No Effect of Imidafenacin, a Novel Antimuscarinic Drug, on Digoxin Pharmacokinetics in Healthy Subjects

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Summary: Plasma digoxin concentrations are increased by the coadministration of anticholinergic drugs, such as propantheline, which decrease gastrointestinal motility. The present study evaluated the effect of imidafenacin, a novel anticholinergic drug, on the pharmacokinetics of digoxin. The effect of imidafenacin on the pharmacokinetics of digoxin was examined in 14 healthy Japanese male subjects in a single-centre, open-label, randomized, two-way crossover study. Subjects received a daily oral dose of digoxin 0.25 mg on days 1 and 2 and digoxin 0.125 mg on days 3 to 8 (period 1). Following a 2-week washout period, digoxin was administered orally for 8 days in a similar manner (period 2). A twice daily dose of imidafenacin 0.1 mg was concomitantly administered with digoxin for 8 days either in period 1 or 2. The geometric mean ratios [GMR] (90% confidence intervals [CIs]) for digoxin Cmax and AUC0-24 (with/without imidafenacin) at steady state were 0.88 (0.74, 1.04) and 1.00 (0.90, 1.10), respectively. The 90% CIs of GMR for digoxin trough concentration, urinary excretion amount and renal clearance at steady state fell within the range of 0.8 to 1.25. The steady-state pharmacokinetics of digoxin is not affected by concomitant administration of imidafenacin in healthy subjects.

Keywords: digoxin; imidafenacin; drug-drug interaction; pharmacokinetics

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urgent condition, with or without urge incontinence, usually accompanied by frequency and nocturia.1 It is a highly prevalent and chronic disease that amounts to a significant burden on quality of life.2,3 Moreover, OAB has emerged as a significant cause of social function deterioration and resultant healthcare costs.4,5

Imidafenacin, 4-(2-Methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide, is an orally active anticholinergic drug, which has been used for the treatment of OAB in Japan.6 Clinical studies have demonstrated that a twice daily dose of imidafenacin 0.1 mg improves symptoms of OAB with sufficient safety and tolerability for the patients. The oral bioavailability of imidafenacin is approximately 60%. Peak plasma concentrations occur approximately 1.5 hours after administration, and the half-life of the drug is approximately 3 hours.7–9 The pharmacokinetics of imidafenacin in the elderly are similar to those seen in younger subjects.10 Imidafenacin is excreted partially in urine (approximately 10% of a given dose) and is eliminated primarily by metabolism. In vitro studies indicate that imidafenacin is primarily metabolized by CYP3A4 and UGT1A4.11 The plasma protein binding ratio of imidafenacin is approximately 88% and the binding proteins are albumin and α1-acid glycoprotein.

Anticholinergic drugs such as imidafenacin have the potential to interact with digoxin, a commonly prescribed drug for the treatment of arrhythmias and heart failure. Because digoxin has a narrow therapeutic index, small alterations in digoxin pharmacokinetics may lead to decreased therapeutic effect or serious toxicity. It has been reported that plasma digoxin concentrations are increased by the coadministration of anticholinergic drugs, such as propantheline, which decrease gastrointestinal motility.12,13 Therefore, this trial was performed to assess the effect of imidafenacin on the pharmacokinetics of digoxin.

Methods

Subjects: Fourteen healthy male subjects, age range
21–35 and body mass index range 19.2–24.9 kg/m², participated in this study after obtaining informed consent. Subjects were determined to be in good health based on medical history, physical examination, vital signs, electrocardiograms (ECGs), and laboratory test values. Subjects were required to abstain from taking any medication without prior consent of the investigator, drinking alcohol, smoking, and consuming food or beverages containing grapefruit, St John’s wort, and caffeine.

Twelve of the 14 subjects completed the study. One subject (No. 10) was withdrawn from the study between the two treatment periods (on the eleventh day from day 1 in period 1 of the digoxin alone phase) because of cervical dis­copathy. Another subject (No. 2) was withdrawn on day 7 in Period 2 of the digoxin alone phase because of persistent vomiting following digoxin administration. And thus, data from 12 of the 14 subjects were included in the pharmacokinetic analysis; all subjects were included in the safety analysis. This study was approved by the local Institutional Review Board and was conducted at the Kitasato Institute Bio-Iatric Center (Tokyo, Japan).

**Study design:** This was a single-centre, open-label, randomized, two-way crossover study. During both treatment periods, subjects received daily oral loading doses of digoxin (DIGOSIN® Tablet, Chugai Pharmaceutical, Tokyo, Japan) 0.25 mg in the morning on days 1 and 2 followed by 0.125 mg daily doses on days 3 to 8. Either during period 1 or 2, imidafenacin (Kyorin Pharmaceutical, Tokyo, Japan) 0.125 mg, the only dose approved in Japan, was administered twice daily in the morning and evening for 8 days. On day 8, imidafenacin and digoxin were coadministered in the morning after an overnight fast. Food intake was restricted during the 4 hours post drug administration on day 8; water was allowed ad libitum. There was a 14-day washout period between the last dose of Period 1 and the first dose of Period 2. The doses of digoxin used in this study were a quarter of the upper limit of the loading and maintenance doses approved in Japan.

Blood samples (2 mL) were collected for digoxin plasma concentration measurements before drug administration on days 1 through 8 and on day 8 at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-digoxin dose. For imidafenacin concentration measurements, blood samples (8 mL) were collected on day 8 of the imidafenacin and digoxin com­bination therapy period. The blood was collected on the same schedule as digoxin. Samples were collected into tubes containing sodium heparin and centrifuged; plasma was harvested from samples and stored below −20°C until analysis. Urine samples for digoxin assay were collected before drug administration on day 1 and on day 8 over 0 to 6, 6 to 12, and 12 to 24 hours post-digoxin. At the end of each collection period, the total urine volume was recorded and aliquots (approximately 10 mL) were stored below −20°C until analysis.

In both treatment periods, clinical examination and vital sign measurements (blood pressure, pulse rate, respiration rate and body temperature) were performed pre-digoxin and 2, 4, 8 and 24 (day 8 only) hours post-digoxin on days 1 and 8 as well as pre-digoxin on day 2 through day 7. Lead-II ECGs were monitored from pre-digoxin to 4 hours post-digoxin on day 1, and 12-lead ECGs were measured pre-digoxin on day 1, and 2 and 24 hours post-digoxin on day 8. Blood and urine samples were collected on days 1 and 9 for laboratory tests (haematology, biochemistry and urinalysis). These safety assessments were also monitored two weeks after the last dose of Period 2. Adverse events were monitored throughout the study.

**Assays of digoxin:** Plasma and urine concentrations of digoxin were determined by liquid chromatography coupled with a tandem mass spectrometer (LC/MS/MS). Plasma and urine samples (0.2 mL) containing the internal standard were added to 0.05 mL of 0.1 mol/L ammonium acetate buffer (pH 9.5) and applied to Oasis® HLB cartridges which were first conditioned with methanol and water. The cartridges were washed with 0.25 mL of 0.1 mol/L ammonium acetate buffer (pH 9.5) and then again washed with 0.25 mL of methanol/water (1:1). The analytes were then eluted with 100 μL of methanol twice. The eluate was added to 0.2 mL of water and injected onto the LC/MS/MS for quantification. The quantitative ranges of analytes in plasma and urine were 0.02–5 ng/mL and 0.5–100 ng/mL, respectively. Quality control samples in duplicate at three concentrations were incorporated into each assay run. At least five of every six QC samples were within ±15% of their respective nominal values in each assay run.

**Assays of imidafenacin:** Plasma concentrations of imidafenacin were determined by LC/MS/MS. Plasma samples (1 mL) containing internal standards were applied to C18 solid-phase extraction columns, which had first been conditioned with 1 mL of methanol and 1 mL of water. After adsorption of the samples, cartridges were washed with 1 mL of water twice. Analytes were then eluted with 1 mL of methanol, evaporated to dryness under a stream of nitrogen, and reconstituted in 100 μL of mobile phase (65% water containing 0.1% formic acid and 35% acetonitrile). 20 μL of reconstituted samples were injected onto LC/MS/MS for quantification. The quantitative range was 10–500 pg/mL. Quality control samples at three concentrations were within ±10% of their respective nominal values.

**Pharmacokinetic analysis:** The area under the plasma concentration versus time curve from 0 to 24 hours or infinity (AUC₀–₂₄ for digoxin and AUC₀–∞ for imidafenacin) were estimated using the linear trapezoidal rule. The peak plasma concentration (Cₘₐₓ) values, time associated with the maximal concentration (tₘₓ), and trough plasma concentration (Cₘᵦ) values were obtained from the observed data. The Cₘᵦ values of digoxin were evaluated from day 4 to day 8. These parameters were calculated using WinNonlin Professional Ver. 4.0.1 software (Pharsight Corp., Mountain View, California). Urinary excretion of digoxin in each specified
time interval was calculated by multiplying digoxin urine concentration by urine volume voided in that particular time period. The 24-hour urinary excretion (Ue, 0–24) was the sum of urinary excretion from each interval. Renal clearance (CLR) of digoxin was calculated as Ue, 0–24/AUC0–24. Analysis of urine digoxin was performed using Microsoft Excel 2002 (Microsoft Corporation, Redmond, Washington).

Statistical methods: Assuming that imidafenacin has no interaction with digoxin, a sample size of 14 had more than 80% power to ensure that the 90% confidence interval (CI) for the treatment ratio (digoxin + imidafenacin/digoxin) of the geometric means for AUC0–24 and Cmax would be contained within the interval of 0.8 to 1.25, based on previous intraindividual variability. The AUC0–24 and Cmax of digoxin were log-transformed and then analyzed in SAS using an analysis of variance model, which allowed for the effects of subject, period, and treatment. Treatment effects were presented as the ratios of the geometric means for digoxin with or without imidafenacin, and 90% CIs were calculated. A lack of interaction was concluded if the 90% CI lay between 0.8 and 1.25. Also, the ratios of the geometric means and 90% CIs for the Cmin, Ue, 0–24 and CLR of digoxin were evaluated as references.

Results

Digoxin pharmacokinetics: The mean plasma concentration profiles of digoxin were comparable for digoxin alone or in combination with imidafenacin, as depicted in Figure 1. The summary pharmacokinetic parameters and the results of the statistical analysis of digoxin with or without imidafenacin are presented in Table 1. The mean AUC0–24 of digoxin with imidafenacin was 7.91 ng·h/mL, which was 0.9% lower than that of digoxin alone. Similarly, the mean Cmax of digoxin with imidafenacin was 0.850 ng/mL, which was 12.5% lower than that of digoxin alone. Median tmax values were identical. The geometric mean ratio (digoxin with imidafenacin/digoxin alone) for AUC0–24 (90% CI) was 1.00 (0.90, 1.10). This value was well within the pre-specified margin of 0.8 to 1.25. However, the geometric mean ratio for Cmax (90% CI) was 0.88 (0.74, 1.04), and the 90% CI was outside the pre-specified bounds, with lower bounds below 0.8. No specific patterns were observed in the individual Cmax alterations of digoxin in combination with imidafenacin, as shown in Figure 2. However, a high degree of variability in Cmax was observed in subject No. 14 who exhibited a 60.8% lower plasma digoxin concentration in the presence of imidafenacin than with digoxin alone. This likely explains why the 90% CI of Cmax fell outside pre-specified bounds. In contrast, all of the 90% CIs of Cmin from day 4 to day 8 were within 0.8 to 1.25.

Urinary excretion of digoxin was similarly unaltered by the coadministration of imidafenacin, as shown in Table 1.

Table 1. Comparison of pharmacokinetic parameters for digoxin on day 8 after administration of digoxin alone (0.25 mg on days 1–2, 0.125 mg on days 3–8) or in combination with imidafenacin (0.1 mg twice daily on days 1–8)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Digoxin alone  (n = 12)</th>
<th>Digoxin + Imidafenacin  (n = 12)</th>
<th>Geometric Mean Ratio</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–24, ng·h/mL</td>
<td>7.98 ± 1.16</td>
<td>7.91 ± 0.90</td>
<td>1.00</td>
<td>(0.90, 1.10)</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>0.971 ± 0.232</td>
<td>0.850 ± 0.196</td>
<td>0.88</td>
<td>(0.74, 1.04)</td>
</tr>
<tr>
<td>Cmin(day4), ng/mL</td>
<td>0.217 ± 0.042</td>
<td>0.225 ± 0.045</td>
<td>1.04</td>
<td>(0.90, 1.19)</td>
</tr>
<tr>
<td>Cmin(day5), ng/mL</td>
<td>0.224 ± 0.026</td>
<td>0.217 ± 0.035</td>
<td>0.96</td>
<td>(0.87, 1.07)</td>
</tr>
<tr>
<td>Cmin(day6), ng/mL</td>
<td>0.220 ± 0.033</td>
<td>0.214 ± 0.037</td>
<td>0.97</td>
<td>(0.87, 1.08)</td>
</tr>
<tr>
<td>Cmin(day7), ng/mL</td>
<td>0.230 ± 0.045</td>
<td>0.213 ± 0.032</td>
<td>0.93</td>
<td>(0.82, 1.06)</td>
</tr>
<tr>
<td>Cmin(day8), ng/mL</td>
<td>0.267 ± 0.040</td>
<td>0.248 ± 0.038</td>
<td>0.93</td>
<td>(0.84, 1.03)</td>
</tr>
<tr>
<td>tmax, h</td>
<td>1</td>
<td>1</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Ue, 0–24, µg</td>
<td>602 ± 108</td>
<td>562 ± 78</td>
<td>0.94</td>
<td>(0.83, 1.06)</td>
</tr>
<tr>
<td>CLR, L/h</td>
<td>7.68 ± 1.60</td>
<td>7.23 ± 1.51</td>
<td>0.94</td>
<td>(0.80, 1.11)</td>
</tr>
</tbody>
</table>

NE, not estimated; AUC0–24, area under the concentration-time profile over 1 dose interval (24 hours); Cmax, maximal concentration; Cmin, minimum (trough) concentration; tmax, time to the maximal concentration; Ue, 0–24, cumulative amount of drug excreted in urine over 24 hours; CLR, renal clearance.

a. Median values.
which was 6.6% lower than that of digoxin alone. Similarly, the mean Cl of digoxin with imidafenacin was 5.9% lower than that of digoxin alone. Statistical analysis showed that the 90% CIs for both treatment ratios fell within 0.8 to 1.25.

**Imidafenacin pharmacokinetics:** The mean concentration-time profile of imidafenacin on day 8 was shown in Figure 3. The plasma imidafenacin concentration reached the maximum concentration at 1.5 hour after dosing, and then eliminated ($t_1/2 = 3.3 \pm 0.3$ h). The $C_{\text{max}}$ and AUC$_{0-12}$ were $563 \pm 105$ pg/mL and $2690 \pm 550$ pg·h/mL, respectively.

**Clinical safety:** All 14 subjects who entered the study were included in the safety analysis. One subject (No. 10) was withdrawn from the study due to serious adverse events (neck pain and hypoaesthesia) in the washout period following the digoxin treatment period. This subject was diagnosed with cervical discopathy and his symptoms resolved in approximately two weeks. These two severe adverse symptoms were not likely related to imidafenacin since the symptom onset occurred prior to the beginning of imidafenacin administration. Another subject (No. 2) was withdrawn on day 7 in Period 2 of the digoxin alone phase because of persistent vomiting following digoxin administration. Eight of the 14 subjects reported a total of 25 clinical adverse events. Of these, 8 were reported in 3 subjects during the digoxin with imidafenacin treatment period, 13 were reported in 5 subjects during the digoxin treatment period, and 4 were reported in 2 subjects during the washout or follow-up period. The most frequent adverse event for all the treatments was headache. With the exception of neck pain and hypoaesthesia, which were regarded as severe, all other adverse events were mild. Two adverse events of dry mouth were reported in one subject during the digoxin with imidafenacin treatment period and may have been attributable to imidafenacin. ECGs and vital signs showed no clinically significant changes.

**Discussion**

Results of this study demonstrate that imidafenacin has no clinically significant effect on the pharmacokinetics of digoxin. The mean plasma concentration profiles of digoxin were comparable during digoxin alone or in combination with imidafenacin. Although the $C_{\text{max}}$ confidence interval fell slightly outside of the limits of the pre-specified margin, the AUC$_{0-24}$ confidence interval fell within the pre-specified margin of 0.8 to 1.25. Moreover, all the $C_{\text{min}}$ from day 4 to day 8 as well as the $U_{e,0-24}$ and $CL_{\text{R}}$ fell within the bioequivalence range. One likely explanation for why the mean $C_{\text{max}}$ fell outside the pre-specified margin was the high degree of $C_{\text{max}}$ variability in subject No. 14 during combination treatment. The exact reason for $C_{\text{max}}$ variability in this subject No. 14 remains unknown. However, since significant variability was not observed in the AUC, it is presumable that variability in this individual’s absorption rate caused the high degree of $C_{\text{max}}$ variability.

Although 14 subjects were recruited, 2 subjects dropped out of the study. Thus, the statistical power with a sample size of 12 was evaluated retrospectively. Assuming that imidafenacin has no interaction with digoxin, a sample size of 12 had 99% and 59% power for AUC$_{0-24}$ and $C_{\text{max}}$ to ensure that the 90% CI of the geometric means ratio for AUC$_{0-24}$ and $C_{\text{max}}$ would be contained within the interval of 0.8 to 1.25, based on intraindividual variability obtained in this study. If data from subject No. 14 were excluded, the $C_{\text{max}}$ confidence interval fell within the pre-specified margin, and the power for $C_{\text{max}}$ was more than 90%. The statistical investigation suggested that sample size ($n=12$) had adequate statistical power for AUC, however the influence of data from subject No. 14 resulted in insufficient sample size for $C_{\text{max}}$.

The premise for this study was to address whether or not imidafenacin, like propantheline, might raise plasma digoxin levels. Propantheline, an anticholinergic drug, decreases gastrointestinal motility and prolongs the retention of digoxin in the gastrointestinal tract, which results in imidafenacin treatment period.
creased plasma digoxin concentrations.\textsuperscript{12,13} Thus, imidafenacin, also being an anticholinergic drug, may potentially increase plasma digoxin concentration by a similar mechanism. However, in this 8-day trial (coadministration of imidafenacin 0.1 mg twice daily with digoxin), imidafenacin had no clinically significant effect on the pharmacokinetics of digoxin. These results are consistent with the data from non-clinical study demonstrating imidafenacin 30 mg/kg did not affect enteric transportability in mice (data not shown). Propantheline has no selectivity for muscarinic receptor subtypes,\textsuperscript{16} whereas imidafenacin has higher affinities for M3 and M1 receptors than for M2 receptors.\textsuperscript{17} However, the physiological roles of these receptor subtypes have not been completely elucidated, hence, it is unclear that subtype selectivity contributed to the difference between propantheline and imidafenacin.

For examining the influence of digoxin on imidafenacin, the pharmacokinetic parameters of imidafenacin with and without digoxin, obtained from this study and the previous report,\textsuperscript{9} respectively, were compared. The AUC in the presence and absence of digoxin were $2690 \pm 550 \text{ pg h/mL}$ and $2400 \pm 610 \text{ pg h/mL}$, respectively; the values were comparable. Furthermore, imidafenacin is primarily metabolized by CYP3A4 and UGT1A4,\textsuperscript{11} and digoxin does not inhibit these metabolic enzymes. Therefore, digoxin was considered to be unlikely to influence the pharmacokinetics of imidafenacin.

Results of this study support the relative safety of administering digoxin and imidafenacin in combination. No significant differences were observed in the vital signs and ECG intervals of subjects when receiving digoxin and imidafenacin versus when receiving digoxin alone. Two severe adverse events reported in subject No. 10 were deemed unrelated to imidafenacin given symptom onset prior to the imidafenacin administration period. No clinically significant adverse effects were reported during the coadministration of digoxin and imidafenacin at all participants in this study. Coadministration of digoxin and imidafenacin was well tolerated.

Interaction between imidafenacin and drugs other than digoxin is discussed hereunder. Imidafenacin does not inhibit major cytochrome P450 enzymes.\textsuperscript{11} Although the effects of imidafenacin on P-gp are unclear, the results of this study suggested that imidafenacin would not cause clinically significant effects on P-gp. Therefore, imidafenacin is unlikely to affect pharmacokinetics of various concomitant drugs. In fact, there is no report of severe adverse events caused by concomitant drugs in imidafenacin clinical trials on OAB patients. However, coadministration of itraconazole, a potent CYP3A4 inhibitor, increased imidafenacin AUC by about 1.8 fold.\textsuperscript{18} Therefore, coadministration with potent CYP3A4 inhibitors should be carefully monitored for adverse effects (eg. dry mouth, anuresis, etc.) attributable to anticholinergic activity.

In conclusion, the steady-state pharmacokinetics of digoxin is not affected by concomitant administration of imidafenacin. Therefore, no dosage adjustments are necessary when imidafenacin is administered concomitantly with digoxin.

**References**


