BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **27**: 103–110 (2006)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/bdd.488

The Effect of Ciprofloxacin and Clarithromycin on Sildenafil Oral Bioavailability in Human Volunteers

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ABSTRACT: Sildenafil is the first oral therapeutic agent for the management of male erectile dysfunction. Its oral bioavailability is only 40% due to extensive presystemic elimination, mainly by CYP3A4. This study examined the effect of coadministration of ciprofloxacin or clarithromycin, which inhibit CYP3A4, on the bioavailability and pharmacokinetics of sildenafil. Twelve healthy male volunteers received sildenafil alone or after pretreatment with the inhibitors in a balanced three-way crossover design. The pharmacokinetic analysis showed that ciprofloxacin coadministration with sildenafil significantly increased the *AUC* from 1407 ± 380 to $2986 \pm 917\,\mu g\,h/l$ (90% confidence interval 119%–159%) and the C_{max} from 287 ± 67 to $623 \pm 192\,\mu g/l$ (90% confidence interval 127%–152%). Similarly, clarithromycin coadministration increased sildenafil *AUC* from 1407 ± 380 to $3209 \pm 762\,\mu g\,h/l$ (90% confidence interval 127%–161%) and C_{max} from 287 ± 67 to $694 \pm 259\,\mu g/l$ (90% confidence interval 132%–157%). Ciprofloxacin coadministration and clarithromycin coadministration with sildenafil did not affect the rate of sildenafil absorption significantly. These results indicate that coadministration of ciprofloxacin and clarithromycin significantly increased sildenafil bioavailability which can be attributed to the inhibitory effect of ciprofloxacin and clarithromycin on CYP3A4. Dose adjustment of sildenafil is thus necessary when administered with such drugs. Copyright © 2005 John Wiley & Sons, Ltd.

Key words: sildenafil; bioavailability; pharmacokinetic interactions; CYP3A4 inhibitors

Introduction

Sildenafil is the first oral therapeutic agent introduced for the management of male erectile dysfunction. This drug is a potent selective inhibitor of phosphodiesterase type 5 (PDE5), the predominant isoenzyme responsible for the metabolism of cyclic guanosine monophosphate (cGMP). During sexual stimulation the cavernous nerves release nitric oxide which induces cGMP formation and smooth muscle relaxation in the corpus cavernosum. Sildenafil inhibition of the PDE5 mediates a sequence of events starting with an elevation in the cGMP, which causes corpus cavernosum smooth muscle relaxation, leading to an increase in the blood flow and enhancement in the erectile function [1,2].

The inhibition of PDE5, which is present in the systemic circulation, can lead to vasodilatation and a subsequent reduction in the blood pressure. Sildenafil has been shown to produce a moderate reduction in the systolic and diastolic blood pressure in the range of doses used clinically [3]. It also produces vasodilatation-related side effects including headache, flushing, rhinitis, dizziness, dyspepsia and visual abnormalities [4]. Although the incidence of these side effects is low, serious cardiovascular events including profound hypotension with compromised cerebral and cardiac blood flow can occur

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Received 18 February 2005
Revised 22 August 2005
Accepted 25 October 2005

in patients with congestive heart failure and patients with low blood volume and hypotension. Also, patients taking organic nitrates are at higher risk of developing these side effects due to the additive vasodilatation effect, while patients taking other drugs that can increase the systemic bioavailability of sildenafil may develop these adverse effects due to higher sildenafil blood concentrations [2–4].

Sildenafil is rapidly absorbed after oral administration with the peak plasma concentration achieved in approximately 1 h. The half life of sildenafil is about 4 h and the plasma protein binding is about 96%. Sildenafil is primarily eliminated from the body by metabolism with only 15% of the bioavailable dose excreted unchanged in urine [5]. After oral administration, sildenafil is well absorbed from the gastrointestinal tract (about 90%), however, its systemic bioavailability is only about 40% due to extensive presystemic elimination. This extensive presystemic elimination is mediated primarily by the cytochrome P450 isoenzyme CYP3A4 [6,7]. The resulting n-desmethyl metabolite is pharmacologically active and accounts for about 20% of sildenafil pharmacological activity.

Several drugs are known to inhibit CYP3A4, the principal isoenzyme responsible for the metabolism of sildenafil. These include cimetidine, ciprofloxacin, macrolide antibiotics such as erythromycin and clarithromycin, antifungals such as ketoconazole and itraconazole, and protease inhibitors such as saquinavir and ritonavir. Inhibitors of CYP3A4 are expected to increase the plasma concentrations of sildenafil resulting in augmentation of the pharmacological and the adverse effects of sildenafil. It has been reported that coadministration of sildenafil with cimetidine, erythromycin, protease inhibitors and grapefruit juice significantly increased the plasma concentrations of sildenafil in healthy male volunteers. This suggests that lower sildenafil doses are required for patients receiving such drugs [8–11].

Ciprofloxacin and clarithromycin are known inhibitors of CYP3A4, which have been reported to produce clinically significant interactions with a number of other therapeutic agents that are substrates for this isoenzyme [12–15]. Because of the widespread use of sildenafil and since ciprofloxacin and clarithromycin are widely used antibiotics, it is very likely that some patients may use these drugs simultaneously. The current research was performed to investigate the interaction of sildenafil with ciprofloxacin and clarithromycin. In this study the effect of ciprofloxacin and clarithromycin on sildenafil bioavailability and pharmacokinetics was investigated in normal healthy male volunteers.

Materials and Methods

Materials

Sildenafil citrate was obtained from MUP (Ismailia, Egypt) and dexamethasone was obtained from Sigma Chemical Co. (St Louis, USA). Acetonitrile, methanol and sodium dihydrogen phosphate were purchased from Merck Chemical Co. (Darmstadt, Germany). Diethyl ether was obtained from Honil Ltd (London, UK). All chemicals were of analytical reagent grade and all solvents were HPLC grade. The drug products sildenafil citrate (Viagra® 50 mg, Pfizer Egypt, Cairo, Egypt), ciprofloxacin (Ciprofloxacin® 500 mg, Amriya Pharm. Ind., Alexandria, Egypt) and clarithromycin (Claribiotic® 500 mg, Amriya Pharm. Ind., Alexandria, Egypt) were utilized in the study.

Study design

Twelve healthy male volunteers were recruited to participate in the three periods of the study (mean $\pm$ SD): age 32 ± 6.6 years; height 171 ± 9.1 cm; weight 75 ± 7.1 kg. The study protocol was approved by the ethical committee at Tanta University. The nature of the study was explained to the volunteers and written consent was obtained from each volunteer. All the volunteers had normal kidney and liver functions and were free from any chronic disease such as hypertension, diabetes, hypotension or liver abnormalities. A balanced three-way crossover study with one week washout period between each treatment was employed. Each volunteer received sildenafil tablet (50 mg) alone, ciprofloxacin tablet (500 mg) plus sildenafil tablet 50 mg and clarithromycin tablet (500 mg) plus sildenafil tablet 50 mg on three different occasions during the three phases of the study.

Pharmacokinetic study

The subjects were instructed not to take any drugs for at least 72 h prior to and throughout each study period. They were instructed to fast overnight for at least 8 h before drug administration. All the volunteers were given the same meals throughout the study period. On the day of the study, each volunteer received one tablet of sildenafil (50 mg) either alone, 2 h after taking one tablet of ciprofloxacin (500 mg) or 2 h after taking one tablet of clarithromycin (500 mg). After the washout period, each volunteer received a different treatment until all the three phases of the study were completed. The volunteers were allowed to eat 3 h after sildenafil administration. Blood samples were obtained before drug administration (blank) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after sildenafil administration. The blood samples (3 ml) were collected in heparinized tubes. These tubes were pretreated with one drop of heparin 5000 U/ml the day before the experiment and were left to dry at room temperature. Plasma was separated by centrifugation at 1000 *g* for 10 min and was frozen at −20 °C until analysis. Plasma samples were analysed for sildenafil using an HPLC method.

Sample analysis

Plasma samples were analysed for sildenafil using the HPLC method developed in our laboratory. A set of clean test tubes was spiked with 50 µl of the internal standard solution, 20 µg/ml dexamethasone in methanol, and the methanol was left to evaporate in a water bath at 45 °C. To each of these tubes, 0.5 ml of the plasma samples was added and the tube contents were vortex mixed for 1 min. The plasma samples spiked with the internal standard (2 µg/ml) were extracted with 4 ml of ether by mechanical shaking for 3 min before centrifugation for 10 min. The ether layer in each tube was transferred to a clean test tube and was evaporated in a water bath at 50 °C. The residue was dissolved in 150 µl of the mobile phase and 50 µl of the resulting solution was injected onto the HPLC.

The mobile phase consisted of 35% acetonitrile in 20 mmol sodium dihydrogen phosphate. Separation was achieved at ambient temperature using a reversed-phase column 15 cm × 3.9 mm (i.d.) C_{18}, 4 µm Nova-pack (Waters® Inc., MA, USA) at a flow rate of 1.3 ml/min. The column effluent was monitored by UV detector at 240 nm.

Blank plasma was spiked with the internal standard and known amounts of sildenafil to produce standard samples with concentrations in the range of 50–1000 µg/l. Calibration curves were constructed from the obtained peak area ratio (drug peak area/internal standard peak area) and the concentration of sildenafil in each standard sample. The concentrations of sildenafil in the unknown samples were determined from the calibration curves.

The assay was fully validated for selectivity, linearity, precision, accuracy and stability. There was no interference between the endogenous peaks in the plasma and the peaks for sildenafil and the internal standard. The calibration standard was linear in the entire range of the assay (50–1000 µg/l) and the coefficient of variation (CV) for the slopes of the calibration curves obtained during the study period ($n = 6$) was 8.6%. Within-day precision was determined from the analysis of three calibration curves on the same day and the CV for the peak area ratio for each concentration was in the range 1.1%–7.8%. Between-day precision was determined from the analysis of six different calibration curves on six different days during the study period, and the CV for the peak area ratio was in the range 3.2%–9.4%. The accuracy of the assay, determined from the predicted sildenafil concentration in each standard, was in the range 92%–110%. Stability of sildenafil samples at −20 °C during the study period was determined by the analysis on two separate occasions of samples obtained from two volunteers, i.e. at the beginning and at the end of the study. The difference between the measured concentrations in the two analyses was less than 15% indicating that sildenafil was stable while stored at −20 °C during the study period.

Pharmacokinetic analysis

A noncompartmental approach was used to analyse sildenafil pharmacokinetic characteristics under the different study conditions. The

maximum plasma sildenafil concentration (C_{max}) and the time to achieve C_{max} (t_{max}) were determined directly from the individual concentration-time profiles. The elimination rate constant (k) was determined for each individual from log-linear regression of plasma concentration-time curve during the terminal elimination phase. The elimination half life ($t_{1/2}$) was determined as $0.693/k$. The area under the plasma concentration-time curve (AUC_{0-t}) was determined by the linear trapezoidal rule, and the $AUC_{t-\infty}$ was determined as C_{last}/k, where C_{last} is the last measured concentration. The total $AUC_{0-\infty}$ was determined from the sum of AUC_{0-t} and $AUC_{t-\infty}$.

Statistical analysis

The pharmacokinetic parameters estimated during the three different treatments were compared by ANOVA to test the effect of ciprofloxacin and clarithromycin on sildenafil pharmacokinetics. Values of $P < 0.05$ were considered significant. To evaluate the significance of the interaction between ciprofloxacin and clarithromycin with sildenafil, the standard procedures for bioequivalence were applied [16]. A one-sided Student's t-test was carried out to test if the interaction between ciprofloxacin and sildenafil, and the interaction between clarithromycin and sildenafil have a significant effect on sildenafil C_{max} and AUC. A significant interaction was assumed if the 90% confidence interval for the difference between the log-transformed values for AUC and C_{max} estimated for sildenafil alone and sildenafil with the interacting drug fall outside the range 80%–125% of the mean value for sildenafil parameters when administered alone.

Results

Sildenafil was absorbed rapidly after oral administration reaching a maximum plasma concentration in about 1.5 h; the drug was eliminated with an average half life of 2.5 h. Coadministration of ciprofloxacin with sildenafil resulted in much higher plasma sildenafil concentrations, which was reflected in a significant increase in AUC from 1407 ± 380 µg h/l to 2986 ± 917 µg h/l and a significant increase in C_{max} from 287 ± 67 µg/l to 623 ± 192 µg/l (Figure 1). The effect of ciprofloxacin represents about a 110% increase in AUC and about a 117% increase in C_{max} of sildenafil. The elimination of sildenafil was also significantly delayed; the elimination rate constant was decreased from $0.296 \pm 0.086\ h^{-1}$ to $0.229 \pm 0.092\ h^{-1}$ and the elimination half life was prolonged from 2.5 ± 0.566 h to 3.44 ± 1.09 h (Table 1).

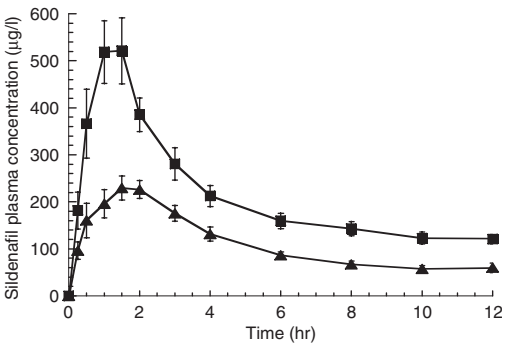

Figure 1. Sildenafil plasma concentration-time profile after a single dose of sildenafil 50 mg alone (▲) and after ciprofloxacin pretreatment (■). Data presented as mean ± SE ($n = 12$)

Coadministration of clarithromycin with sildenafil significantly increased the plasma sildenafil concentration also resulting in a significant increase in sildenafil AUC from 1407 ± 380 µg-h/l to 3209 ± 762 µg-h/l and in C_{max} from 287 ± 67 µg/l to 694 ± 260 µg/l (Figure 2). The effect of clarithromycin represents about a 128% increase in AUC and about a 140% increase in the C_{max} of sildenafil. Sildenafil elimination was not affected which was apparent from the non-significant difference in the sildenafil elimination rate constant and half life (Table 1).

Coadministration of ciprofloxacin or clarithromycin with sildenafil did not significantly affect the rate of sildenafil absorption as is apparent from the non-significant difference in t_{max}. The effect of the interaction of ciprofloxacin and clarithromycin with sildenafil on sildenafil AUC and C_{max} indicates that this is a clinically significant interaction (Figure 3). The 90% confidence intervals for the difference between the log-transformed values for sildenafil AUC and C_{max} estimated for sildenafil with ciprofloxacin

Table 1. The effect of ciprofloxacin and clarithromycin coadministration on sildenafil pharmacokinetic parameters

$t_{1/2}$ (h)	k (h^{-1})	$AUC_{0-\infty}$ (μg.h/l)	t_{max} (h)	C_{max} (μg/l)	Treatment
2.50 ± 0.566	0.296 ± 0.086	1407 ± 380	1.5 ± 0.74	287 ± 67	Sildenafil alone
3.44[a] ± 1.09	0.229 ± 0.092	2986[a] ± 917	1.13 ± 0.36	623[a] ± 192	Sildenafil + ciprofloxacin
2.96 ± 1.07	0.267 ± 0.098	3209[a] ± 762	1.29 ± 0.52	694[a] ± 259	Sildenafil + clarithromycin

Data are presented as mean ± SD, $n = 12$.
[a]significantly different from sildenafil alone ($p < 0.05$).
C_{max}, maximum plasma concentration; t_{max}, time required to achieve maximum plasma concentration; $AUC_{0\rightarrow\infty}$, area under the curve; k, elimination rate constant; $t_{1/2}$, half-life.

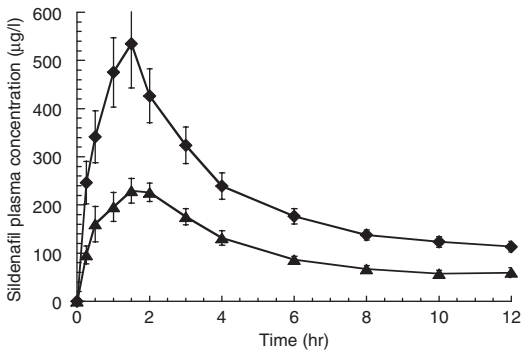

Figure 2. Sildenafil plasma concentration-time profile after a single dose of sildenafil 50 mg alone (▲) and after clarithromycin pretreatment (◆). Data presented as mean ± SE ($n = 12$)

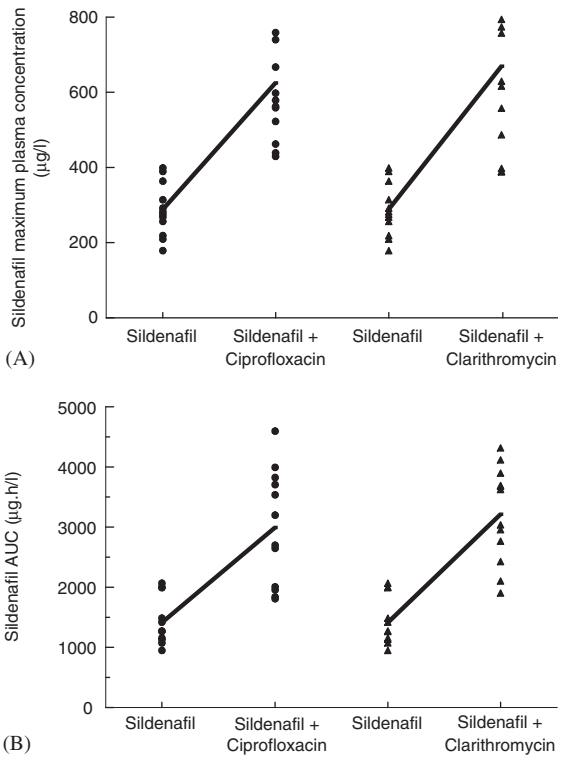

Figure 3. The individual sildenafil C_{max} (A), and sildenafil *AUC* (B) in the 12 volunteers when sildenafil was administered alone and in combination with ciprofloxacin or clarithromycin. The line represents the change in the mean value of the each parameter due to administration of ciprofloxacin or clarithromycin

relative to *AUC* and C_{max} for sildenafil alone were 119%–159% and 127%–152%, respectively. The 90% confidence intervals for the difference between the log-transformed values for sildenafil *AUC* and C_{max} estimated for sildenafil with clarithromycin relative to *AUC* and C_{max} for sildenafil alone were 127%–161% and 132%–157%, respectively. The results of this study indicated that ciprofloxacin and clarithromycin could increase the extent of sildenafil absorption significantly resulting in significantly higher sildenafil concentrations in humans.

Discussion

Sildenafil is the most widely used drug in the management of erectile dysfunction. The use of sildenafil is also expected to increase due to its efficacy in the management of other cardiovascular conditions [17]. For this reason, it is very important to ensure the safety of this drug in a variety of conditions, and to study the potential drug–drug interactions with a wide variety of drugs. The current study was performed to investigate the possible interaction between

sildenafil and ciprofloxacin or clarithromycin. These drugs were selected because they are widely used antibiotics and are known to inhibit CYP3A4, the major cytochrome P450 isoform responsible for sildenafil metabolism [12–15].

Sildenafil is a relatively safe drug in the general population when used in the recommended therapeutic doses. The most common side effects result from sildenafil vasodilator effects resulting in headache, flushing, rhinitis, dizziness and hypotension. Other reported adverse effects include dyspepsia and burning sensation which result from relaxation of the esophageal sphincter, and in higher doses visual disturbance and myalgia can occur [2]. Patients with moderate to severe cardiovascular diseases and patients who are taking organic nitrates may be at higher risk of developing serious cardiovascular adverse effects with sildenafil therapy. Nitrates can produce profound hypotension in patients taking sildenafil leading to decreased coronary perfusion and myocardial infarction. For this reason, sildenafil is contraindicated in patients who are taking organic nitrate [2].

Sildenafil is almost completely absorbed after oral administration, however, its systemic availability is only 40% due to the extensive first-pass effect. For drugs that are completely absorbed like sildenafil, the clearance estimated after oral administration is the intrinsic clearance of the drug. Sildenafil metabolism in humans is primarily mediated by the cytochrome P450 3A4 isozyme. This low affinity high capacity CYP3A4 is also responsible for extensive presystemic metabolism of sildenafil leading to its incomplete bioavailability [6,7]. So, it is expected that inhibitors of the CYP3A4 can increase sildenafil bioavailability and slow its elimination rate. It has been reported that the pharmacokinetic characteristics of sildenafil were significantly altered in healthy volunteers who took the protease inhibitors saquinavir or ritonavir. The inhibition of CYP3A4 by saquinavir and ritonavir significantly increased the bioavailability and slowed the elimination of sildenafil [10]. A similar increase in sildenafil plasma concentrations was observed when sildenafil was administered with the known cytochrome P450 inhibitors cimetidine and erythromycin [8,9].

The current study selected two of the commonly prescribed drugs which are known to inhibit CYP3A4. Ciprofloxacin has been shown to inhibit CYP3A4 and affect the pharmacokinetics of drugs that are eliminated by this cytochrome P450 isoform [12,13]. When sildenafil was administered to the volunteers after taking ciprofloxacin there was more than a two-fold increase in the *AUC* and C_{max} and the 90% confidence interval for the ratio of the *AUC* and C_{max} indicated a significant drug interaction. Ciprofloxacin also prolonged the elimination half life of sildenafil by about 35%. Prolongation of the half life can result from decreasing the total body clearance or increasing the volume of distribution of the drug. It is very unlikely that ciprofloxacin which is only 40% bound to plasma protein, can affect the volume of distribution of sildenafil. Therefore, the effect of ciprofloxacin on the sildenafil elimination rate constant and half life is probably due to a proportional decrease in its total body clearance. Since the small (35%) but significant increase in sildenafil elimination half life cannot account for the two fold increase in the *AUC* and C_{max}, ciprofloxacin could be considered to affect sildenafil bioavailability to a larger extent. The results clearly indicated that ciprofloxacin significantly increased sildenafil bioavailability and to a lesser extent decreased sildenafil clearance.

Clarithromycin is a commonly used macrolide antibiotic which is known to inhibit CYP3A4. Studies have shown that clarithromycin can affect the bioavailability of drugs such as amprenavir, simvastatin, ropivacaine and repaglinide due to inhibition of CYP3A4 [18–21]. In our study sildenafil administration to the volunteers after taking clarithromycin significantly increased sildenafil *AUC* and C_{max} by more than two-fold, and the 90% confidence interval for the ratio of the *AUC* and C_{max} indicated a significant drug interaction. The elimination rate constant of sildenafil was not affected by administration of clarithromycin which was indicated by the unchanged half life. This indicates that the effect of clarithromycin on sildenafil is mainly due to the increase in sildenafil bioavailability. This increased sildenafil bioavailability is caused by inhibition of its presystemic metabolism.

The results clearly demonstrate that both ciprofloxacin and clarithromycin significantly increased sildenafil bioavailability, however, only ciprofloxacin slowed sildenafil clearance. The current study was performed by studying sildenafil pharmacokinetics after a single dose administration of ciprofloxacin and clarithromycin. It is expected that at steady state higher ciprofloxacin and clarithromycin concentrations are achieved and it is possible that these two drugs can affect sildenafil bioavailability and clearance to a greater extent. It is also important to note that none of the volunteers who participated in our study complained of increased adverse effects when they received sildenafil with ciprofloxacin or clarithromycin. The same was true in the interaction study of sildenafil with saquinavir and ritonavir [10]. Although the significant increase in the plasma concentrations of sildenafil was not associated with increased adverse effects in these healthy volunteers, the effect of higher sildenafil plasma concentrations may be different in patients with cardiovascular diseases. Drug interactions with sildenafil that can increase the plasma sildenafil concentrations may have clinical significance when sildenafil is administered to patients at higher risk of developing adverse effects with the interaction becoming potentially dangerous with regular administration of the interacting drugs.

Conclusions

Concurrent administration of sildenafil with ciprofloxacin or clarithromycin can result in significantly higher sildenafil plasma concentrations. This increase in plasma sildenafil concentrations is due to inhibition of CYP3A4 by ciprofloxacin and clarithromycin. The inhibition of CYP3A4 can lead to higher sildenafil bioavailability and possibly slower clearance. Since the higher sildenafil concentrations can be associated with increased adverse effects, patients who are taking ciprofloxacin or clarithromycin may need smaller doses of sildenafil. It is recommended that patients at higher risk of developing sildenafil adverse effects and who are taking ciprofloxacin or clarithromycin should seek medical advice before taking their sildenafil therapy.

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