*Full Paper***Open-Label Study of the Safety and Pharmacokinetics of Solifenacin in Subjects With Hepatic Impairment**Mirjam Kuipers¹, Ronald Smulders^{1,*}, Walter Krauwinkel¹, and Timothy Hoon²¹Astellas Pharma Europe BV, Leiderdorp, The Netherlands²Astellas Pharma US, Deerfield, IL 60015, USA

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Abstract. Determining the pharmacokinetics and safety of solifenacin succinate, a once-daily, oral antimuscarinic agent indicated for treatment of overactive bladder, in subjects with hepatic impairment. In this open-label study, 16 subjects (eight with moderate hepatic impairment [defined as a Child-Pugh score of 7–9], eight healthy) received a single oral 10 mg solifenacin dose. Blood and urine were collected for pharmacokinetic assessments. Pharmacokinetic parameters (primary: area under the plasma concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$] and maximum plasma concentration [C_{max}]) and safety were evaluated for solifenacin and its metabolites. There were no clinically relevant differences in safety. Moderate hepatic impairment increased $AUC_{0-\infty}$ by 60%, and the mean elimination half-life of solifenacin and several of its metabolites was longer versus healthy subjects. Mean C_{max} values were comparable between the groups. A single oral dose of solifenacin was well tolerated in hepatically impaired and healthy subjects; however, moderate hepatic impairment influenced solifenacin pharmacokinetics. In patients with mild hepatic impairment, solifenacin may be used without special caution; however, in patients with moderate hepatic impairment, doses greater than 5 mg are not recommended and the 5 mg dose should be used with caution.

Keywords: hepatic impairment, overactive bladder, pharmacokinetics, safety and tolerability, solifenacin

Introduction

Overactive bladder (OAB) is a distressing medical condition characterized by urgency, with or without urge incontinence, and usually accompanied by frequency and nocturia (1, 2). The symptoms suggest urodynamically demonstrable detrusor muscle overactivity, and they occur in the absence of local pathologic factors that might account for them. An estimated 50–100 million persons worldwide have symptoms of OAB (3). A European population-based survey estimated that the prevalence of OAB symptoms was 16.6% in persons aged 40 years and older, with the overall prevalence of OAB being slightly greater in women than men (4). The prevalence of OAB increases with age, with men aged 60 years and older having a higher prevalence rate than

women in the same age group. OAB and its associated incontinence adversely affect both physical and mental health dimensions of quality of life, with greater impairment in quality of life as symptom severity increases (5). The mainstay of therapy for OAB has been the muscarinic receptor antagonists (e.g., oxybutynin, tolterodine), although their usefulness is limited by their side-effect profiles (6, 7).

Solifenacin succinate is a once-daily, oral antimuscarinic agent available for the treatment of OAB (8). In clinical studies, solifenacin has statistically significantly improved all key symptoms of OAB, including urgency (9–15). In a study with healthy male volunteers, the mean absolute bioavailability of solifenacin was 88% (16). It is also highly protein bound to human plasma protein, primarily to α_1 -acid glycoprotein (α_1 -AGP) (86.0%–89.2%) (17), and it demonstrates a mean steady-state volume of distribution of 599 L (16). Metabolism plays a major role in the elimination of solifenacin; of the 69.2% of a single oral dose excreted

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in urine, less than 15% was recovered as intact solifenacin (18). Four main metabolites of solifenacin have been analyzed in the present study, three of which are primarily formed in the liver by the cytochrome P450 (CYP) isoenzyme 3A4 (19). These are the M2 (solifenacin *N*-oxide)-, M3 (4*R*-hydroxy solifenacin)-, and M4 (4*R*-hydroxy solifenacin *N*-oxide)-metabolites (18). The M5-metabolite (solifenacin *N*-glucuronide) occurs as a result of the direct glucuronidation of solifenacin. Therefore, hepatic impairment may alter the pharmacokinetics (PK) and impact the clinical activity of solifenacin (20). The objectives of the present study were to determine the effects of hepatic impairment on the safety and PK of solifenacin.

Materials and Methods

Study design

A single-centre, open-label, parallel-group study was performed. Subjects with moderate hepatic impairment and healthy subjects received a single oral 10-mg dose of solifenacin. Plasma and urine samples were collected for determination of PK parameters. The study was conducted at the Institute of Preventive and Clinical Medicine in Bratislava, Slovak Republic, in accordance with the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements. The study was approved by the independent ethics committee, and all subjects gave written, informed consent before participating in the study.

Subjects

Eight subjects with moderate hepatic impairment [defined as a Child-Pugh score of 7–9] and eight gender- and age-matched healthy subjects were enrolled in the study. Eligibility criteria included men and women 18–80 years of age with moderate hepatic impairment

defined as a Child-Pugh score of 7–9 diagnosed by clinical and biochemical assessments or with cirrhosis confirmed by ultrasound. The Child-Pugh score is a composite rating (range 5–15) based on total bilirubin, serum albumin, prothrombin time, and presence of ascites and encephalopathy (21).

Subjects with hepatic impairment could have no other major organ dysfunction or clinically relevant disease. Women had to be either post-menopausal for at least 1 year, surgically sterile for at least 3 months, or non-pregnant, non-lactating and using an approved method of contraception, from 14 days prior to study entry to 14 days following study completion.

Study treatment

All study subjects received a single oral 10-mg dose of solifenacin formulated as a tablet, which was administered in the morning following an overnight fast that was continued for 4 h post-dose. Study subjects were admitted to the clinical study unit the day before dosing and remained until Day 8 post-dose. Subjects with hepatic impairment returned on Days 9, 11, and 13, and they were readmitted to the unit on Day 14 for 24 h. Approximately 1 week after final discharge, all subjects returned for a post-study follow-up visit.

Procedures

The overall study design and schedule of procedures are illustrated in Fig. 1. Safety and tolerability assessments included a physical examination at the pre- and post-study screenings and assessment of vital signs at the pre- and post-study screenings, on admission to the study unit, pre-dose, 6 and 12 h post-dose, and on Days 2–8 and 14 (subjects with hepatic impairment). The study protocol defined normal ranges for vital sign data as follows: pulse 40 to 80 beats per minute, systolic blood pressure (bp) 90 to 140 mmHg, and diastolic blood pressure 50 to 90 mmHg. Monitoring for adverse events (AEs) was done throughout the study to the post-

Days	–21 until –1	0	1 until 8	9, 11, 13	14 until 15	15 until 22	22 until 29
Healthy volunteers	Screening	Admission	Single dose solifenacin succinate + blood and urine collection			Post-study screening	
Patients with impaired liver	Screening	Admission	Single dose solifenacin succinate + blood and urine collection	Blood collection	Blood and urine collection		Post-study screening

Fig. 1. Schematic of study schedule.

study screening visit, and clinical laboratory testing (hematology, biochemistry, urinalysis) was performed at the pre- and post-study screenings, on admission to the study unit, at 24 and 144 h post-dose, and on Day 14 (subjects with hepatic impairment).

Pharmacokinetic procedures

Plasma and urine samples were collected to evaluate plasma and urine concentrations of solifenacin and its metabolites. However, the primary parameters for evaluating the effect of hepatic impairment were the area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of solifenacin. Serial blood samples were collected pre-dose and at 1, 2, 3.5, 5, 6.5, 8, 12, 24, 48, 72, 96, 132, and 168 h post-dose. Additional collection times for subjects with hepatic impairment were on Days 9, 11, 13, 14, and 15 post-dose. In healthy subjects, solifenacin has a terminal elimination half-life ($t_{1/2}$) of about 50 h (16). Collecting samples over 168 h corresponds to approximately $3 \times t_{1/2}$, which is sufficient to get reliable estimates of all PK parameters. Because an increase in $t_{1/2}$ was expected in subjects with hepatic impairment, samples were obtained over a longer period of time. Blood samples were stored on ice and centrifuged within 30 min of collection at $2500 \times g$ for 10 min at 4°C to obtain the plasma fraction. Plasma samples were stored at -20°C for a maximum of 24 h and thereafter at -70°C until shipped and assayed.

Urine collection times were pre-dose and at 0–6, 6–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144, and 144–168 h post-dose. In addition, a single 24-h urine collection was done (on either Day 14 or 15) for subjects with hepatic impairment. Urine samples were stored at 4°C until aliquots (four of 3 mL each) were taken for analysis. The aliquots were stored and shipped at -70°C .

Analyses of solifenacin and its metabolite concentrations were performed centrally by the Bioanalysis & Drug Metabolism of BDD, Astellas Pharma Europe BV, The Netherlands. High performance liquid chromatography with tandem mass spectrometry was used for analyses of parent drug and metabolite concentrations in both plasma and urine. The lower limit of quantification (LLQ) was 0.5 ng/mL in plasma and 5 ng/mL in urine for solifenacin and its metabolites.

Statistical methods

Statistical analyses were performed by Focus Clinical Drug Development GmbH (Neuss, Germany) under the supervision of the biostatistics section of Astellas Pharma Europe BV, using SAS[®] version 8.2.

Noncompartmental PK analysis was performed by the

Clinical Pharmacology Research Department of Astellas Pharma Europe BV, using WinNonlin 3.1 (Pharsight Corp. Mountain View, CA, USA). The linear-logarithmic trapezoidal rule was used to calculate AUC values. The primary PK variable ($AUC_{0-\infty}$) was calculated by the following equation:

$$AUC_{0-\infty} = AUC_{0-\text{last}} + C_t/\lambda_z$$

where $AUC_{0-\text{last}}$ is the AUC from time 0 to the last time point measured $\geq \text{LLQ}$, C_t is the last plasma concentration measured $\geq \text{LLQ}$, and λ_z is the terminal elimination rate constant determined by least squares regression analysis of terminal log-linear portions of the plasma concentration-time profile. The AUC and C_{max} values were logarithmically transformed and subjected to analysis of variance (ANOVA) to obtain 90% confidence intervals (CI) for the ratio of subjects with hepatic impairment to healthy subjects. If the 90% CI lay within the prespecified ranges of 0.80 to 1.25 for $AUC_{0-\infty}$ and 0.7 to 1.43 for C_{max} , it would be reasonable to conclude that moderate hepatic impairment had no clinically relevant effect on the PK of solifenacin. Other PK variables determined for solifenacin and its metabolites included time to reach maximum plasma concentration (t_{max}), $t_{1/2}$, apparent total body clearance (CL/F), and apparent volume of distribution (V_z/F). The PK parameters for urine included the amount of solifenacin excreted in urine over 168 h, measured in mg, the percentage of the dose excreted, and renal clearance (CL_R).

Results

Patients

A total of 16 subjects (eight with hepatic impairment, eight healthy) were enrolled in and completed the study. All subjects were white (five men, three women in each group), and the mean age was 44.3 years for each group. The respective mean body weight and mean body mass index were 80.8 kg and 26.0 kg/m^2 in the hepatic impairment group and 74.8 kg and 24.5 kg/m^2 in the healthy group. All subjects with hepatic impairment had stable cirrhosis and Child-Pugh classification scores of 7–9. In healthy subjects, a serum $\alpha 1$ -AGP concentration of (mean $\pm$ S.D.) $20.06 \pm 6.86 \mu\text{mol/L}$ on Day 0 was observed, while in subjects with hepatic impairment, a lower value of $11.56 \pm 3.10 \mu\text{mol/L}$ was found.

Pharmacokinetic findings

Plasma PK parameters for solifenacin are summarized in Table 1. Analysis of variance of the log transformed $AUC_{0-\infty}$ values showed a 60% increase in $AUC_{0-\infty}$ in subjects with moderate hepatic impairment compared with healthy subjects (point estimate of ratio impaired/healthy: 1.596), with the 90% CI for the ratio of AUC

Table 1. Plasma pharmacokinetic parameters for solifenacin in healthy subjects and in subjects with hepatic impairment

Pharmacokinetic parameter	Subjects	
	Healthy (n = 8)	Hepatic impairment (n = 8)
AUC _{0–last} (ng · h/mL)	621 ± 403	890 ± 237
AUC _{0–∞} (ng · h/mL)	749 ± 528	1042 ± 328
C _{max} (ng/mL)	11.0 ± 6.0	10.3 ± 3.3
t _{max} (h)	5.96 ± 0.77	4.77 ± 2.53
t _{1/2} (h)	49.9 ± 19.9	106 ± 48
CL/F (L/h)	13.7 ± 6.2	7.84 ± 2.26
V _z /F (L)	854 ± 244	1095 ± 326

Data are each a mean ± S.D. AUC_{0–∞} = area under the plasma concentration-time curve from time 0 to infinity, AUC_{0–last} = area under the plasma concentration-time curve from time 0 to time of last quantifiable sample, C_{max} = maximum plasma concentration, CL/F = apparent total body clearance, t_{max} = time to reach maximum plasma concentration, t_{1/2} = terminal elimination half-life, V_z/F = apparent volume of distribution.

Fig. 2. Mean plasma concentration-time profile of solifenacin in healthy subjects (n = 8) and in subjects with hepatic impairment (n = 8) after a single oral 10-mg dose of solifenacin.

values (impaired versus healthy) falling outside the prespecified level (90% CI, 1.05–2.43; coefficient of variation (CV), 50%). The mean ratio of C_{max} did not differ between groups (point estimate, 0.989; 90% CI, 0.70–1.40; CV, 40%). The mean plasma concentration-time profile indicated a slower elimination rate for solifenacin in subjects with hepatic impairment than in healthy subjects (Fig. 2). The t_{1/2} in subjects with hepatic impairment was approximately 2-fold higher when compared with healthy subjects (106 vs 50 h). Mean t_{max} was slightly shorter in subjects with hepatic impairment.

Urine PK parameters of solifenacin are summarized in Table 2. A smaller proportion of the dose was excreted renally as solifenacin through Day 8 (168 h post-dose) in subjects with hepatic impairment compared with healthy

Table 2. Urine pharmacokinetic parameters for solifenacin in healthy subjects and in subjects with hepatic impairment

Pharmacokinetic parameter	Subjects	
	Healthy (n = 8)	Hepatic impairment (n = 8)
Ae _{0–168h} (mg)	0.855 ± 0.293	0.598 ± 0.236
Percent excreted	11.3 ± 3.9	7.93 ± 3.13
CL _R (L/h)	1.51 ± 0.59	0.933 ± 0.452

Data are each a mean ± S.D. Ae_{0–168h} = amount excreted unchanged in the urine from time 0 to 168 h post-dose, CL_R = renal clearance.

subjects (mean ± S.D.: 7.9 ± 3.13% vs 11.3 ± 3.90%; CV: 39.5% vs 34.3%). However, this smaller amount was probably due to the longer t_{1/2} in patients with hepatic impairment; over an infinite period of time, the expected amount of solifenacin excreted would become approximately 0.89 mg, only slightly less than that expected amount excreted in healthy subjects. The CL_R of solifenacin was also lower in subjects with hepatic impairment (0.9 ± 0.45 vs 1.5 ± 0.59 L/h; CV: 48.4% vs 38.9%).

Plasma PK parameters for the four metabolites of solifenacin are summarized in Table 3, and the urine PK parameters are shown in Table 4. The M2 and M4 metabolites showed similar patterns in PK alterations. In subjects with hepatic impairment, mean maximum plasma concentrations of the M2 and M4 metabolites were approximately 1.5- to 1.6-fold lower and urinary excretion was approximately half that in healthy subjects. The t_{1/2} of both M2 and M4 was >90 h in subjects with hepatic impairment compared with 56–60 h in healthy subjects. Renal clearance of these metabolites in subjects with hepatic impairment was similar to that in healthy subjects (Table 4).

For the M3 and M5 metabolites, the mean plasma concentration-time profiles were not well defined as most samples were below the LLQ. The amount of M3 metabolite excreted in the urine was similar in both groups. The t_{1/2} of the M5 metabolite could not be determined due to insufficient plasma and urine data.

Safety and tolerability

The single oral dose of solifenacin 10 mg was well tolerated. Three of the 16 subjects reported a total of four AEs, with none being serious. Two AEs (increases in alanine aminotransferase and gamma glutamyl transferase) that occurred in one healthy subject were judged as mild and possibly related to solifenacin. Two AEs (menstrual disorder and back pain), reported by two subjects with hepatic impairment, were judged as moderate and unrelated to solifenacin administration.

Table 3. Plasma pharmacokinetic parameters for metabolites of solifenacin in healthy subjects and in subjects with hepatic impairment

Group (n = 8 each)	$t_{\max}$ (h)	$C_{\max}$ (ng/mL)	$AUC_{0-\text{last}}$ (ng · h/mL)	$t_{1/2}$ (h)
M2				
Healthy subjects	21.2 ± 8.0	2.81 ± 0.67	218 ± 42	60.5 ± 21.9
Hepatic impairment	3.90 ± 8.16	1.81 ± 0.91	77.7 ± 56.6	91.1 ± 37.1
M3				
Healthy subjects	49.0 ± 32.2	0.538 ± 0.030	9.94 ± 13.5	87.4 ± 25.4*
Hepatic impairment	6.52 ± 1.22	0.573 ± 0.043	7.60 ± 11.8	117 ± 34*
M4				
Healthy subjects	18.0 ± 6.4	1.67 ± 0.58	103 ± 33	56.0 ± 12.3*
Hepatic impairment	12.4 ± 8.1	1.15 ± 0.75	63.1 ± 70.7	96.5 ± 32.5
M5				
Healthy subjects	4.71 ± 1.27	0.872 ± 0.193	4.43 ± 2.02	ND
Hepatic impairment	5.00 ± 1.73	1.29 ± 0.78	26.4 ± 53.9	ND

Data are each a mean ± S.D. *Based on urinary excretion data, not plasma data. $AUC_{0-\text{last}}$ = area under the plasma concentration-time curve from time 0 to time of last quantifiable sample, $C_{\max}$ = maximum plasma concentration, ND = not determined, $t_{\max}$ = time to reach maximum plasma concentration, $t_{1/2}$ = terminal elimination half-life.

Table 4. Urine pharmacokinetic parameters for metabolites of solifenacin in healthy subjects and in subjects with hepatic impairment

Group	Ae_{0-168h} (mg)	Percent excreted	CL_R (L/h)
M2			
Healthy subjects	1.57 ± 0.37 (n = 8)	19.9 ± 4.7 (n = 8)	6.76 ± 1.49 (n = 8)
Hepatic impairment	0.83 ± 0.43 (n = 8)	10.5 ± 5.4 (n = 8)	6.96 ± 1.49 (n = 7)
M3			
Healthy subjects	0.412 ± 0.117 (n = 8)	5.23 ± 1.49 (n = 8)	ND
Hepatic impairment	0.384 ± 0.141 (n = 8)	4.88 ± 1.79 (n = 8)	ND
M4			
Healthy subjects	0.503 ± 0.127 (n = 8)	6.13 ± 1.55 (n = 8)	4.00 ± 0.90 (n = 8)
Hepatic impairment	0.286 ± 0.172 (n = 8)	3.48 ± 2.09 (n = 8)	3.76 ± 1.37 (n = 6)
M5			
Healthy subjects	0.0480 ± 0.0397 (n = 8)	0.43 ± 0.35 (n = 8)	ND
Hepatic impairment	0.136 ± 0.117 (n = 7)	1.21 ± 1.05 (n = 7)	ND

Data are each a mean ± S.D. Ae_{0-168h} = amount of solifenacin excreted in urine over 168 h, CL_R = renal clearance, ND = not determined.

Other than expected alterations in hepatic enzymes in subjects with hepatic impairment and the two elevations noted above in healthy subjects, there were no clinically relevant differences in laboratory parameters. In addition, there were no clinically relevant differences in physical examination findings. Mean data for vital signs measurements are shown in Table 5; there were no statistically significant differences in any of the para-

meters between healthy subjects and hepatically impaired patients at any time point.

Discussion

The objectives of this study were to evaluate the safety and PK of solifenacin in subjects with moderate hepatic impairment. The single oral 10-mg dose of

Table 5. Vital signs data throughout the study for healthy subjects and subjects with hepatic impairment receiving solifenacin

Characteristic	Screening	Day 0	Day 2 (t = 24 h)	Day 8 (t = 168 h)	Day 14
Systolic BP (mmHg)					
Healthy subjects	121.25 ± 16.14	123.06 ± 19.03	112.38 ± 14.19	117.00 ± 16.73	N/A
Hepatic impairment	119.06 ± 13.02	114.38 ± 12.66	110.31 ± 6.19	114.06 ± 8.76	108.13 ± 2.91
Diastolic BP (mmHg)					
Healthy subjects	78.69 ± 10.32	79.00 ± 9.92	73.38 ± 9.12	79.31 ± 11.62	N/A
Hepatic impairment	73.75 ± 11.65	72.81 ± 8.28	74.38 ± 6.91	76.88 ± 4.58	72.81 ± 2.48
Sitting pulse (bpm)					
Healthy subjects	69.19 ± 8.31	67.81 ± 10.30	61.44 ± 8.14	74.19 ± 11.54	N/A
Hepatic impairment	72.13 ± 2.85	70.75 ± 6.78	63.88 ± 6.05	73.88 ± 6.38	71.63 ± 7.58
Heart rate (bpm)					
Healthy subjects	63.9 ± 9.1	65.5 ± 9.2	56.0 ± 3.8	65.9 ± 8.0	N/A
Hepatic impairment	69.9 ± 12.6	65.4 ± 10.6	62.9 ± 11.3	62.4 ± 8.4	59.5 ± 8.1

Data are each a mean ± S.D. BP = blood pressure, bpm = beats per minute, N/A = not applicable.

solifenacin was well tolerated in healthy subjects and in subjects with moderate hepatic impairment, with no AEs of a serious nature during the study. Evaluations of vital signs and clinical laboratory parameters did not reveal any safety issues with solifenacin administration.

The study found that moderate hepatic impairment influenced the PK of solifenacin. The $AUC_{0-\infty}$ was increased by 60% in subjects with hepatic impairment compared with healthy subjects, with the 90% CI for the ratio of AUC falling outside the pre-specified limits for determining no effect of hepatic impairment on the PK of solifenacin. There was no difference in C_{max} between groups, but there was a 2-fold increase in $t_{1/2}$ in subjects with hepatic impairment. The increase in $t_{1/2}$ appeared to be more pronounced than the increase in AUC, suggesting that V_z/F was increased in subjects with hepatic impairment. The increased volume of distribution may also have contributed to the smaller amount of solifenacin excreted in urine over the collection period of 168 h. Plasma concentrations and urinary excretion of the M2 and M4 metabolites of solifenacin were lower and the $t_{1/2}$ longer, in subjects with hepatic impairment.

In healthy subjects and in subjects with hepatic impairment, an irregular plasma concentration-time profile of the M3 metabolite was obtained with concentrations close to the LLQ. Consequently, this may have affected the accuracy with which the values of C_{max} and $AUC_{0-\infty}$ could be estimated. The number of quantifiable plasma samples was insufficient to estimate $t_{1/2}$, but a sufficient number of urine samples were obtained to allow the calculation of $t_{1/2}$. The plasma profile of the metabolite M5 could only be followed over a period of

approximately 12 h. In two out of eight healthy subjects, all plasma concentrations remained below the LLQ. The number of quantifiable urine samples was insufficient to allow the estimate of $t_{1/2}$. The PK profile of solifenacin in healthy subjects in the present study was comparable to that previously determined in healthy subjects (16, 22).

The finding that hepatic impairment alters the PK of solifenacin is not unexpected since solifenacin is metabolized in the liver by CYP3A4 (18), the metabolic capacity of which is reduced by hepatic impairment (23). The increase in $AUC_{0-\infty}$ observed in subjects with hepatic impairment is probably attributable in large measure to a decrease in hepatic clearance of solifenacin rather than an increase in its absolute bioavailability, which previously was determined to be 88% (16). The increase in $t_{1/2}$ observed in this study supports decreased hepatic clearance as the explanation for the increase in $AUC_{0-\infty}$. The excretion data also suggested a decrease in the CL_R of solifenacin in subjects with hepatic impairment (20).

The M2, M3, and M4 metabolites of solifenacin are formed by CYP3A4, while the M5 metabolite is formed by direct glucuronidation (Astellas EU, Clinical Study Report CL-008: Open study to evaluate the pharmacokinetics of ^{14}C -labelled YM905 after single oral administration of 10 mg YM905 in healthy male volunteers. 2002). The lower plasma concentrations and urinary excretion of the M2 and M4 metabolites in subjects with hepatic impairment suggest a reduced hepatic metabolic capacity leading to decreased metabolite formation. The higher plasma concentrations of the M5 metabolite that were detectable over a longer period in subjects with

hepatic impairment compared with healthy subjects in this study suggest that its formation by glucuronidation is not reduced by hepatic impairment. In fact, this pathway probably plays a compensatory role in the metabolic elimination of solifenacin in hepatic impairment patients. However, an accurate assessment of M5 clearance is needed to prove this point.

The plasma concentration of $\alpha 1$ -AGP may be reduced in cases of hepatic impairment, possibly affecting a drug's clearance and distribution. Subjects with hepatic impairment in this study did have a low $\alpha 1$ -AGP concentration on Day 0 compared with that in healthy subjects (20.06 ± 6.86 vs 11.56 ± 3.10 $\mu\text{mol/L}$). Solifenacin is normally highly bound to $\alpha 1$ -AGP (free fraction 2%) in healthy subjects (17). The lower $\alpha 1$ -AGP concentration may have led to an increase in the unbound fraction of solifenacin. Unfortunately, plasma concentrations were too low to allow the estimate of the unbound fraction. The possible increase in the unbound fraction of solifenacin may have contributed to the increase in V_z/F observed in subjects with hepatic impairment.

Metabolism plays a major role in the elimination of solifenacin; 69.2% of a single oral dose is excreted in the urine (18). In the present study, recovery of solifenacin in the urine as the parent compound and metabolites was lower in subjects with hepatic impairment (28% vs 43% of the dose). However, this apparent decrease in the amount excreted may be attributable to the difference in $t_{1/2}$ between the two groups of subjects. Urine was collected over a period of 168 h, which corresponds to approximately 3.4 half-lives in healthy subjects, during which 91% of the dose will be eliminated. In subjects with hepatic impairment, a collection time of 168 h corresponds to 1.6 half-lives, during which only 67% of the dose will have been eliminated.

The CL_R of the M2 and M4 metabolites was unaffected and was higher than that of the parent compound in subjects with hepatic impairment, suggesting that these metabolites were more easily eliminated by the kidney compared with the parent compound. The $t_{1/2}$ values for the M2 and M4 metabolites were longer in subjects with hepatic impairment than in healthy subjects, but similar to that of the parent compound in patients with hepatic impairment. The within-group (healthy and hepatically impaired) similarities of the half-lives of solifenacin, M2, and M4 suggest the apparent $t_{1/2}$ of the metabolites may represent the rate at which each was formed from solifenacin (flip-flop kinetics). Since in healthy subjects and in subjects with hepatic impairment the concentration-time profile of M3 was not well defined, any difference between the two groups of subjects may have been obscured. However, the amounts excreted in urine were close in both groups

of subjects, suggesting the formation of M3 is similar in both groups of subjects. Comparison of the $t_{1/2}$ of the M3 metabolite and solifenacin suggested that the elimination of M3 may proceed at a slower rate than that of the parent compound, particularly in healthy subjects.

One limitation of the study was that it included only a single dose of solifenacin. However, in healthy subjects it was found that solifenacin and its metabolites M2 – M5 follow linear PK over a wide dose range [5 – 100 mg after a single dose in the case of solifenacin (22) and 5 – 10 mg at steady-state for solifenacin and its metabolites (24)]. Furthermore, the PK of solifenacin did not change during multiple dosing. Assuming that the same is true in subjects with moderate hepatic impairment, one would expect the average plasma concentrations of solifenacin over a dosing interval to be higher in subjects with hepatic impairment than in healthy subjects and that twice as much time would be needed before steady-state was reached. The $t_{1/2}$ of solifenacin in healthy subjects amounted to 49.9 h; therefore steady-state with once-daily dosing would be expected to be reached after approximately 8 days. In subjects with moderate hepatic impairment, $t_{1/2}$ increased to 106 h, indicating that steady-state in these patients would be reached after approximately 16 – 18 days. As $t_{1/2}$ of the M2, M3, and M4 metabolites were close to that of solifenacin in patients with hepatic impairment, it could be expected that steady-state for these metabolites would also be reached after approximately 16 – 18 days. Although the $t_{1/2}$ of the M5 metabolite could not be determined, the AUC (along with the AUC of the other metabolites) remained much lower than that of solifenacin in these patients. Therefore, in subjects with moderate hepatic impairment, the steady-state plasma concentration of solifenacin given at the dose of 5 mg once daily would be comparable to that of solifenacin at a dose of 8 mg once daily in healthy subjects. This is acceptable, as both 5 and 10 mg once-daily are marketed doses. A 5 mg once-daily dose of solifenacin can therefore be used in subjects with moderate hepatic impairment, but with caution, as there may be individuals in whom higher plasma concentrations are reached than those observed in this study. Increasing the dose of solifenacin to 10 mg once daily in patients with moderate hepatic impairment may result in a plasma concentration comparable to that of a non-marketed dose of 16 mg in healthy subjects, and is therefore not recommended in these patients.

The PK profile of a single oral 10-mg dose of solifenacin was altered by moderate hepatic impairment, resulting in a higher exposure and a longer $t_{1/2}$. As solifenacin is to be administered chronically, solifenacin

may be used without special caution in patients with mild hepatic impairment; doses less than or equal to 5 mg may be used safely in patients with moderate hepatic impairment, while doses greater than 5 mg should be used with caution.

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