to Cmin, Cmax, AUCτ, tmax, or CLR.

Furthermore, the combination of digoxin plus voriconazole appeared to be as safe and well tolerated as digoxin plus placebo. There were no reported serious adverse events, discontinuations or dose reductions due to adverse events or safety tests in either group. All adverse events reported were of either mild or moderate severity, with the majority being reported when digoxin was administered concomitantly with either voriconazole or placebo. Only seven subjects had adverse events that were considered to be treatment related.

Although other azoles, such as itraconazole and ketoconazole, have been shown to interact significantly with digoxin, there is a sound theoretical basis to suggest why no clinically significant drug interaction was observed with voriconazole and digoxin.

Digoxin is excreted for the most part as unchanged drug, and it is estimated that about 10% of the absorbed drug undergoes hepatic metabolism [20]. Digoxin is known to be a substrate of the multidrug transporter P-gp, and in rats has also been identified as a substrate for CYP3A23. Both CYP3A4 and P-gp reduce the intracellular concentration of digoxin, by metabolism and transmembrane efflux, respectively [27]. Although many P-gp inhibitors are also substrates and/or inhibitors of CYP3A4, it is considered that CYP3A4 inhibition is not necessarily an intrinsic characteristic of P-gp inhibitors [28, 29].

The elimination of voriconazole occurs almost exclusively by metabolic clearance, with in vitro studies using human liver microsomes demonstrating that voriconazole is metabolized by CYP2C9 and CYP2C19, and to a lesser extent by CYP3A4 [9]. There is no evidence to suggest that voriconazole is either a substrate and/or inhibitor of P-gp (Pfizer data on file). This is supported by the results of the current study, which indicated that voriconazole had no clinically significant effect on the P-gp-mediated excretion of digoxin by the kidney, as indicated by the lack of effect on the renal clearance (CLR). Furthermore, as concomitant voriconazole administration was not associated with a significant decrease in the tmax of digoxin, compared with placebo, voriconazole does not appear to inhibit P-gp-mediated digoxin absorption in the gut.

The difference in the interactions between digoxin and voriconazole or digoxin and itraconazole or ketoconazole may therefore be due primarily to effects on P-gp. Itraconazole has also been shown to inhibit P-gp-mediated digoxin secretion in renal tubular cells in both a guinea pig model [30] and in human volunteers [20]. In addition, ketoconazole has been shown to potently inhibit basolateral to apical flux of digoxin across MDCK cell lines with an IC50 of approximately 2 μmol l−1 and to inhibit completely the transport of digoxin in CaCO2 cells at concentrations of 10 μmol l−1 [27, 31]. These observations, together with the results of the present study, suggest that the inhibition of P-gp may therefore be molecule-specific rather than azole-specific effects.

In conclusion, the present study demonstrated that voriconazole had no clinically significant effect on the pharmacokinetics of digoxin, suggesting that this novel broad-spectrum antifungal agent can be administered concomitantly with digoxin without the need for routine monitoring of plasma concentrations.

References

