Absolute bioavailability of imidafenacin after oral administration to healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The absolute bioavailability of imidafenacin in rats and dogs is 5.6% and 36.1%, respectively.
- The pharmacokinetic profiles of imidafenacin after oral administration have been revealed.
- Imidafenacin is primarily metabolized to metabolites by CYP3A4 and UGT1A4.

WHAT THIS STUDY ADDS

- The absolute bioavailability of imidafenacin in human is 57.8%.
- The pharmacokinetic profiles of imidafenacin after intravenous administration are revealed.
- The formation of metabolites in the plasma is caused mainly by first-pass effects.

AIMS

To investigate the absolute bioavailability of imidafenacin, a new muscarinic receptor antagonist, a single oral dose of 0.1 mg imidafenacin was compared with an intravenous (i.v.) infusion dose of 0.028 mg of the drug in healthy subjects.

METHODS

Fourteen healthy male subjects, aged 21–45 years, received a single oral dose of 0.1 mg imidafenacin or an i.v. infusion dose of 0.028 mg imidafenacin over 15 min at two treatment sessions separated by a 1-week wash-out period. Plasma concentrations of imidafenacin and the major metabolites M-2 and imidafenacin-N-glucuronide (N-Glu) were determined. The urinary excretion of imidafenacin was also evaluated. Analytes in biological samples were measured by liquid chromatography tandem mass spectrometry.

RESULTS

The absolute oral bioavailability of imidafenacin was 57.8% (95% confidence interval 54.1, 61.4) with a total clearance of 29.5 ± 6.3 l h⁻¹. The steady-state volume of distribution was 122 ± 28 l, suggesting that imidafenacin distributes to tissues. Renal clearance after i.v. infusion was 3.44 ± 1.08 l h⁻¹, demonstrating that renal clearance plays only a minor role in the elimination of imidafenacin. The ratio of AUC_t of both M-2 and N-Glu to that of imidafenacin was reduced after i.v. infusion from that seen after oral administration, suggesting that M-2 and N-Glu in plasma after oral administration were generated primarily due to first-pass metabolism. No serious adverse events were reported during the study.

Conclusions

The absolute mean oral bioavailability of imidafenacin was determined to be 57.8%. Imidafenacin was well tolerated following both oral administration and i.v. infusion.

Introduction

Imidafenacin, 4-(2-methyl-1*H*-imidazol-1-yl)-2, 2-diphenylbutanamide, is a novel synthetic orally active muscarinic receptor antagonist developed for the treatment of overactive bladder (OAB). Imidafenacin, given at 0.1 mg twice daily, improved the symptoms of OAB with good tolerability and safety in clinical studies in Japan. OAB is defined by the International Continence Society as urgency, with or without urge incontinence, typically presenting with frequency and nocturia [1]. OAB, a highly prevalent, chronic disease that significantly impacts quality of life [2–5], has emerged as a significant cause of increasing healthcare costs and deterioration in social function [6, 7].

In preclinical animal studies, imidafenacin was rapidly absorbed with an absolute bioavailability of 5.6% in rats and 36.1% in dogs after oral administration. In Phase I clinical studies, imidafenacin was rapidly absorbed, reaching maximal plasma concentrations ($C_{\max}$) 1–3 h after oral administration. The drug was eliminated with a half-life of approximately 3 h, displaying dose-linear pharmacokinetics. Approximately 15% of imidafenacin is excreted in the urine; the drug is primarily eliminated by metabolism. *In vitro* studies using human hepatic microsomes have indicated that imidafenacin is primarily metabolized by CYP3A4 and UGT1A4. The oxidized form of the drug (M-2) and the N-glucuronide conjugate (N-Glu) are the major metabolites identified in human plasma after oral administration. These results indicate that CYP3A4 plays a role in metabolizing imidafenacin to M-2, whereas UGT1A4 plays a role in metabolizing imidafenacin to N-Glu.

This study sought to evaluate the absolute oral bioavailability of imidafenacin by comparing drug pharmacokinetics after oral administration and intravenous (i.v.) infusion.

Methods

Subjects and study design

Fourteen healthy male subjects, aged 18–45 years, were eligible for participation in this study. Subjects were judged to be in good health based on medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory variables. Exclusion criteria included a history of drug abuse, excessive alcohol consumption, smoking within the past 6 months, significant infection or known inflammatory process, acute gastrointestinal symptoms at the time of screening or admission, acute infection at the time of screening or admission, use of prescription drugs within 4 weeks of study medication dosing, and use of over-the-counter medications, excluding routine vitamins and paracetamol, but including meta-dose vitamin therapy, within 1 week of dosing with study medication.

Food or beverages containing grapefruit or St John's Wort were not allowed for at least 1 week prior to dosing with the study medication.

This was a single-centre (Kendle Clinical Pharmacology Unit, Utrecht, the Netherlands), open-labelled, randomized, single-dose, two-way crossover study, conducted in accordance with good clinical practice. The study protocol, written subject information sheet and consent form were approved by the Ethics Committee of the Stichting Therapeutische Evaluatie Geneesmiddelen Medisch Ethische Toetsingscommissie (Duivendrecht, the Netherlands). Written informed consent was obtained from each subject upon entering the study.

The 14 subjects were randomly divided into two groups (groups A and B) at a 1 : 1 ratio. Subjects in group A received a single oral dose of 0.1 mg imidafenacin on day 1 and an i.v. infusion of 0.028 mg imidafenacin on day 8, whereas subjects in group B received an i.v. infusion of 0.028 mg imidafenacin on day 1 and a tablet of 0.1 mg imidafenacin on day 8. The tablet was administered orally in the morning with 200 ml of water. Imidafenacin (3 ml) aqueous injection ($12.5 \mu\text{g ml}^{-1}$) was mixed with physiological saline to make a 20-ml solution. The prepared injection solution was administered intravenously to subjects in the morning at an infusion rate of 1 ml min^{-1} for 15 min using a constant rate infusion pump. For each treatment session, subjects fasted from midnight to 4 h post-dose. Both the oral and i.v. infusion formulations of imidafenacin were manufactured in accordance with Good Manufacturing Practice. Tablets, each containing 0.1 mg imidafenacin, were manufactured by Kyorin Pharmaceutical Co., Ltd. (Tokyo, Japan), whereas the i.v. infusion formulation was manufactured by Pro Pharma (Glasgow, UK).

The oral dose of 0.1 mg imidafenacin, the dose used in clinical studies for the treatment of OAB, was well tolerated. The predicted maximum plasma concentration ($C_{\max}$) after the 0.028-mg i.v. dose over 15 min was less than the $C_{\max}$ of a 0.5-mg oral dose, for which tolerability was confirmed in the Phase I studies of Japanese and White individuals.

Pharmacokinetic sampling

To determine the plasma concentrations of imidafenacin and its major metabolites, M-2 and imidafenacin-N-glucuronide (N-Glu), 15-ml blood samples were collected into heparinized tubes from the forearms of subjects. For patients receiving oral administration, samples were taken predose and at 30, 60 and 90 min and 2, 3, 4, 6, 8, 12 and 24 h postdose. For patients receiving i.v. infusions, blood samples were acquired predose and at 5, 10, 15, 20, 30, 45 and 75 min and 2, 4, 6, 8, 12 and 24 h postdose. Blood samples were centrifuged at 4°C at $1500\text{--}1800 g$ for 10 min; the resulting plasma samples were stored below -80°C until the day of analysis. Complete urine samples were collected for 12 h prior to and at 0–3, 3–6, 6–12, 12–24 and 24–48 h after oral administration or i.v. infusion. At the

end of each collection period, the total volume was recorded and aliquots (10 ml) were stored at -20°C until analysis.

Analytical method

Plasma concentrations of imidafenacin, M-2 and N-Glu and urine concentrations of imidafenacin were determined by liquid chromatography with tandem mass spectrometry (LC/MS/MS) (API3000; Applied Biosystems, Foster City, CA, USA/MDS Sciex, Concord, ON, Canada).

Plasma concentrations of imidafenacin and M-2

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). Reconstituted samples (20 μl) were injected onto LC/MS/MS for quantification. Protonated molecules were used as precursor ions with multiple reaction monitoring of the following transitions for imidafenacin, M-2 and internal standard, respectively: m/z 320 > 238, m/z 352 > 238 and m/z 334 > 238. The quantitative ranges detectable for both imidafenacin and M-2 were 10–500 pg ml^{-1} . Quality control samples at three concentrations (20, 100 and 400 pg ml^{-1}) were used. The overall precision [% coefficient of variation (CV)] for imidafenacin and M-2 ranged from 2.8 to 8.5% and 5.8 to 8.6%, respectively. The accuracy (bias %) for imidafenacin and M-2 ranged from -13.5 to 13.0% and -14.5 to 11.5%, respectively.

Plasma concentration of N-Glu

Plasma samples (0.2 ml) containing internal standards and 0.7 ml of water containing 0.1% formic acid were applied to OASIS HLB[®] columns (Waters, Milford, MA, USA), which had first been conditioned with 1 ml of methanol and 1 ml of water containing 0.1% formic acid. After adsorption of the samples, cartridges were washed four times with 1 ml of water containing 5% methanol. 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 (73% water containing 0.1% formic acid and 27% acetonitrile). Reconstituted samples (20 μl) were injected onto LC/MS/MS for quantification. Protonated molecules were used as precursor ions with multiple reaction monitoring of the following transitions for N-Glu and internal standard, respectively: m/z 496 > 238 and m/z 334 > 238. The quantitative range for N-Glu measurement was 50–5000 pg ml^{-1} . Quality control samples at three concentrations (100, 500 and 4000 pg ml^{-1}) were used. The overall

precision (% CV) and the accuracy (bias %) ranged from 9.2 to 12.4% and -12.1 to 14.0%, respectively.

Urine concentration of imidafenacin

Urine samples (1 ml) containing internal standards were applied to C18 solid-phase extraction columns, which had first been conditioned with 1 ml of methanol, 1 ml of water and 1 ml of 0.2 mol l^{-1} boric acid buffer (pH 9.0). After adsorption of the samples, cartridges were washed twice with 1 ml of 0.2 mol l^{-1} boric acid buffer (pH 9.0). 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 (80% water containing 0.1% formic acid and 20% acetonitrile). Reconstituted samples (10 μl) were injected onto LC/MS/MS for quantification. Protonated molecules were used as precursor ions with multiple reaction monitoring of the above-mentioned transitions for M-2 and internal standard. The quantitative range for urinary imidafenacin was 0.2–50 ng ml^{-1} . Quality control samples at three concentrations (0.5, 5 and 40 pg ml^{-1}) were used. The overall precision (% CV) and the accuracy (bias %) ranged from 4.4 to 11.3% and -12.0 to 7.0%, respectively.

Pharmacokinetic analysis

Pharmacokinetic analyses of plasma imidafenacin, M-2 and N-Glu were performed using WinNonlin Professional[®] software, Ver.4.0.1 (Pharsight Corp., Mountain View, CA, USA). The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained directly from the original data. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2$ divided by the elimination rate constant (k_{el}), which was determined by linear regression analysis of the log-linear part of the plasma concentration–time curve. The area under the plasma concentration–time curve from time zero to the time of the last measurable concentration (AUC_t) was calculated using the linear trapezoidal rule and the AUC_{∞} by dividing the last measurable concentration by k_{el} . For imidafenacin, we also calculated the absolute bioavailability (BA) with 95% confidence intervals (CI), the total clearance (CL_{tot}), the steady-state volume of distribution (V_{ss}) and the oral clearance (CL/F). The BA was estimated from the equation $\text{BA} = (\text{AUC}_{\infty(\text{po})} \times \text{dose}_{(\text{iv})}) / (\text{AUC}_{\infty(\text{iv})} \times \text{dose}_{(\text{po})})$, where $\text{dose}_{(\text{iv})}$ is the dose administered intravenously and $\text{dose}_{(\text{po})}$ is the dose administered orally.

The amount and percentage of the imidafenacin dose excreted in the urine from zero to 48 h were also calculated from the urine concentration and urine volume. The renal clearance (CL_r) of imidafenacin was calculated as the amount of imidafenacin excreted in the urine divided by AUC_{∞} . All pharmacokinetic parameters were summarized by descriptive statistics.

A sample size of 14 was chosen to ensure that complete datasets from at least 12 subjects would be available for pharmacokinetic analysis. A sample size of 12 subjects was considered sufficient to estimate the difference in bioavail-

ability after oral administration and i.v. infusion, based on a CV of AUC in the previous study.

Safety and tolerability

Safety assessments were conducted at regular intervals until the patient was discharged 48 h after drug administration. The schedule was the same for both study sessions. The subjects returned for follow-up 5–7 days after receiving the last formulation.

The following safety parameters were assessed: vital signs, including blood pressure, pulse and respiration rate (at screening, on each admission, before drug administration, 5, 14 and 30 min and 1, 2, 3, 4, 6, 8, 12, 24 and 48 h after each dose, and at follow-up), oral temperature (at screening, on each admission, before drug administration, 24 and 48 h after each dose, and at follow-up), 12-lead ECG (at screening, on each admission, before drug administration, 13 min and 1, 2, 4, 8, 24 and 48 h after each dose, and at follow-up), lead II ECG (1 h before drug administration until 6 h after each dose), physical examination (at screening, on each admission, prior to discharge after each study session, and at follow-up), laboratory variables, including haematology, biochemistry, coagulation and urinalysis (at screening, on each admission, 24 and 48 h after drug administration, and at follow-up) and any adverse events (throughout).

Results

Subjects

Fourteen healthy male White subjects were enrolled in the study. The mean age of subjects was 32 years (range 21–45), with a mean body weight of 80.6 kg (range 63.1–101.4). All 14 subjects completed both study sessions. All subjects were included in the safety assessments and pharmacokinetic analyses of plasma imidafenacin, M-2 and N-Glu. One subject was excluded from the urinary analysis of imidafenacin, because the urine collection from 24 to 48 h after i.v. infusion was not performed according to schedule.

Pharmacokinetics

The plasma concentration–time profiles of imidafenacin after oral administration and i.v. infusion are shown in Figure 1, and the pharmacokinetic parameters of imidafenacin, M-2 and N-Glu after oral administration and i.v. infusion are summarized in Table 1. Following i.v. infusion, plasma concentrations of imidafenacin exhibited biphasic decline.

After oral administration, the plasma concentrations of imidafenacin increased rapidly, reaching C_{max} between 0.5 and 2 h postdose. The slopes of the terminal elimination phases for the plasma concentration–time curves after oral administration and i.v. infusion were parallel, indicating similar elimination half-lives of approximately 3 h. The

Figure 1

The mean + SD plasma concentration profiles of imidafenacin after a single oral administration (0.1 mg) (○) or single intravenous (i.v.) infusion (0.028 mg over 15 min) (●) in healthy subjects. The ordinate is a (A) linear scale or (B) log scale

absolute bioavailability of oral imidafenacin, calculated from the AUC_{∞} following i.v. infusion and oral administration, was 57.8% (95% CI 54.1, 61.4).

CL_{tot} , CL_r and V_{ss} following i.v. infusion were $29.5 \pm 6.3 \text{ l h}^{-1}$, $3.44 \pm 1.08 \text{ l h}^{-1}$ and $122 \pm 28 \text{ l}$, respectively. The differences between CL_{tot} and CL_r allowed us to estimate the nonrenal clearance at approximately 26 l h^{-1} .

The percentages of the intact dose excreted in the urine over the 48 h following oral administration and i.v. infusion were 7.8% and 11.9%, respectively. Urinary excretion of imidafenacin was nearly complete at 24 h; the percentage of the intact dose excreted in the urine from 24 to 48 h was only 0.1% after either treatment.

M-2 and N-Glu were detectable at only a few time points in most subjects after i.v. infusion. Therefore, the pharmacokinetic parameters of M-2 and N-Glu ($t_{1/2}$ and AUC_{∞}) after i.v. infusion could not be calculated. The ratio of

Table 1

Pharmacokinetic parameters of imidafenacin, M-2, and N-Glu after a single oral administration (0.1 mg) or single intravenous (i.v.) infusion (0.028 mg over 15 min) in healthy subjects ($n = 14$)

Pharmacokinetic parameters	Imidafenacin Oral	i.v.	M-2 Oral	i.v.	N-Glu Oral	i.v.
$C_{\max}$ (pg ml ⁻¹)	416 (103)	476 (169)	82.4 (21.7)	10.9 (6.4)	417 (88)	85.2 (32.4)
$t_{\max}$ (h)*	1.0 (0.50–2.0)	0.25 (0.17–0.25)	1.5 (1.0–3.0)	2.0 (1.3–4.0)‡	2.0 (1.5–3.0)	4.0 (2.0–6.0)†
$t_{1/2}$ (h)	3.0 (0.3)	3.2 (0.4)	4.1 (0.8)	NC	3.9 (0.6)	NC
AUC_{∞} (pg ml ⁻¹ h ⁻¹)	2060 (570)	993 (200)	546 (126)	NC	3051 (846)	NC
AUC_t (pg ml ⁻¹ h ⁻¹)	1910 (520)	899 (200)	477 (124)	53.0 (47.3)	2560 (720)	443 (240)
CL_{tot} (l h ⁻¹)	–	29.5 (6.3)	–	–	–	–
V_{ss} (l)	–	122 (28)	–	–	–	–
CL/F (l h ⁻¹)	52.0 (13.6)	–	–	–	–	–
Urinary excretion rate (% of dose)	7.8 (2.3)	11.9 (4.0)	–	–	–	–
CL_r (l h ⁻¹)	3.99 (1.00)†	3.44 (1.08)†	–	–	–	–
Absolute bioavailability (%)	57.8 (95% CI: 54.1, 61.4)	–	–	–	–	–

Values are arithmetic mean ($\pm$ SD). *Median (range). † $n = 13$. ‡ $n = 11$. CI, Confidence interval; NC, not calculated.

the AUC_t of M-2 to that of imidafenacin was 0.25 (95% CI 0.20, 0.29) following oral administration; this value was significantly lower at 0.073 (95% CI 0.049, 0.096) following i.v. infusion of the drug. The ratio of the AUC_t of N-Glu to that of imidafenacin was 1.38 (95% CI 1.19, 1.57) following oral administration, which was higher than that seen for N-Glu following i.v. infusion at 0.55 (95% CI 0.41, 0.69).

Safety and tolerability

Imidafenacin was well tolerated after both oral and i.v. doses. Five subjects (35.7%) reported a total of five adverse events following oral administration, whereas six subjects (42.9%) reported a total of nine adverse events following i.v. infusion. There were no serious adverse events. All of these were mild; none required any treatment and none led to withdrawal from the study. The most commonly reported adverse events were related to cannula or venepuncture sites. There were minimal differences between treatments with respect to treatment-related adverse events; one subject had a headache, another reported fatigue after oral treatment, one reported dizziness and increased urine output, one reported a reaction at the cannula site, and one reported skin pain following i.v. infusion. Few laboratory values were outside the normal range; none of these was clinically significant. Although some abnormalities were noted in the 12-lead ECG recordings (intermittent first-degree heart block, sinus bradycardia with sinus arrhythmia) after study drug administration, these were few and were considered clinically acceptable in all cases. There were no clinically relevant changes in any ECG intervals. One subject, however, exhibited a clinically significant change in the continuous ECG recording (sustained ventricular escape rhythm) on two occasions, but this arrhythmia was not observed on repeat recordings. Vital signs following both administrations were similar and did not demonstrate any clinically significant changes from pretreatment values.

Discussion

In this study, imidafenacin exhibited rapid oral absorption, achieving peak plasma concentrations approximately 1 h after administration. This observation is consistent with the results of previous Phase I studies. Following i.v. infusion, the V_{ss} of imidafenacin was high, suggesting that imidafenacin is distributed throughout tissues.

The absolute oral bioavailability of imidafenacin was determined to be 57.8%. In a previous mass balance study, no ¹⁴C-imidafenacin could be detected in faeces following administration of ¹⁴C-imidafenacin (0.25 mg) to healthy adult males [9]. This result suggests that imidafenacin is almost completely absorbed from the gastrointestinal tract after oral administration. These results allow us to estimate that the first-pass effect after oral administration was approximately 40%.

Furthermore, the fact that the percentage of the intact dose excreted in the urine after i.v. infusion was low infers that renal clearance plays a minor role in the elimination of imidafenacin. Based on results indicating that the nonrenal clearance ($CL_{\text{tot}} - CL_r$) was 26 l h⁻¹ and the blood/plasma distribution ratio of ¹⁴C-imidafenacin, determined in an *in vitro* study, was 0.64, we estimated nonrenal blood clearance at 41 l h⁻¹. Human hepatic blood flow is approximately 1.2 l h⁻¹ kg⁻¹ [8]; thus, in this study, the mean hepatic blood flow of our subjects (mean weight 80.6 kg) was approximately 97 l h⁻¹. Assuming that nonrenal clearance can be attributed to hepatic clearance, the hepatic extraction rate (hepatic clearance/hepatic blood flow $\times$ 100) was approximately 42%. This value closely approximates the rate of imidafenacin elimination (around 40%) caused by the first-pass effect; consequently, the majority of the first-pass effect is thought to be associated with hepatic metabolism.

For both M-2 and N-Glu, the ratio of the AUC_t of imidafenacin to the metabolite was lower after i.v. infusion

than after oral administration. This result suggests that the greatest contributor to the formation of M-2 and N-Glu in the plasma after oral dosing of imidafenacin is the first-pass effects.

Treatments were well tolerated; no serious adverse events were reported during the study. Dry mouth, the most commonly reported adverse event of anticholinergic agents, was not observed in any subject.

In conclusion, this study has shown tolerability of 0.1 mg imidafenacin given orally and 0.028 mg imidafenacin given by i.v. infusion. The absolute bioavailability of imidafenacin after oral administration was 57.8%.

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