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ORIGINAL ARTICLE

Dapoxetine, a novel treatment for premature ejaculation, does not have pharmacokinetic interactions with phosphodiesterase-5 inhibitors

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Potential pharmacokinetic interactions between dapoxetine, a serotonin transporter inhibitor developed for the treatment of premature ejaculation (PE), and the phosphodiesterase-5 inhibitors tadalafil and sildenafil, agents used in the treatment of erectile dysfunction (ED), were investigated in an open-label, randomized, crossover study ($n = 24$ men) comparing dapoxetine 60 mg, dapoxetine 60 mg + tadalafil 20 mg, and dapoxetine 60 mg + sildenafil 100 mg. Plasma concentrations of dapoxetine, tadalafil, and sildenafil were determined by liquid chromatography–tandem mass spectrometry. Tadalafil did not affect the pharmacokinetics of dapoxetine, whereas sildenafil increased the dapoxetine AUC_{inf} by 22%; these effects were deemed not clinically important. Dapoxetine did not appear to affect the pharmacokinetics of tadalafil or sildenafil. Most adverse events were mild in nature. Thus, dapoxetine has no clinically important pharmacokinetic interactions with tadalafil or sildenafil, and the combinations are well tolerated.
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Introduction

Premature ejaculation (PE) is a common form of male sexual dysfunction, which has been shown to cause significant distress in men and their partners.[1–3] Although they are not indicated for the treatment of PE, conventional selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly used to treat the condition.[4–6]

A new serotonin transporter inhibitor, dapoxetine, has been developed specifically for the treatment of PE.[7] Results from placebo-controlled, randomized, multicenter phase III trials have demonstrated that men with PE receiving dapoxetine 30 or 60 mg experienced increased intravaginal ejaculatory latency and higher levels of control over ejaculation and satisfaction with sexual intercourse.[7] Dapoxetine was effective when taken on-demand, 1–3 h before intercourse. In contrast, large-scale studies ($N > 100$) of efficacy and safety in men with PE have not been conducted with conventional SSRI antidepressants, and studies of these agents for the treatment of PE have rarely been placebo controlled.

A significant proportion of men with PE also present with erectile dysfunction (ED).[8,9] While a few of the studies have evaluated the effectiveness of ED treatments in men with comorbid PE and ED,[10,11] very few have examined the prevalence of these comorbid conditions. A large survey that included 12 134 men from the United States, Germany, and Italy recently found that 7.2% of men met the criteria for both PE and ED.[12] Overall, 32% of men with PE also reported ED, whereas 44% of men with ED also reported PE.

Given the significant proportion of men with both PE and ED, the use of phosphodiesterase (PDE)-5 inhibitors, including tadalafil (CIALIS®; Lilly ICOS, LLC, Indianapolis, IN, USA) or sildenafil (VIAGRA®; Pfizer Inc., New York, NY, USA), may be anticipated in patients taking dapoxetine.[9] As such, these PDE-5 inhibitors are likely to be a common concomitant medication, and the potential for drug–drug interactions with dapoxetine must be evaluated.

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Dapoxetine is extensively metabolized to numerous phase I and phase II metabolites by multiple cytochrome *P*450 (CYP) isoforms, with no single enzyme predominating (unpublished data). As there are multiple, parallel pathways for the metabolism of dapoxetine, significant metabolic-based pharmacokinetic interactions between dapoxetine and inhibitors or inducers of CYP isoforms are unlikely. *In vitro* studies have indicated that tadalafil does not inhibit or induce CYP isoforms,[13] and is therefore not expected to have clinically important pharmacokinetic interactions with dapoxetine. Sildenafil does not induce CYP isoforms *in vitro*, but may inhibit some CYP isoforms weakly;[14] however, the peak plasma concentrations (1 μM) associated with the maximum dose of 100 mg are unlikely to affect dapoxetine pharmacokinetics or metabolism.

Although the known metabolic pathways and *in vitro* inhibition and induction results for dapoxetine, sildenafil, and tadalafil suggested that coadministration would result in few pharmacokinetic effects, this definitive clinical study was conducted for several reasons. First, *in vitro* data do not always reliably predict *in vivo* pharmacokinetic interactions,[15] and an appropriately designed clinical study is required to evaluate the potential for an *in vivo* drug–drug interaction definitively. Second, *in vitro* data do not provide any information regarding the safety and tolerability of concomitantly administered drugs. Even in the absence of a pharmacokinetic drug–drug interaction, it is possible that safety and tolerability may be altered when two drugs are coadministered. Lastly, because many men suffer from both PE and ED and are likely to be treated concomitantly for both conditions, PDE-5 inhibitors are the most likely concomitant medications to be used with dapoxetine. Thus, the potential for interactions must be evaluated in a clinical study.

Consequently, this study investigated the effects of the PDE-5 inhibitors tadalafil and sildenafil on the pharmacokinetics and tolerability of dapoxetine in healthy male volunteers. Sildenafil and tadalafil were chosen as representative PDE-5 inhibitors, because they are commonly prescribed and differ in their pharmacokinetic properties. Sildenafil has a short half-life of about 4 h,[14] while tadalafil has a longer half-life of 17.5 h.[13]

Materials and methods

Subjects

Healthy males (ages 18–45 years, $N = 24$) within 20% of normal weight for height and build and with blood pressure (BP) within the range of 90–140 mmHg systolic and 50–90 mmHg diastolic were eligible to participate. Subjects were excluded if they had any clinically relevant abnormalities as determined by medical history, physical examination, blood chemistry, complete blood count (CBC), urinalysis, and electrocardiogram (ECG), or if they had a positive urine drug screen or alcohol breath test. All subjects were required to use a medically acceptable method of contraception throughout the entire study period and for 3 months after study completion. Alcohol, caffeine, and grapefruit consumption were not permitted within 48 h before each dose, and caffeine was limited to $\leqslant$450 mg/day; smoking or tobacco use within the previous 3 months was not permitted. Subjects were excluded if they had used any prescription or over-the-counter medications (except for acetaminophen or vitamins) within 7 days before each day of dosing, in order to minimize the effect of extraneous factors in the study.

Study design

This was a single-center, open-label, randomized, three-treatment, three-period, six-sequence, crossover study approved by the Ethics Committee (EC) of the study center (Charterhouse Clinical Research Center, Ravenscourt Park Hospital, London, UK), and conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, including the ethical principles that have their origin in the Declaration of Helsinki on biomedical research involving human subjects. Before participation, each subject was required to read, sign, and date an EC-approved consent form explaining the nature, purpose, possible risks and benefits, and duration of the study.

Subjects were randomly assigned to one of the six treatment sequences and received each of the following three treatments (Figure 1): a single dose of dapoxetine 60 mg (dapoxetine HCl; Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, USA); a single dose of dapoxetine 60 mg with a single dose of tadalafil 20 mg; or a single dose of dapoxetine 60 mg with a single dose of sildenafil 100 mg. Each treatment was followed by a washout period of 6–14 days. The study center purchased commercially available tadalafil and sildenafil. The number of subjects enrolled was consistent with that of other drug–drug interaction studies and in accordance with FDA guidelines for *in vivo* drug metabolism/drug interaction studies.

Assessments

At the initial screening, the following were performed and/or assessed: a physical exam, a medical history, standard laboratory tests (including blood chemistry, CBC (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, and platelet count), and urinalysis), vital signs (pulse rate (PR), BP, and respiratory rate), a urine

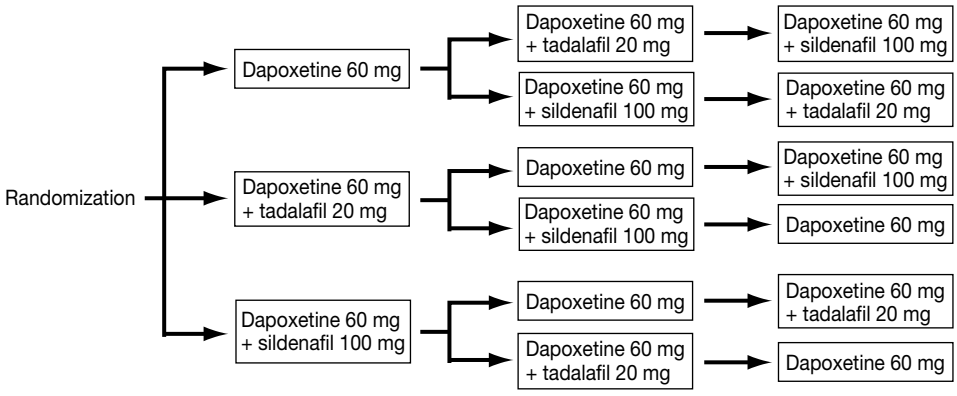

Figure 1 Randomization protocol. At enrollment, subjects were randomized to one of the six treatment sequences, in which each subject received all three study treatments. Pharmacokinetic analyses were performed for subjects who completed all treatments.

drug screen, and an ECG. An alcohol breath test and a urine drug screen were performed before each treatment. Vital signs were measured at 0 (predose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 h following each of the three treatments; an ECG was performed at 0, 2, and 24 h after each dose; and blood samples for pharmacokinetic analysis were collected (as described below). At study termination, a physical exam was performed, along with standard laboratory tests and an ECG, and vital signs were recorded. Subjects were required to fast for 10 h before and 4 h after receiving study medications.

Adverse events (AEs) were assessed in terms of severity and relationship to study drug, and followed until resolution or until the event was medically stable.

Blood sampling and analysis

Blood samples (7 ml) for the determination of plasma concentrations of dapoxetine were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 h following each of the three treatments. Tadalafil and sildenafil exposure were confirmed through analysis of blood samples taken at 0, 1, 2, 6, 10, and 24 h and at 0, 1, 2, 6, and 24 h after dosing with dapoxetine + tadalafil and dapoxetine + sildenafil, respectively. Plasma samples were analyzed for dapoxetine and the PDE-5 inhibitors using validated liquid chromatography–tandem mass spectrometry (LC/MS/MS) methods.

Briefly, internal standard (dapoxetine-d_7, tadalafil-d_3, or sildenafil-d_8) was added to plasma samples, and the analytes and internal standards were extracted from plasma. Plasma extracts were evaporated to dryness and reconstituted in an appropriate solvent before injection onto the LC/MS/MS (for dapoxetine, a SCIEX instrument platform with an electrospray ionization interface was used). The assay was validated using samples from this study, with a minimum quantifiable level of 1.00 ng/ml for dapoxetine, tadalafil, and sildenafil.

For dapoxetine, the calibration curve was linear in the range of 1.00–1000 ng/ml, with an average correlation coefficient of 0.9990. The interassay accuracy (% bias) ranged from −3.36 to −1.15, and the interassay precision (% coefficient of variation) ranged from 3.69 to 17.9.

For tadalafil and sildenafil, the calibration curves were linear in the range of 1.00–500 ng/ml, with an average correlation coefficient of 0.995 and 0.9974, respectively. For tadalafil, the interassay accuracy (% bias) ranged from −12.8 to −1.0, and the interassay precision (% coefficient of variation) ranged from 1.4 to 5.3. For sildenafil, the interassay accuracy (% bias) ranged from −4.6 to 7.0, and the interassay precision (% coefficient of variation) ranged from 8.9 to 11.3.

Pharmacokinetic analyses

Pharmacokinetic parameters (maximum plasma concentration, C_{max}; time to C_{max}, T_{max}; area under the plasma concentration-versus-time curve, AUC; and half-life, $t_{1/2}$) were estimated using standard methods.[16] In addition, dapoxetine pharmacokinetics were further characterized using a two-compartment model with first-order absorption and first-order elimination (WinNonMix software, version 2.0.1, Pharsight Corporation, Mountain View, CA, USA).

Statistical analyses

A mixed-effect analysis of variance model, which included treatment, period, sequence, fixed effects, and subject-within-sequence random effect was used to determine if there was a pharmacokinetic interaction between dapoxetine and tadalafil or sildenafil ($\alpha = 0.05$).[17] Comparison of pharmacokinetic parameters among the three treatment groups was performed according to FDA guidelines, using the least-squares estimate of the mean parameters for the ratios of dapoxetine + tadalafil and dapox-

etine + sildenafil to dapoxetine alone, and the corresponding 90% confidence intervals (CI).[18] The Wilcoxon rank-sum test was used to compare T_{max} between treatments. Data from any subject who vomited at or before two times the median T_{max} of study drug were to be excluded from the analyses.

Results

Subject disposition

Of the 24 subjects enrolled, 22 received all three treatments and completed all study procedures. One subject was withdrawn for nonadherence before the second treatment, and another withdrew consent before the third treatment; all were evaluated for safety and tolerability.

Pharmacokinetic analyses

Pharmacokinetic parameters for dapoxetine across the three treatment groups are summarized in Table 1, and the corresponding plasma concentration profile is presented in Figure 2.

Dapoxetine pharmacokinetics were similar with administration of dapoxetine alone and coadministration of tadalafil or sildenafil; the three treatments demonstrated comparable plasma concentration profiles for dapoxetine. Dapoxetine absorption was rapid, and was not affected by coadministration of tadalafil or sildenafil. Following the peak (i.e., C_{max}), dapoxetine elimination was rapid and biphasic with all three treatments, with an initial half-life of 1.5–1.6 h and a terminal half-life of 14.8–17.1 h. Plasma dapoxetine concentrations were less than 5% of C_{max} by 24 h. Dapoxetine AUC_{inf} remained unchanged when tadalafil was administered concomitantly; concomitant administration of sildenafil increased the dapoxetine AUC_{inf} by 22% (Table 1). The analysis methodology is further detailed in the Materials and methods section.

Table 1 Mean (s.d.) pharmacokinetic parameters for dapoxetine alone and in combination with tadalafil or sildenafil

	Dapoxetine 60 mg[a]	*Dapoxetine 60 mg + tadalafil 20 mg*	*Dapoxetine 60 mg + sildenafil 100 mg*
Dapoxetine			
C_{max} (ng/ml)	372 (140)	370 (160)	386 (160)
T_{max} (h)	1.36 (0.77)	1.37 (0.44)	1.59 (0.69)
$t_{1/2}$ (h)[b]	16.4 (5.4)	17.0 (9.4)	15.1 (4.0)
Initial $t_{1/2}$ (h)[c]	1.57 (0.3)	1.51 (0.1)	1.62 (0.1)
Terminal $t_{1/2}$ (h)[c]	16.7 (5.4)	17.1 (8.0)	14.8 (4.1)
AUC_{inf} (ng.h/ml)	2070 (1100)	2100 (1100)	2530 (1600)

C_{max} = maximum plasma concentration; T_{max} = time to C_{max}; s.d. = standard deviation; $t_{1/2}$ = half-life.
[a] $n = 22$ for all three treatments.
[b] $n = 21$ for dapoxetine and dapoxetine + sildenafil; $n = 22$ for dapoxetine + tadalafil.
[c] Estimated using a two-compartment model with first-order absorption and first-order elimination, given as mean estimated value.

Tadalafil and sildenafil

When coadministered with dapoxetine, tadalafil and sildenafil had half-life values of 22.6 and 3.42 h, respectively, which are similar to published values (17.5 and 3.7 h, respectively).[19,20] Previously reported values of T_{max} for tadalafil ranged from 30 min to 6 h, which is comparable to the 4.8 h observed with dapoxetine and tadalafil.[13] The observed T_{max} of sildenafil when administered with dapoxetine (1 h) was also similar to the previously reported value for sildenafil (2 h).[14] Slight differences with established values may have resulted from the limited number of tadalafil samples in the study, which was not designed to definitively assess the pharmacokinetics of tadalafil or sildenafil.

Statistical analyses

The statistical analyses evaluating the effects of tadalafil and sildenafil on log-transformed pharmacokinetic parameters of dapoxetine are summarized in Table 2.

Tadalafil did not affect the pharmacokinetics of dapoxetine (Table 2); the 90% CIs for the mean ratios of C_{max} and of AUC_{inf} were within the standard no-effect boundary of 80–125%[18,21] for dapoxetine. The T_{max} value for dapoxetine was also unaffected by coadministration of tadalafil ($P > 0.52$ for all, by Wilcoxon rank-sum test) (Table 1).

Sildenafil had a small effect on dapoxetine pharmacokinetics (Table 2). For dapoxetine, the 90% CI of the ratio of dapoxetine + sildenafil to dapoxetine alone was within the no-effect boundary

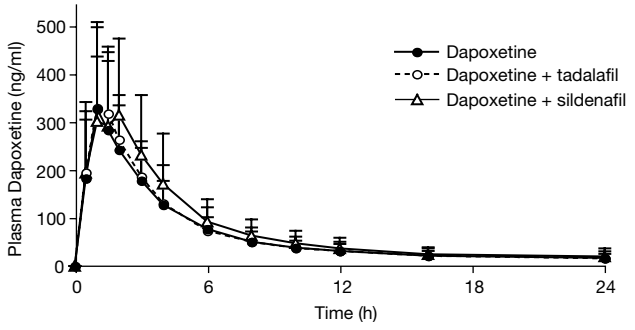

Figure 2 Plasma concentrations of dapoxetine after administration of dapoxetine alone or with tadalafil or sildenafil. Mean plasma concentrations (± standard deviation) of dapoxetine after administration of a single dose of dapoxetine 60 mg alone, or in combination with single doses of tadalafil 20 mg or sildenafil 100 mg are seen. Plasma concentrations were measured using a validated LC/MS/MS method.

of 80–125% for ln C_{max} (the natural logarithm of C_{max}), but was outside that range for ln AUC_{inf}. The T_{max} for dapoxetine was comparable between treatments ($P = 0.23$).

Safety

AEs were reported by 10 of 23 subjects (43.5%) after treatment with dapoxetine alone, by 10 of 23 subjects (43.5%) after dapoxetine + tadalafil, and by 11 of 23 subjects (47.8%) after dapoxetine + sildenafil; AEs reported by ⩾2 subjects are listed in Table 3. Nausea and diarrhea were the most frequently reported AEs. All AEs were of mild or moderate severity, and most were assessed as possibly or probably related to treatment.

Coadministration of tadalafil or sildenafil with dapoxetine did not result in clinically important changes to PR, BP, ECG, or clinical laboratory values during the study or between the pre- and poststudy assessments. Figure 3 shows mean systolic and diastolic BP over time after administration of dapoxetine with or without tadalafil or sildenafil; mean average, minimum, and maximum values for BP and PR are presented in Table 4.

Table 2 Statistical analysis of the log (ln)-transformed pharmacokinetic parameters for dapoxetine

Parameter	*Contrast*[a]	*Ratio (%)*	*Power*[b] *(%)*	*90% CI*	
				Lower (%)	*Upper (%)*
Dapoxetine[c]					
ln(AUC_{inf})	D + T/D	103.1	92.6	92.62	114.85
	D + S/D	119.1	92.6	106.90	132.57
ln(C_{max})	D + T/D	98.5	97.2	89.55	108.23
	D + S/D	104.0	97.2	94.63	114.37

[a]D = dapoxetine 60 mg; D + T = dapoxetine 60 mg + tadalafil 20 mg; D + S = dapoxetine 60 mg + sildenafil 100 mg.
[b]Power to detect a difference equal to 20% of the reference mean, at a significance level of 0.05, expressed as a percentage of the reference mean (i.e., dapoxetine alone).
[c]$n = 22$ for all treatments.

Table 3 Adverse events reported in ⩾2 subjects

Adverse event	*Dapoxetine 60 mg*[a]	*Dapoxetine 60 mg + tadalafil 20 mg*	*Dapoxetine 60 mg + sildenafil 100 mg*
Nausea, *n* (%)	2 (8.7)	6 (26.1)	5 (21.7)
Diarrhea, *n* (%)	5 (21.7)	3 (13.0)	4 (17.4)
Vomiting, *n* (%)	1 (4.3)	1 (4.3)	3 (13.0)
Dizziness, *n* (%)	3 (13.0)	4 (17.4)	2 (8.7)
Headache, *n* (%)	3 (13.0)	4 (17.4)	1 (4.3)

[a]$N = 23$ for each treatment group; a subject may contribute to more than one adverse event per treatment group.

Discussion

This study investigated the effects of two PDE-5 inhibitors, tadalafil and sildenafil, on the pharmacokinetics and tolerability of dapoxetine, a medication being developed as a treatment for PE. As some patients with PE also have ED,[8,9] a subset of patients with PE may also be treated for ED using these PDE-5 inhibitors. Results from this study indicate that neither tadalafil nor sildenafil have clinically important effects on the pharmacokinetics and metabolism of dapoxetine, and that dapoxetine has no apparent effect on the pharmacokinetics of tadalafil or sildenafil. This study tested the maximum marketed doses of tadalafil (20 mg) and sildenafil (100 mg), in their approved on-demand dosing regi-

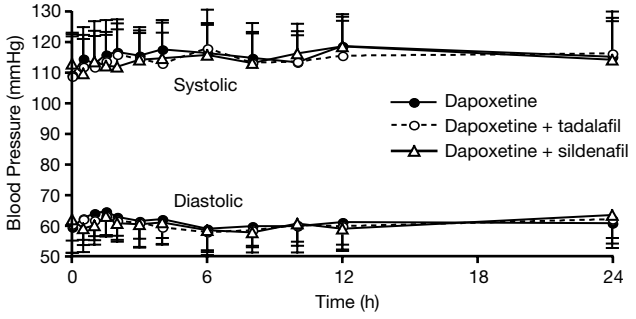

Figure 3 Systolic and diastolic BP after coadministration of dapoxetine with tadalafil or sildenafil. Mean systolic and diastolic blood pressures (±standard deviation) after administration of a single dose of dapoxetine 60 mg alone, or in combination with single doses of tadalafil 20 mg or sildenafil 100 mg are shown.

Table 4 Vital signs

	Dapoxetine 60 mg, mean (s.d.)	*Dapoxetine 60 mg + tadalafil 20 mg, mean (s.d.)*	*Dapoxetine 60 mg + sildenafil 100 mg, mean (s.d.)*
Systolic BP (mmHg)			
Minimum[a]	103.5 (9.8)	98.2 (11.6)	102.7 (7.8)
Maximum[b]	126.0 (9.9)	128.2 (10.3)	127.7 (9.8)
Average[c]	115.8 (8.0)	114.7 (8.8)	115.0 (7.4)
Diastolic BP (mmHg)			
Minimum	53.7 (5.5)	52.7 (5.5)	52.2 (4.5)
Maximum	69.4 (6.4)	69.5 (6.3)	69.7 (5.8)
Average	61.0 (6.2)	60.4 (5.3)	60.5 (5.0)
PR (b.p.m.)			
Minimum	53.8 (6.9)	53.6 (7.2)	56.5 (9.1)
Maximum	77.1 (8.9)	79.0 (11.6)	80.6 (14.0)
Average	65.0 (7.9)	67.2 (8.1)	67.7 (11.6)

BP = blood pressure; b.p.m. = beats per minute; PR = pulse rate.
[a]Overall mean of each subject's lowest measured value over 24 h.
[b]Overall mean of each subject's highest measured value over 24 h.
[c]Overall mean of each subject's average measured value over 24 h.

men, and the highest dapoxetine dosage strength investigated in an on-demand dosing regimen in phase III studies (60 mg).[7]

Dapoxetine did not appear to affect the pharmacokinetics of tadalafil or sildenafil. While the limited number of samples precluded a definitive characterization of the pharmacokinetics of the two PDE-5 inhibitors, half-life and T_{max} were estimated with the available data, and were similar to previously reported values.[19,20] These results are in marked contrast to the reported pharmacokinetic interactions reported for tadalafil with ritonavir, ketoconazole, and rifampin,[13] and for sildenafil with ritonavir and erythromycin.[14] Ketoconazole, a selective and potent inhibitor of CYP3A4, increased the tadalafil AUC by 312%, and ritonavir increased the tadalafil AUC by 124%. Rifampin, a CYP3A4 inducer, reduced the tadalafil AUC by 88%.[13] Coadministration of sildenafil with the HIV protease inhibitor ritonavir, which is a highly potent CYP inhibitor, resulted in a 1000% increase in the sildenafil AUC.[14] Erythromycin, a specific CYP3A4 inhibitor, increased the sildenafil AUC by 182%.[14] Furthermore, cimetidine, a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with sildenafil.[14]

These results suggest not only that dapoxetine does not affect the pharmacokinetics of sildenafil and tadalafil but also that dapoxetine does not significantly inhibit or induce CYP3A4 *in vivo*, as both sildenafil and tadalafil are predominately metabolized by CYP3A4 and have been shown, as outlined above, to be very sensitive to CYP3A4 inhibitors and inducers. This is an important finding, as CYP3A4 is involved in the metabolism of many drugs, and inhibition or induction of this enzyme can result in clinically important drug interactions.[22,23]

The results of this definitive clinical study, which demonstrated no significant pharmacokinetic interactions of dapoxetine with either sildenafil or tadalafil, are in agreement with what is known about the metabolic pathways for dapoxetine and *in vitro* CYP inhibition and induction profiles for sildenafil and tadalafil. Dapoxetine is extensively metabolized to numerous phase I and phase II metabolites by multiple enzymes, including CYP3A4 and CYP2D6, and *in vitro* inhibition and induction studies have shown that dapoxetine is a very weak inhibitor of CYP3A4 (unpublished data). Therefore, significant metabolic-based pharmacokinetic interactions between dapoxetine and inhibitors or inducers of CYP isoforms are unlikely.

Tadalafil and sildenafil are reported to be (at most) weak inhibitors and/or inducers of one or more CYP isoforms. Tadalafil reversibly inhibits several CYP isoforms (I/K_i ratios of 0.05, 0.03, 0.03, and 0.14 were obtained for CYP3A4, CYP2C9, CYP2C19, and CYP1A2, respectively).[24] As the I/K_i ratios for this inhibition are <1, it is unlikely that an interaction between tadalafil and dapoxetine would occur via reversible inhibition.[25] In addition, tadalafil can result in weak mechanism-based inhibition and induction of CYP3A4. However, clinical studies demonstrated that tadalafil does not have clinically significant pharmacokinetic interactions with established *in vivo* substrates of CYP3A4 (midazolam or lovastatin), suggesting that any *in vivo* induction and inhibition offset each other.[24] Together, these results and the known metabolism of dapoxetine suggest that tadalafil would not significantly affect the pharmacokinetics of dapoxetine.

Similar to tadalafil, sildenafil is reported to have either no effect or only weak inhibitory effects on CYP isoforms. Sildenafil weakly inhibited the CYP isoforms 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 ($IC_{50} > 150\,\mu M$).[14] As peak plasma concentrations of sildenafil are approximately $1\,\mu M$ after a 100-μg dose, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes. Assuming that the K_i values are similar to the reported IC_{50} values, the I/K_i ratios associated with the inhibition of these enzymes would be <1, suggesting that sildenafil would not appreciably inhibit CYP isoforms *in vivo*.[25] Therefore, sildenafil and dapoxetine were unlikely to have clinically significant pharmacokinetic interactions.

Based on the results of this study and what is known about the metabolism of vardenafil and sildenafil, it is reasonable to anticipate that vardenafil would not significantly alter the pharmacokinetics of dapoxetine and that dapoxetine would not alter the pharmacokinetics of vardenafil. As is the case with sildenafil and tadalafil, vardenafil is metabolized predominantly by CYP3A4, and has either no or only weak inhibitory effects on CYP isoforms.[26] However, definitive statements cannot be made, as the combination of vardenafil and dapoxetine was not evaluated in this clinical trial.

The incidence of nausea appears to increase when dapoxetine is administered with tadalafil or sildenafil, whereas the incidence of diarrhea appears to decrease. It is difficult to draw definitive conclusions regarding these findings, as phase I drug–drug interaction studies are not sufficiently powered to evaluate differences between AE profiles.

The lack of pharmacokinetic interaction between dapoxetine and tadalafil or sildenafil has important implications for the treatment of men presenting with both PE and ED. Conventional SSRI antidepressants may be used in the treatment of PE, but have been associated with increased side effects in combination with PDE-5 inhibitors; combination therapy using paroxetine (10 mg daily for 21 days, followed by 20 mg as needed) and sildenafil (50 mg as needed) resulted in a significant increase in the incidence of side effects compared to paroxetine alone.[27] To have an effect on PE, conventional SSRIs usually require chronic daily dosing;[28] however,

this schedule may increase the probability of metabolic interactions with PDE-5 inhibitors and may cause unwanted sexual side effects. By contrast, dapoxetine is effective on the first dose, may be taken on-demand, has minimal accumulation, has a low incidence of unwanted sexual side effects,[7] and does not have clinically relevant pharmacokinetic interactions with the PDE-5 inhibitors tadalafil and sildenafil.

Conclusions

Definitive clinical assessment has demonstrated that tadalafil 20 mg and sildenafil 100 mg have no clinically important effects on the pharmacokinetics of dapoxetine 60 mg. Similarly, dapoxetine did not appear to alter the pharmacokinetics of tadalafil or sildenafil, and the combinations were well tolerated.

Acknowledgments

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