DOI:10.1111/j.1365-2125.2006.02638.x

Multiple doses of the antimuscarinic agent solifenacin do not affect the pharmacodynamics or pharmacokinetics of warfarin or the steady-state pharmacokinetics of digoxin in healthy subjects

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Keywords
digoxin, overactive bladder, pharmacokinetics, solifenacin succinate, warfarin, YM905

Received
14 January 2004
Accepted
13 January 2006
Published *OnlineEarly*
9 June 2006

Aims
Solifenacin succinate is used for the treatment of overactive bladder (OAB). The potential for pharmacokinetic and/or pharmacodynamic interactions between solifenacin and warfarin or digoxin was investigated.

Methods
The solifenacin–warfarin study was a two-period crossover trial conducted in healthy males. Subjects received warfarin on the 10th day of 16 days of dosing with either solifenacin or placebo. The solifenacin–digoxin study was an one-sequence crossover trial conducted in healthy males and females. Following a phase-in period for digoxin, solifenacin was administered concomitantly with the drug on days 9–18.

Results
The $AUC_{PT;\ 0-168\ h}$ following a single dose of warfarin was unchanged in the presence of solifenacin [point estimate = 1.005; 90% confidence interval (CI) 0.98, 1.02)]. The $AUC_{0-\infty}$ values for both warfarin enantiomers were also unchanged. A small increase in the C_{max} of digoxin was observed during treatment with solifenacin, but for $AUC_{ss,tau}$ and C_{max} the 90% CI fell within the prespecified interval of 0.80–1.25. Combined administration of solifenacin and warfarin or digoxin was well tolerated.

Conclusions
Since the pharmacokinetics and pharmacodynamics of a single dose of warfarin and the steady-state pharmacokinetics of digoxin were not affected by coadministration of solifenacin in healthy subjects, the need for dosing adjustments for digoxin and/or warfarin does not seem warranted.

Introduction

Overactive bladder (OAB) is a chronic, debilitating disorder associated with high economic and social costs [1]. It is characterized by symptoms of urgency, with or without urge incontinence, and is usually accompanied by frequency and nocturia [2, 3]. Overactive bladder affects up to 22% of European and American adults, with higher prevalence rates at older ages [4, 5]. Therapy with antimuscarinic agents remains the mainstay of treatment for OAB, but patient compliance can be limited by the occurrence of anticholinergic side-effects [6].

Solifenacin is a once-daily oral antimuscarinic agent for the treatment of OAB, which has demonstrated functional selectivity for bladder compared with other

organs in preclinical studies and a phase I clinical study [7–10]. In phase II and III trials, treatment with solifenacin 5 mg and 10 mg daily decreased all major symptoms of OAB and was associated with a favourable tolerability profile [7, 11].

Solifenacin is extensively metabolized in the liver by cytochrome P450 (CYP) 3A4, which is responsible for metabolizing the majority of currently marketed drugs [12, 13]. The potential of other forms of CYP to metabolize solifenacin was minor compared with CYP3A4. Because the prevalence of OAB increases with age, the population likely to receive treatment with solifenacin are also likely to be taking other medication, and thus it is important to evaluate the potential for interactions between solifenacin and other substrates of CYP3A4.

Warfarin is a racemic mixture of S- and R-enantiomers. The S-enantiomer has much greater anticoagulant activity than the R-enantiomer and is mainly metabolized by CYP2C9 [14]. As the R-enantiomer of warfarin is a substrate of CYP3A4 (as well as CYP1A2) and as the anticoagulant effects of warfarin have a narrow therapeutic window [15], we investigated the potential for a pharmacokinetic or pharmacodynamic interaction between solifenacin and racemic warfarin. The tolerability of warfarin and solifenacin administered concomitantly was also evaluated.

P-glycoprotein (P-gp) (the multidrug-resistant transporter MDR1) is a membrane efflux transport protein which is recognized as a major determinant of the oral absorption and renal excretion of a number of drugs, including the cardiac glycoside digoxin [16–18]. Modulators of P-gp have been reported to affect the bioavailability of digoxin in humans [19, 20] and to inhibit its renal clearance *in vitro* [16]. Solifenacin is a weak inhibitor of P-gp (IC_{50} = 5.1 μM) [21], and therefore we have investigated the potential effect of solifenacin on the steady-state pharmacokinetics of digoxin and the tolerability of solifenacin and digoxin administered concomitantly.

Since solifenacin is an antimuscarinic drug, it may affect gastrointestinal motility and consequently, the rate and/or extent of absorption of warfarin and digoxin.

In summary, the aim of these studies was to evaluate the potential interactions between solifenacin and warfarin and digoxin.

Subjects and methods

Subjects

The solifenacin–warfarin study was conducted in 12 healthy men aged 18–45 years and weighing 60–100 kg. All subjects gave informed consent before participation in the study. Women were excluded because of the teratogenic potential of warfarin. The solifenacin–digoxin study was conducted in 24 healthy subjects (12 men, 12 women) aged 18–55 years, weighing 60–100 kg (men) and 45–85 kg (women). Both studies were conducted at a single centre.

Exclusion criteria, which were similar in both studies, included known allergy to any study drug, clinically significant upper gastrointestinal tract symptoms likely to interfere with drug absorption, any clinically relevant medical history or condition likely to interfere with the objectives of the study or safety of the subject, a positive test for drugs of abuse or alcohol on the day of admission to the clinical unit, use of any drug (excluding paracetamol or contraceptives) within 2 weeks prior to the study and participation in any other clinical study within 3 months prior to initiation of the present study.

Study designs

The solifenacin–warfarin study was conducted in England and employed a randomized, double-blind, placebo-controlled, two-period crossover design. The two study periods were separated by 10 days (corresponding to approximately five times the elimination half-life determined in previous studies) to allow for complete elimination of solifenacin prior to the start of the next period. Subjects received a single 25-mg oral dose of warfarin on the 10th of 16 days of dosing with either solifenacin 10 mg once daily or matching placebo. The study was a randomized, double-blind, crossover design with regard to solifenacin *vs.* placebo and an open-label design with regard to the administration of warfarin.

Samples of venous blood were collected for assay of R- and S-warfarin before each dose of warfarin and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h postdose. Samples of venous blood for the determination of solifenacin concentrations were taken on study day 10 of each study period before administration of solifenacin and at 1, 2, 3, 4, 6, 8 and 12 h postdose. Additional predose samples were taken on study days 8, 9, 11, 12, 14 and 16.

The solifenacin–digoxin study was conducted in the Netherlands and employed an open-label, multiple-dose, one-sequence, crossover design. Twenty-four subjects were admitted to the clinical unit for 21 days. Subjects received a loading dose of 0.250 mg digoxin on day 1, followed by daily doses of 0.125 mg digoxin on days 2–18. Solifenacin 10 mg daily was administered concomitantly with digoxin on days 9–18.

Samples of venous blood for the assay of digoxin were collected into glass serum tubes before and at the following times after dosing with digoxin on study days 8 and 18: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 and 24 h.

On days 6, 7, 16 and 17 predose specimens were collected for the measurement of trough digoxin values. On days 8 and 18, urine samples for the determination of digoxin concentrations were collected over 24 h after dosing. Blood samples for the assay of solifenacin were taken on day 18 before the drug was administered and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18 and 24 h postdose. On days 16 and 17, predose specimens were collected for the measurement of trough solifenacin values.

An independent ethics committee of the 'Stichting Beoordeling Ethiek Bio-medisch Onderzoek', Assen, the Netherlands, approved the digoxin study protocol and the Independent Ethics Committee, Medeval Limited, Manchester, UK approved the warfarin protocol. Both studies were conducted in accordance with the principles of the Declaration of Helsinki and of the International Conference on Harmonization Guidelines for Good Clinical Practice.

Determination of warfarin, digoxin and solifenacin concentrations in plasma, serum and urine

Blood samples for R- and S-warfarin were collected into tubes containing lithium-heparin and centrifuged within 30 min of collection. Plasma was harvested and stored within 30 min at −70 °C until assay. Analysis of R- and S-warfarin was performed by Pharma Bio-Research Group B.V., the Netherlands. R- and S-warfarin were extracted from 500 µl plasma under acidic conditions with 5 ml of n-heptane and dichloromethane (5 : 1, v/v). After evaporation of the organic phase, the residue was redissolved in 250 µl of mobile phase of which 25 µl was injected. Separation was performed by two-dimensional reversed-phase high-performance liquid chromatography, using first a 5 µm Lichrosphere® 100RP C18 (EC) column (125 × 3 mm) (conditioned at approximately 30 °C) with a mobile phase consisting of a mixture of 0.5 M sodium perchlorate buffer (pH 3.0) and acetonitrile (60 : 40, v/v) and second a Chiracel OD-R® column (250 × 4.6 mm) with a mobile phase consisting of a mixture of 0.5 M sodium perchlorate buffer (pH 3.0) and acetonitrile (40 : 60, v/v). The flow rate was 0.8 ml min^{-1}. Quantification was performed by UV-detection at a wavelength of 310 nm. No internal standard was added. For both enantiomers, the lower and upper limits of quantification were 50 and 4000 ng ml^{-1}, respectively. The precision of the method varied between 6% and 7% for R-warfarin and between 6% and 8% for S-warfarin. The accuracy ranged from −0.5% to 3% for R-warfarin and from −0.8% and 3% for S-warfarin.

Blood samples for the digoxin assay were allowed to coagulate at room temperature for 1 h and then centrifuged. Serum was harvested and stored at −20 °C within 30 min. The volume of urine was noted and an aliquot was stored without preservative at −20 °C. The amount of drug excreted in urine between $t = 0$ and 24 h ($Ae_{0-24\,h}$), the percentage of the dose excreted over 24 h and the renal clearance (CL_R) of digoxin were calculated. Serum and urine samples were analysed for digoxin by MDS Pharma Services, Canada, using a commercial validated radioimmunoassay (Coat-A-Count® Digoxin Kit; Diagnostic Products Corp., Los Angeles, CA, USA). Concentrations were determined over the range 0.10–8.0 ng ml^{-1}. The precision of the plasma assay varied between 5.7% and 13.9% and the accuracy between −9.2% and 2.9%. The precision of the urine assay varied between 2.9% and 13.1% and the accuracy between −3.7% and 4.4%.

Blood samples for the analysis of solifenacin were collected into tubes containing lithium-heparin as anticoagulant, and plasma was harvested by centrifugation and stored within 30 min at −70 °C until assay. Analysis of solifenacin was performed by the Bioanalysis and Drug Metabolism section of the Biological Development Department of Yamanouchi Europe B.V., the Netherlands (solifenacin–warfarin study) and Analytico Medinet, the Netherlands (solifenacin–digoxin study). After addition of 100 ng internal standard and 1 ml saturated $NaHCO_3$ solution to 1 ml of plasma, solifenacin and the internal standard were extracted with 5 ml of t-butyl methyl ether. The organic layer was evaporated to dryness and the residue was reconstituted in 150 µl of 20 mM acetic acid and methanol (2 : 1 v/v). Separation was performed on a reversed phase (Waters Symmetry C18 stainless steel, 150 × 3.9 mm, dp = 5 µm) HPLC system with tandem mass spectrometric detection (Thermo Finnigan TSQ7000 API2 equipped with APCI interface). Solifenacin concentrations were determined over the range 0.5–1000 ng ml^{-1}. The precision varied between 6.3% and 7.4% and the accuracy between 8.3% and 3.8%.

Determination of prothrombin time

Prothrombin time (PT) has been frequently used as a measurement of anticoagulation in other warfarin drug interaction studies using a similar study design [22–25]. As intraindividual assessments of the PT were measured under two conditions (with and without solifenacin) by the same laboratory using the same batch of reagents for all samples, this index of coagulation was used rather than the International Normalized Ratio (INR). Blood samples were collected (into tubes containing sodium citrate) for PT determination prior to dosing on day 10 of each study period and at the fol-

lowing time points postdose: 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h (Figures 1 and 2). All PT measurements were performed on fresh blood samples using a SYSMEX CA1000 analyser (Diamond Diagnostics, Holliston, MA, USA) with Dade reagents. The quality control of the assay was performed using Dade Citrol (Dade Behring, Deerfield, IL, USA) and Diagen (Diagen Corp., Brackenridge, PA, USA) reference controls.

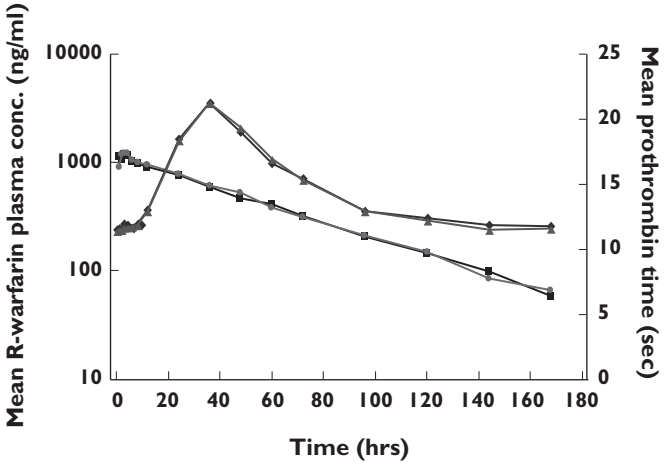

Figure 1

Mean plasma concentration. Warfarin with solifenacin (■), warfarin without solifenacin (●), and prothrombin time, warfarin with solifenacin (◆), warfarin without solifenacin (▲) *vs.* time profiles of R-warfarin in the absence and presence of solifenacin

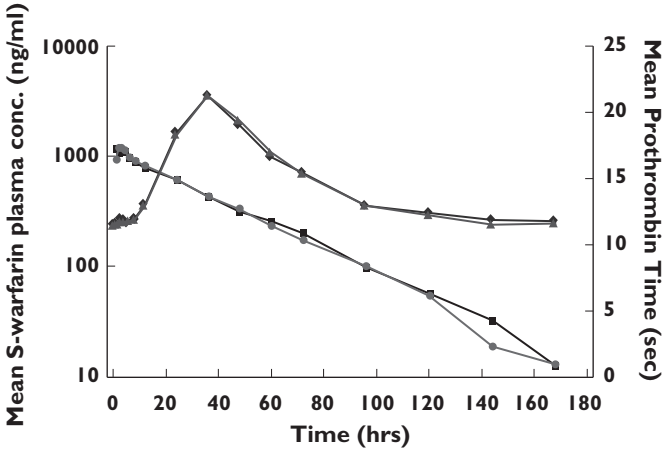

Figure 2

Mean plasma concentration. Warfarin with solifenacin (■), warfarin without solifenacin (●), and prothrombin time, warfarin with solifenacin (◆), warfarin without solifenacin (▲) *vs.* profiles of S-warfarin in the absence and presence of solifenacin

Pharmacokinetic and pharmacodynamic analyses

WinNonlin version 3.1 software (Pharsight Corp., Mountain View, CA, USA) was used to analyse the data. Noncompartmental analysis was used exclusively.

$AUC_{PT;\,0–168\,h}$ was calculated using the linear trapezoidal rule. $AUC_{0–\infty}$ for R- and S-warfarin was calculated using the linear-logarithmic trapezoidal rule, as follows:

$$AUC_{0–\infty} = AUC_{last} + C_t/\lambda_Z$$

where AUC_{last} is AUC from 0 to the last time point measured above the lower limit of quantification, C_t is the last plasma concentration measured above the lower limit of quantification and λ_Z is the elimination rate constant determined by least squares regression analysis of terminal log-linear portions of the plasma concentration–time profile. $AUC_{ss,tau}$ values for digoxin and solifenacin were calculated using the linear-logarithmic trapezoidal rule.

Statistical analysis

In the solifenacin–warfarin study, the primary pharmacodynamic endpoint was the area under the PT *vs.* time curve from 0 to 168 h after dosing with warfarin ($AUC_{PT;\,0–168\,h}$). Secondary endpoints were maximum PT (PT_{max}) and time to reach PT_{max} (t_{PTmax}). The primary pharmacokinetic endpoint was the area under the plasma concentration–time curve extrapolated to infinity ($AUC_{0–\infty}$) for both the R- and S-enantiomers of warfarin. Secondary endpoints for warfarin were the area under the plasma concentration–time curve from $t = 0$ to the time at which the last quantifiable sample was obtained (AUC_{last}), the maximum observed plasma drug concentration (C_{max}), the time to C_{max} (t_{max}), the terminal elimination half-life ($t_{1/2}$) and the apparent oral clearance (CL/F) of unchanged drug for each warfarin enantiomer. The secondary pharmacokinetic endpoints for solifenacin were the area under the plasma concentration–time curve from $t = 0$–24 h ($AUC_{ss,tau}$), C_{max}, the trough concentration of drug in plasma (C_{trough}) and t_{max}.

Three primary parameters ($AUC_{PT;\,0–168\,h}$ and $AUC_{0–\infty}$ for R- and S-warfarin) were used to determine whether solifenacin affects the pharmacokinetics and pharmacodynamics of warfarin. Absence of a drug–drug interaction was assumed if the 90% confidence interval (CI) for the ratio 'warfarin + solifenacin/warfarin + placebo' for each of the three primary parameters fell within the prespecified interval 0.80–1.25. With a power of 94% for each of the three equivalence tests, and an estimated intrasubject coefficient of variation (CV) of 11%, 12 subjects were required for an overall power of ≥82%.

The three primary parameters were logarithmically transformed, and subjected to analysis of variance

(ANOVA). Based on these analyses, the ratio 'warfarin + solifenacin/warfarin + placebo' and its 90% CI were calculated for the three primary parameters taking into account the factors: treatment, period, sequence and subject within sequence. Individual measured PTs were used to obtain the secondary parameters PT_{max} and t_{PTmax} directly. The primary analysis was repeated for PT_{max} and C_{max} of R- and S-warfarin. The variables t_{PTmax} and t_{max} were compared using a Wilcoxon test according to the method of Hauschke and colleagues [26].

In the solifenacin–digoxin study, the primary pharmacokinetic parameters were digoxin $AUC_{ss,tau}$ and C_{max}. Secondary parameters for digoxin were C_{trough}, t_{max}, $Ae_{0–24\,h}$, CL/F and CL_R, and those for solifenacin were $AUC_{ss,tau,}$ C_{max}, C_{trough} and t_{max}. In order to conclude that solifenacin does not affect the pharmacokinetics of digoxin at steady state, the 90% CI for both the ratio '$AUC_{ss,tau}$ with solifenacin/$AUC_{ss,tau}$ without solifenacin' and the ratio 'C_{max} with solifenacin/C_{max} without solifenacin' was required to fall within the prespecified interval 0.80–1.25. With a power of 90% for each test, a CV of 20% for $AUC_{ss,tau}$ of digoxin and an expected ratio of 1 for '$AUC_{ss,tau}$ with solifenacin/$AUC_{ss,tau}$ without solifenacin', 24 subjects were required for an overall power of ≥80%.

$AUC_{ss,tau}$ and C_{max} values were logarithmically transformed and subjected to ANOVA taking into account the factors: subject and treatment. Based on these analyses, the ratio 'digoxin + solifenacin/digoxin + placebo' and the 90% CI were calculated. The ratio 'digoxin + solifenacin/digoxin + placebo' (with the 90% CI) was also estimated for CL_R, using the same model as described for the primary parameters.

Clinical assessment

Subjects were questioned about adverse events at regularly scheduled time intervals. Haematology (complete blood count and differential), biochemistry (serum electrolytes, calcium, creatinine, liver function tests, glucose), urinalysis and physical examination were performed on the day of admission to the clinical unit and before and after the study. Vital signs were measured and electrocardiograms (ECGs) were performed daily during the solifenacin–digoxin study and on day 10 of each study period in the solifenacin–warfarin study. In the solifenacin–warfarin study, measures of coagulation (PT and activated partial thromboplastin time) were also performed. In the solifenacin–digoxin study, blood samples were taken for the determination of serum digoxin concentrations on days 2, 4, 6, 10, 12 and 14 immediately before the morning dose of medication. If after that dose the trough concentration exceeded 3.0 ng ml^{-1} without digoxin-related symptoms or 2.0 ng ml^{-1} with related symptoms (abdominal pain, diarrhoea, irregular heartbeat, nausea, or vomiting), no further digoxin was given.

Results

In the solifenacin–warfarin study, the mean age of the 12 males was 24.9 years (range 20–36 years) and the mean body weight was 75.3 kg (range 61–91 kg). In the solifenacin–digoxin study, the mean age of the 12 males and 12 females was 28.7 years (range 19–53 years) and the mean body weight was 72.0 kg (range 46–92 kg). All subjects completed each study, with the exception of one female in the solifenacin–digoxin trial who withdrew on day 2 due to an adverse event not linked to the study treatment (moderate myalgia starting on day 0 prior to drug dosing). No subject in either study was considered to have any clinically significant medical history.

Once-daily administration with 10 mg solifenacin for 10 days resulted in a mean C_{max} of solifenacin of 34.9 ng ml^{-1} and an $AUC_{ss,tau}$ of 640 ng h^{-1} ml^{-1}. The point estimate for the ratios of the value during treatment with warfarin and solifenacin to the value during treatment with warfarin and placebo for the primary pharmacodynamic measure ($AUC_{PT;\ 0–168\,h}$) was 1.005 (90% CI 0.984, 1.025). Similarly, the point estimates for the primary pharmacokinetic ($AUC_{0–\infty}$ for R- and S-warfarin) parameters were 0.967 (90% CI 0.872, 1.073) for R-warfarin and 0.982 (90% CI 0.879, 1.097) for S-warfarin. The estimated 90% CIs for all three primary parameters fell within the prespecified interval 0.80–1.25.

The point estimate for the ratio of the value during treatment with warfarin and solifenacin to the value during treatment with warfarin and placebo for PT_{max} was 0.997 (90% CI 0.995, 1.041). The point estimate for the median difference in t_{PTmax} between warfarin plus solifenacin and warfarin plus placebo was 0.025 h (90% CI −0.010, 5.975 h).

The point estimates for the ratio of the value during treatment with warfarin and solifenacin to the value during treatment with warfarin and placebo for C_{max} were 1.019 (90% CI 0.939, 1.109) for R-warfarin and 1.036 (90% CI 0.942, 1.139) for S-warfarin. Thus, the 90% CIs fell within the prespecified interval. The point estimates for the median differences in t_{max} between warfarin plus solifenacin and warfarin plus placebo were 0.000 h (90% CI −1.08, 0.925 h) for R-warfarin and −0.055 h (90% CI −1.08, 0.400 h) for S-warfarin.

Figures 1 and 2 show the mean plasma concentration *vs.* time profiles for each warfarin enantiomer in the presence and absence of solifenacin.

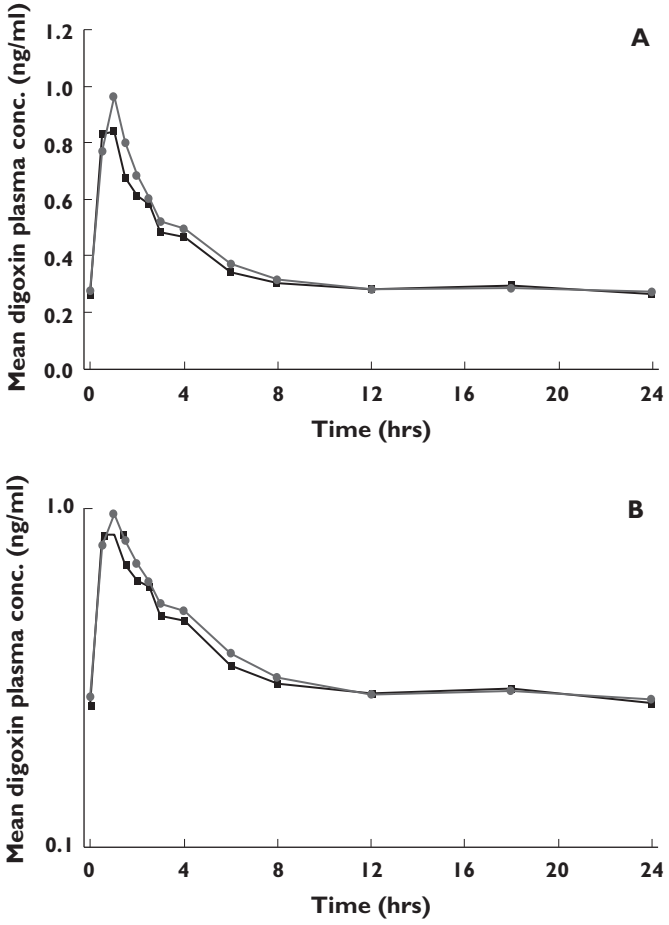

Figure 3
Mean plasma concentration *vs.* time profiles of digoxin in the absence and presence of solifenacin. Digoxin without solifenacin (■), digoxin with solifenacin (●)

Once-daily administration with 10 mg solifenacin for 10 days resulted in a mean C_{max} of solifenacin of 56.0 ng ml^{-1} and an $AUC_{ss,tau}$ of 995 ng h^{-1} ml^{-1}. Figure 3 shows the mean plasma concentration *vs.* time profiles of digoxin in the absence (day 8) and presence (day 18) of solifenacin.

Summary statistics for the serum and urine pharmacokinetic parameters of digoxin in the absence and presence of solifenacin are shown in Table 1. The mean C_{max} in the absence of solifenacin (day 8) was 0.93 ng ml^{-1}, compared with 1.05 ng ml^{-1} when solifenacin was coadministered with digoxin (day 18). The point estimate of the ratio of the C_{max} of digoxin during solifenacin treatment to the value without solifenacin was 1.11 (90% CI 1.03, 1.20), indicating that solifenacin did not affect the C_{max} of digoxin at steady state to a clinically relevant degree. The mean $AUC_{ss,tau}$ in the absence of solifenacin (day 8) was 8.43 ng h^{-1} ml^{-1}, compared with 8.74 ng h^{-1} ml^{-1} in the presence of solifenacin (day 18). The point estimate of the ratio for the $AUC_{ss,tau}$ of digoxin with solifenacin to the value without solifenacin was 1.03 (90% CI 0.98, 1.07), indicating that solifenacin did not affect the extent of absorption of digoxin at steady state. Neither the systemic clearance nor renal elimination of digoxin was significantly affected by coadministration of solifenacin.

Table 1
Digoxin pharmacokinetic measurements in the absence and presence of solifenacin

Parameter	Digoxin Mean (SD)	Digoxin + solifenacin Mean (SD)
t_{max} (h)	0.81 (0.39)	0.98 (0.41)
C_{max} (ng ml^{-1})	0.93 (0.18)	1.05 (0.26)
$AUC_{ss,tau}$ (ng h^{-1} ml^{-1})	8.43 (1.66)	8.74 (2.11)
CL/F (l h^{-1})	15.3 (2.6)	15.1 (3.5)
% dose excreted	53.2 (15.2)	51.5 (11.5)
CL_R (l h^{-1})	7.92 (2.33)	7.61 (2.15)

SD, Standard deviation.

The mean digoxin trough concentrations on days 6–9 and days 16–19 fell within a narrow range of approximately 0.25–0.30 ng ml^{-1}. Thus, on the days of sampling (days 8 and 18), digoxin had attained steady state. Trough digoxin concentrations in the presence and absence of solifenacin were similar.

The coadministration of solifenacin with both warfarin and digoxin was well tolerated. No serious adverse events occurred. In the solifenacin–warfarin study, dry mouth was reported by three subjects (four events) during treatment with solifenacin and warfarin and by one subject (two events) during treatment with placebo and warfarin. All reports were graded mild in severity and all resolved despite continued treatment. In the solifenacin–digoxin study, dry mouth was reported by five subjects during treatment with solifenacin and digoxin and by one subject during treatment with digoxin alone. All reports were graded mild in severity. No significant changes in laboratory parameters, vital signs or ECG occurred in either study.

Discussion

Antimuscarinic agents are the mainstay of treatment for OAB, but can be poorly tolerated by many patients due to anticholinergic side-effects [6]. New agents that maintain or enhance therapeutic efficacy while reducing

adverse events are needed. Solifenacin is a once-daily oral antimuscarinic agent for the treatment of OAB that has been associated with statistically significant decreases in symptoms in multiple clinical trials. In addition, solifenacin has demonstrated a favourable tolerability profile. As the drug is largely metabolized by CYP3A4, we investigated the potential for a pharmacokinetic and/or pharmacodynamic interaction with warfarin, another substrate of CYP3A4 that is commonly used in the older patient population. Similarly, because the bioavailability and renal clearance of digoxin are dependent on the activity of the transport protein P-gp and because preclinical data showed solifenacin to be a weak inhibitor of P-gp, the potential effect of solifenacin on the steady-state pharmacokinetics of digoxin was also investigated.

Coadministration of solifenacin did not produce any changes in the pharmacokinetics or pharmacodynamics of warfarin based on the results of the plasma concentration *vs.* time curve data, the PT *vs.* time profile and the point estimates for the ratios of $AUC_{PT;\ 0–168\ h}$ and $AUC_{0–\infty}$ for both warfarin enantiomers. The secondary pharmacodynamic parameters PT_{max} and t_{PTmax} and the secondary pharmacokinetic parameters C_{max} and t_{max} were similarly unaffected by coadministration of solifenacin.

Solifenacin did not affect the extent or rate of absorption of digoxin at steady state as based on the $AUC_{ss,tau}$ and t_{max} data. A small increase in the C_{max} of digoxin was seen in the presence of solifenacin (1.05 ng ml^{-1}*vs.* 0.93 ng ml^{-1}). However, the 90% CI (1.03, 1.20) fell within the prespecified interval, indicating that the overall plasma concentration *vs.* time profiles of digoxin in the presence and absence of solifenacin were equivalent. The exact cause of the increase in C_{max} is not clear. Since the rate and extent of absorption were unchanged, change in the distribution kinetics of digoxin remains a possible explanation. The renal elimination of digoxin was also unaffected by coadministration of solifenacin.

In both studies the steady-state pharmacokinetics of solifenacin was assessed at the tenth day of continuous dosing with 10 mg drug given once daily. In the digoxin study, the mean C_{max} and $AUC_{ss,tau}$ values observed were in line with those obtained in other studies [27, 28]. However, lower C_{max} and $AUC_{ss,tau}$ values were observed in the warfarin interaction study. Although this could be interpreted as an indication of an effect of warfarin on the pharmacokinetics of solifenacin, it is unlikely that the former drug would lower the bioavailability of solifenacin or induce its elimination. Therefore, the apparently lower values probably occurred by chance. Both the solifenacin–warfarin and solifenacin–digoxin studies were conducted in young healthy subjects without significant medical history. Thus, there may be a question regarding whether these results can be extrapolated to an elderly population, in whom solifenacin may be administered concurrently with other medications. Pharmacokinetic studies evaluating the use of solifenacin in the young and elderly have shown that C_{max} is not significantly changed by age, but t_{max} may occur approximately 1 h later in the elderly [28]. However, the $AUC_{ss,tau}$ is significantly increased by 20% in the elderly and the half-life is increased from approximately 52–56 h in the young to 69–72 h in the elderly [28]. Overall, the magnitude of these pharmacokinetic differences were small, and thus it is likely that, in the elderly, warfarin or digoxin can be used safely in combination with solifenacin.

In conclusion, since the pharmacokinetics and pharmacodynamics of racemic warfarin and the steady-state pharmacokinetics of digoxin were not changed by the coadministration of solifenacin in healthy subjects, the need for dosing adjustment for these two drugs when given with solifenacin does not seem warranted, but standard monitoring should be continued.

This study was supported by Yamanouchi Pharmaceutical Co., Ltd, Tokyo, Japan, of whom the authors were employees at the time the study was conducted.

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