

Original Article

Pharmacokinetic interactions between ilaprazole and clarithromycin following ilaprazole, clarithromycin and amoxicillin triple therapy

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Aim: To investigate the drug interactions between ilaprazole, a new proton pump inhibitor, and clarithromycin following ilaprazole, clarithromycin and amoxicillin combination therapy.

Methods: Twelve healthy Chinese volunteers were recruited in a randomized, open-label, 3-period crossover study. All subjects were administered ilaprazole (5 mg), clarithromycin (500 mg) or a triple therapy, including ilaprazole (5 mg), clarithromycin (500 mg) and amoxicillin (1 g), twice daily for 6 consecutive days. On the 7th day, the drugs were given once, and blood samples were collected and analyzed using a well-validated HPLC/MS/MS method.

Results: Following the triple therapy, the peak concentration (C_{max}) and the area under the concentration-time curve from 0 h to 12 h (AUC_{0-12}) of ilaprazole were significantly decreased, as compared with the single medication group (C_{max} : 1025.0±319.6 vs 1452.3±324.6 ng/mL; AUC_{0-12} : 9777.7±3789.8 vs 11363.1±3442.0 ng·h/mL). Similar changes were found for ilaprazole sulfone (C_{max} : 5.9±0.5 vs 9.3±1.7 ng/mL; AUC_{0-12} : 201.4±32.1 vs 277.1±66.2 ng·h/mL). The triple therapy significantly elevated the C_{max} of clarithromycin (3161.5±702.2 vs 2541.9±476.2 ng/mL).

Conclusion: The *H pylori* eradication therapy with clarithromycin, amoxicillin and ilaprazole may cause pharmacokinetic interactions that decrease the amount of ilaprazole and its metabolites and elevate that of clarithromycin.

Keywords: peptic ulcer; *Helicobacter pylori* infection; eradication therapy; clarithromycin; amoxicillin; ilaprazole; pharmacokinetics; drug interaction

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Introduction

Seventy to 90% of all peptic ulcer disease cases, one of the most common diseases influencing health around the world, are caused by *Helicobacter pylori* (*H pylori*) infection^[1]. The choice of a treatment regimen for *H pylori*-positive cases is based on the principle of infection eradication^[2]. With single antibiotic treatment, the eradication rate achieved is between 15% and 54% when the macrolide antibiotic, clarithromycin (CLR), is given^[3] and is between 20% to 30% when the penicillin antibiotic, amoxicillin (AMX), is administered^[4]. A triple therapy comprised of a proton pump inhibitor (PPI), such as omeprazole, lansoprazole or rabeprazole, with AMX and CLR has been strongly recommended as a first-line therapy for *H*

pylori eradication^[5].

Previous reports indicate that following triple therapy, the rate of *H pylori* eradication achieved was 84%–95%^[4, 6]. The synergistic effect of these therapies is related to pharmacokinetic interactions. It has been confirmed that triple therapy increases both the AUC and C_{max} of clarithromycin and its active metabolite 14-OH-clarithromycin^[7–9]. However, the AUC of omeprazole increased almost 2-fold after concomitant administration of CLR^[7], and the AUC of lansoprazole significantly increased from 3.65 to 4.59 mg·h/L after co-administration of CLR and AMX^[8]. The pharmacokinetic drug interactions are likely a result of alterations in the hepatic metabolism of PPIs following combination therapy with clarithromycin, which is considered a potent inhibitor of CYP3A^[10–12]. Ushijima *et al* previously published data using partial cortisol clearance as a CYP3A activity probe *in vivo* to assess the inhibition of CYP3A activity. In their study, two experimental

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groups were given clarithromycin (400 mg or 800 mg), and they observed a dose-dependent inhibition of *in vivo* CYP3A activity and resultant elevation in plasma lansoprazole concentrations, which were not present in the control group that did not receive clarithromycin^[13].

A new proton pump inhibitor, ilaprazole (IIa), was recently introduced. In a double-blind, parallel, randomized study, ilaprazole was shown to be as effective and well-tolerated as omeprazole for the treatment of gastric and duodenal ulcers (healed in 67.1% *vs* 62.3% and 83.7% *vs* 78.9% of patients, respectively), at a much lower dose (5 *vs* 20 mg, respectively)^[14]. In another multicenter trial, 10 mg ilaprazole was found to be more effective than 20 mg omeprazole and other doses of ilaprazole over a 4-week treatment period^[15].

A study on rat livers using on-line HPLC/ESI mass spectrometry found two metabolites of ilaprazole – a major product, ilaprazole sulfone, and a minor product, hydroxyl-ilaprazole^[16] – implying that ilaprazole might be predominantly metabolized in the liver by CYP3A and partially by CYP2C19 in a manner similar to that of omeprazole and lansoprazole, which are metabolized into sulfoxidation and hydroxylation metabolites. However, data published by Li and Cho *et al* indicate that CYP3A5 and CYP2C19 genotypes have no impact on ilaprazole metabolism^[17,18]. Therefore, further investigation is required to determine whether pharmacokinetic interactions play a role in triple therapy using ilaprazole as a PPI.

Although its pharmacological interaction mechanisms are not fully understood, triple therapy has been used for many years in the treatment of *H pylori*-related peptic ulcer disease. Our study use ilaprazole as a novel PPI within a triple therapy regimen. The present study was designed to determine the effect of (1) clarithromycin and amoxicillin on the pharmacokinetics of ilaprazole and its metabolites and (2) ilaprazole and amoxicillin on the pharmacokinetics of clarithromycin.

Materials and methods

Materials and reagents

Ilaprazole, ilaprazole sulfone and ilaprazole thiol ether standards were obtained from the Livzon Pharmaceutical Group, Inc (purity: 99.1%, Zhuhai, China). Omeprazole standards were obtained from Sigma Chemical Company (purity: 99.5%, USA). Ilaprazole tablets were obtained from the Livzon Pharmaceutical Group, Inc (Zhuhai, China). HPLC-grade acetonitrile, methanol and methyl tert-butyl ether (MTBE) were purchased from Dikma Comp (Guangzhou, China). HPLC-grade water was obtained using a Milli-Q system (Millipore, USA). All other reagents were of analytical grade.

Subjects

This study was conducted under the approval of the Xiangya institutional review boards and with the informed consent of all the subjects. Twelve healthy, Chinese Han male volunteers with normal hepatic, renal, and hematologic function were selected for this study. All results were within the normal limits (see Table 1S). The age of the participants ranged from 21 to 27 years (mean±SD, 23.9±1.9 years), their weight ranged

from 55 to 77 kg (63.7±7.8 kg), and their height ranged from 162 to 178 cm (172.2±4.2 cm). The exclusion criteria included any use of medication within 2 weeks prior to the commencement of the study, the use of tobacco or alcohol during the study, and any clinically significant illness within 3 months prior to the study. A physical examination was performed, and common laboratory parameters for hematological, hepatic and renal functions were determined, before, during and after the study to monitor the safety of drug treatment.

Study protocol

This was a randomized, open-labeled, self-controlled, 3-way crossover study. Twelve subjects were randomized into 3 groups: ilaprazole (5 mg); clarithromycin (500 mg); or ilaprazole (5 mg), clarithromycin (500 mg) and amoxicillin (1 g) combination therapy. All drugs were administered twice daily for 6 consecutive days and only once on the 7th d. After 12 h of fasting, the volunteers were given the drugs with 200 mL tap water on the morning of the 7th d. Then, 5 mL or 8 mL blood samples were collected before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h after drug administration. The whole blood sample was centrifuged immediately, and the upper layer serums were transferred to polyethylene tubes and stored at -80 °C until analysis. After a 7-d drug elimination period between each dose, the subjects proceeded to the next phase.

Measurement of serum drug concentration

The quantitative determination of ilaprazole and its two metabolites was based on an improved LC/MS/MS method published by Zhou *et al*^[16,19]. Briefly, the chromatographic condition included a Thermo HyPURITY C18 column (150 mm×2.1 mm, 5 μm) with a mobile phase consisting of 10 mmol/L ammonium formate water-acetonitrile solution (50:50, *v/v*) at a flow rate of 0.25 mL/min. The API4000 triple quadrupole mass spectrometer (Applied Biosystems, USA) was operated in multiple reactions monitoring mode via positive electrospray ionization interface.

This method displayed linearity over the concentration range of 0.23–2400.00 ng/mL for ilaprazole, 0.05–105.00 ng/mL for ilaprazole thiol ether and 0.06–45.00 ng/mL for ilaprazole sulfone. The lower limits of quantification were 0.23, 0.05, and 0.06 ng/mL for ilaprazole, ilaprazole sulfone and ilaprazole thiol ether, respectively. The intra- and inter-day precisions were all less than 15% in terms of relative standard deviation (RSD), and the accuracy was within 15% in terms of relative error (RE) for ilaprazole, ilaprazole sulfone and ilaprazole thiol ether.

The concentration of clarithromycin in plasma was determined using HPLC-MS/MS. Separation of the analytes and the internal standard (IS), roxithromycin, was performed on a Waters Xterra MS C18 column (2.11 mm×50 mm, 5 μm), with a mobile phase consisting of 20 mmol/L ammonium acetate water-acetonitrile solution (40:60, *v/v*), at a flow rate of 0.25 mL/min. The API4000 triple quadrupole mass spectrometer was operated in multiple reactions monitoring mode via a positive electrospray ionization interface. The standard

curves displayed excellent linearity with no systematic bias. The lower limit of quantification of clarithromycin was 6.035 ng/mL, the intra- and inter-day precisions were all less than 15% for medium and high concentrations and less than 20% for low concentration in terms of the relative standard deviation (RSD), and the accuracy was within 15% in terms of the relative error (RE) for clarithromycin at all concentrations.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated according to a non-compartmental model using Winnonlin (Pharsight Corporation, ver 3.0, Mountain View, CA, USA). The peak concentration (C_{max}) and the time of peak concentration (T_{max}) were directly analyzed by visual inspection of the plasma concentration-time profile. The elimination rate constant (λ) was obtained by the least square fitted terminal log-linear portion of the slope of the plasma concentration-time profile, and the elimination half-life ($t_{1/2}$) was evaluated according to $0.693/\lambda$. The area under the plasma concentration-time curve (AUC_{∞}) was evaluated by the linear trapezoidal rule and further extrapolated to infinity by dividing the last measurable concentration by λ , according to the following equation: $AUC_{\infty} = AUC_{0-t} + C_{last}/\lambda$.

Statistical analysis

All data are expressed as the mean \pm SD. Statistical comparisons of the mean values between different groups were performed using a paired *t*-test or an ANOVA. The data were analyzed using the statistical program SPSS (Statistical Package for the Social Sciences) 11.0 for Windows (SPSS, Chicago, IL, USA). Differences were considered statistically significant at $P < 0.05$. The 90% confidence intervals of the log-values of the AUC and C_{max} were determined for the bio-equivalence test. The resulting data beyond 70%–143% for C_{max} and 80%–125% for AUC in single treatment groups were considered significantly different.

Results

All 12 of the volunteers completed the 3 phases of the study under the well-performed protocol. No severe adverse events or clinically relevant deviations of laboratory parameters occurred during the study.

The pharmacokinetic interaction effect of triple therapy on clarithromycin or ilaprazole and its metabolites (ilaprazole sulfone and ilaprazole thiol-ether) were investigated by comparing the concentration and kinetic parameters of the single administration cycle with combination therapy. The pharmacokinetic parameters for the indicated drugs and ilaprazole metabolites after single and triple drug therapy are summarized in Table 1, and serum concentration-time profiles are presented in Figure 1.

The maximum concentration (C_{max}) of ilaprazole was significantly decreased after combination therapy compared with single treatment (1025.0 ± 319.6 vs 1452.3 ± 324.6 ng/mL, $P = 0.002$). The $AUC_{0 \rightarrow 12}$ and $AUC_{0 \rightarrow \infty}$ of ilaprazole were 9777.7 ± 3789.8 and 9870.5 ± 3910.7 ng·h/mL in the triple therapy group, which were much lower than the corresponding values in the single treatment group (11363.1 ± 3442.0 and 11438.8 ± 3473.5 ng·h/mL, respectively), but the differences did not reach statistical significance.

Following triple therapy, the mean residence time (MRT) and the total clearance/systemic bioavailability (CL_{tot}/f) of ilaprazole increased compared to the single treatment period, whereas the elimination half-life ($t_{1/2}$) decreased slightly.

In the triple therapy group, the 90% confidence intervals (CIs) of C_{max} , $AUC_{0 \rightarrow 12}$, and $AUC_{0 \rightarrow \infty}$ were 58.3% to 80.5%, 70.7% to 99.9%, and 70.7% to 100.1% (Table 2), respectively, which represents a decrease of 24.9%, 8.3%, and 8.2% compared with the corresponding values in the single treatment group, respectively. All of these data fell completely beyond the equivalence range of 80%–125% for AUC and 70%–143% for C_{max} .

The changes tendency of pharmacokinetic parameters of

Table 1. Pharmacokinetic parameters of ilaprazole (Ila) and its metabolites (Sulfone and Thiol ether), clarithromycin (CLR), following single and ilaprazole clarithromycin and amoxicillin (AMX) triple therapy. Mean \pm SD. $n = 12$. ^b $P < 0.05$.

Treatment	$T_{1/2}$ (h)	C_{max} (ng/mL)	T_{max}^* (h)	$AUC_{(0 \rightarrow t)}$ (ng·h/mL)	$AUC_{(0 \rightarrow \infty)}$ (ng·h/mL)	MRT (h)	CL/F (L/h)
Ila	10.1 \pm 3.2	1452.3 \pm 324.6	3 (2–4)	11363.1 \pm 3442.0	11438.8 \pm 3473.5	9.8 \pm 3.0	0.4 \pm 0.2
Ila+AMX+CLR	9.3 \pm 3.7	1025.0 \pm 319.6 ^b	3 (1.5–6)	9777.7 \pm 3789.8 ^b	9870.5 \pm 3910.7 ^b	10.1 \pm 2.9	0.5 \pm 0.2
Sulfone (Ila)	19.1 \pm 9.1	9.3 \pm 1.7	4 (0.5–8)	277.1 \pm 66.2	308.0 \pm 95.6	21.6 \pm 3.1	
Sulfone (Ila+AMX+CLR)	20.8 \pm 6.0	5.9 \pm 0.5 ^b	6 (0.5–12)	201.4 \pm 32.1 ^b	224.7 \pm 47.7 ^b	22.7 \pm 2.5	
Thiol ether (Ila)	11.9 \pm 7.2	15.7 \pm 7.1	4 (1.5–6)	246.0 \pm 178.3	272.8 \pm 214.5	13.6 \pm 5.3	
Thiol ether (Ila+AMX+CLR)	13.1 \pm 6.1 ^b	16.0 \pm 7.7	3 (0.5–6) ^b	268.4 \pm 220.9	279.3 \pm 220.5	17.6 \pm 9.4 ^b	
CLR	10.9 \pm 2.9	2541.9 \pm 476.2	1.5 (1.5–2)	29772.7 \pm 4781.9	30254.9 \pm 5240.4	12.8 \pm 2.6	16.5 \pm 3.0
CLR+AMX+Ila	8.5 \pm 1.4	3161.5 \pm 702.2 ^b	1.5 (1.5–4)	29953.4 \pm 6474.4	30045.5 \pm 6490.6	10.4 \pm 1.2 ^b	16.6 \pm 4.2

* T_{max} was described by median (range).

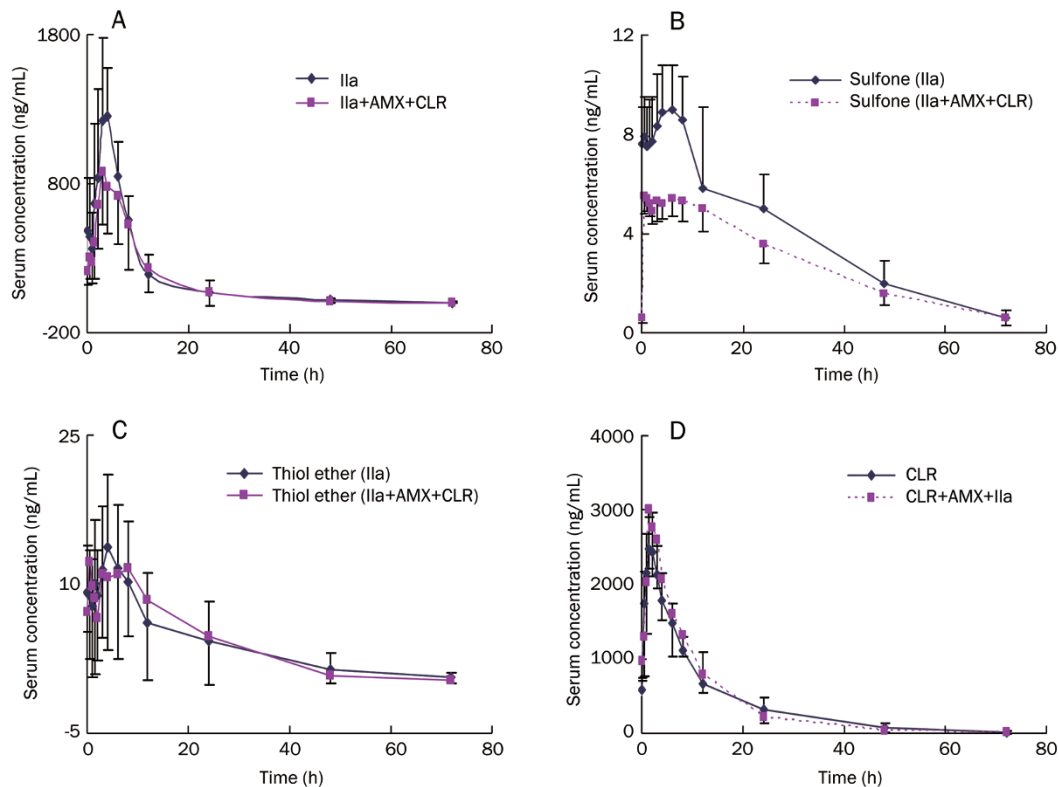


Figure 1. Serum concentrations of ilaprazole (A), ilaprazole sulfone (B), ilaprazole thioether (C), clarithromycin (D), expressed as mean \pm SD and regression line after administration of ilaprazole alone and with amoxicillin and clarithromycin. Ila, ilaprazole; AMX, amoxicillin; CLR, clarithromycin.

Table 2. Test of bio-equivalence after administration of ilaprazole alone and with amoxicillin and clarithromycin.

Treatment	$AUC_{0\rightarrow t}$	Point estimates (90% confidence interval)	
		$AUC_{0\rightarrow\infty}$	C_{max}
Ila	81.4 (70.7–99.9) ^a	84.1 (70.7–100.1) ^a	68.5 (58.3–80.5) ^a
Ila+AMX+CLR	80.4 (69.4–96.4) ^a	83.5 (69.5–96.4) ^a	66.3 (58.4–77.2) ^a
Sulfone	109.1 (69.9–170.3) ^a	107.7 (72.9–159.1) ^a	102.8 (76.8–137.4)
Sulfone (Ila+AMX+CLR)	99.5 (81.5–121.5)	98.4 (80.1–120.9)	122.6 (100.7–149.2) ^a
Thiol ether			
Thiol ether (Ila+AMX+CLR)			
CLR			
CLR+AMX+Ila			

^a Point estimates (90% confidence interval) in triple therapy beyond the set value in single therapy.

ilaprazole sulfone, the major ilaprazole metabolite, was similar to that of its parent drug, ilaprazole. We observed a large difference in the C_{max} values between the triple therapy group (5.9 ± 0.5 ng/mL) and the single therapy group (9.3 ± 1.7 ng/mL; $P=2.25\times 10^{-5}$). A smaller difference was observed between the $AUC_{0\rightarrow 12}$ and $AUC_{0\rightarrow\infty}$ of ilaprazole sulfone following triple therapy and single therapy (201.4 ± 32.1 vs 277.1 ± 66.2 ng·h/mL, $P=1.46\times 10^{-9}$ and 224.7 ± 47.7 ng·h/mL vs 308.0 ± 95.6 ng·h/mL, $P=2.36\times 10^{-8}$, respectively). In the triple therapy group, the 90% CIs of C_{max} , $AUC_{0\rightarrow 12}$ and $AUC_{0\rightarrow\infty}$ were significantly decreased by 30.4%, 22.1%, and 21.3% compared with the corresponding

values in the single treatment group (Table 2).

For ilaprazole thiol ether, the T_{max} was reached at 3 h (median, range 0.5–6 h) after combination treatment, which was significantly faster than that of single treatment, which was reached at 4 h (median, range 1.5–6 h) ($P=0.009$). A small increase was observed in the C_{max} of the combination treatment group (16.0 ± 7.7 ng/mL) compared with the single therapy group (15.7 ± 7.1 ng/mL), but this difference was not significant. A slight increase was observed in $AUC_{0\rightarrow 12}$ and $AUC_{0\rightarrow\infty}$ after combination therapy compared to single therapy (268.4 ± 220.9 vs 246.0 ± 178.3 ng·h/mL, $P=0.728$; 279.3 ± 220.5 vs

272.8±214.5 ng·h/mL, $P=0.736$, respectively). The 90% CIs of AUC_{0-12} and $AUC_{0-\infty}$ in the combination treatment group were beyond 80%–125%, and the C_{max} was within the 70%–143% CI range in the single treatment group.

For clarithromycin, a 29.8% increase in C_{max} was measured after combination treatment compared with single treatment (3161.5±702.2 vs 2541.9±476.2 ng/mL, $P=0.0089$). The 90% CIs of C_{max} following the three-drug regimen was beyond the range of 70%–143%, and the other parameters were altered slightly without any statistical significance.

Discussion

No significant positive synergistic effect was found between ilaprazole, clarithromycin and amoxicillin in this study. Unexpectedly, when combined with clarithromycin and amoxicillin, the plasma concentrations of ilaprazole were lower than those of single ilaprazole administration over a 6-day course of therapy. The mean C_{max} , AUC_{0-12} , and $AUC_{0-\infty}$ were decreased by 24.9%, 8.3%, and 8.2%, respectively, when ilaprazole was given in combination compared to its administration as a single agent. The significant decrease in C_{max} , the decreased AUC and the lack of alteration in the $T_{1/2}$ of ilaprazole in serum indicate that the reduced plasma concentrations observed in our study were likely due to diminished absorption as opposed to alterations in metabolism.

The significant decrease in the C_{max} and AUC of ilaprazole sulfone after triple therapy support this consideration. The same trend was considered to be due to decreased absorption of the parent drug; however, the AUC of ilaprazole thiol ether did not change after triple therapy, which supports Zhou's report demonstrating that it is a relatively minor metabolite^[16].

Early studies investigated the effect of clarithromycin – an accepted, potent inhibitor of CYP3A – on the pharmacokinetics of PPIs because *in vivo* and *in vitro* studies suggested that PPIs, such as omeprazole and lansoprazole, are metabolized, at least in part, by CYP3A4. It was previously demonstrated that the plasma exposure of omeprazole and lansoprazole increased almost 2-fold^[7, 13] and 1.3-fold^[8], respectively, when given simultaneously with clarithromycin. Compared with omeprazole, esomeprazole metabolism is more dependent on CYP3A. One study indicated that clarithromycin decreased the rate of esomeprazole metabolism, which doubled the AUC values, regardless of the CYP2C19 genotype^[9]. The pharmacokinetics of rebeprazole, which is metabolized by a non-enzymatic pathway with minor CYP2C19 and CYP3A4 involvement, were not altered by clarithromycin or verapamil (a potent CYP3A inhibitor), irrespective of the CYP2C19 genotype^[20].

For ilaprazole, Li and Cho reported that the CYP3A5 and CYP2C19 genotypes had no impact on ilaprazole metabolism in healthy Chinese and Korea subjects^[17, 18]. Additionally, our previous study evaluating the effect of the CYP3A phenotype (indicated by 1-OH midazolam/midazolam ratio) on ilaprazole metabolism showed no correlation between the CYP3A phenotype and ilaprazole metabolism. The reduced influence of CYP3A on ilaprazole metabolism may explain why ilapra-

zole and clarithromycin did not produce synergistic effects in our study. To date, no transporters involved in ilaprazole absorption and metabolism have been identified. The reason for the decreased absorption of ilaprazole after triple therapy warrants further investigation.

It is well established that amoxicillin is primarily excreted as a pro-drug and is not metabolized in the liver. Mainz reported that the pharmacokinetics of amoxicillin were not altered by combination therapy with lansoprazole and clarithromycin^[8], which is consistent with other reports that demonstrated no effects of omeprazole on the pharmacokinetics of amoxicillin^[21-23]. Therefore, in present study, we did not compare the plasma concentration of amoxicillin alone with combination therapy because of its non-metabolic characteristics.

In this study, the pharmacokinetic parameters of clarithromycin were comparable with those of other studies^[23, 24]. Early studies found that the AUC of CLR increased when omeprazole was given simultaneously with clarithromycin^[7], whereas only the T_{max} was increased with lansoprazole coadministration^[8]. In our study, an increased C_{max} of CLR was the only alteration observed after combination therapy, and this effect was likely a result of increased absorption due to the effect of ilaprazole on gastric pH elevation^[10, 11]. Because clarithromycin tends to be degraded into an inactive form in low pH environments, one possible reason for the observed synergy was due to the higher bioavailability of clarithromycin in low hypoacidic environments^[10, 11]. Therefore, PPIs may enhance the absorption of clarithromycin due to a sustained elevation of pH^[12].

Our study did not measure ilaprazole concentrations in urine, which may have given us direct evidence of the bioavailability of this compound. However, we observed a decline in the major metabolite of ilaprazole after simultaneous administration with clarithromycin and amoxicillin, which indicates that the decrease in ilaprazole absorption is due to another mechanism. Thus, the urine concentration of clarithromycin should be analyzed in further studies to provide more evidence for this hypothesis.

In summary, our study reveals a drug interaction between a new proton pump inhibitor, ilaprazole, and clarithromycin after triple drug combination therapy. We observed a decrease of ilaprazole and a slight increase of clarithromycin. However, these effects were not dose-dependent and did not affect the therapeutic effects of these drugs.

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Author contribution

Shan CAO, Dong-sheng OU-YANG, Dong GUO, Lan FAN, Hong-hao ZHOU, and Wei ZHANG designed research; Shan CAO, Gan ZHOU, Hui-zi WU, Kui XIAO, Yao CHEN, and Zhi-rong TAN performed research; Hai-tang HU and Xiang-hong QIN contributed new reagents or analytic tools; Shan CAO, Dong-sheng OU-YANG, and Wei ZHANG analyzed data; Shan CAO, Lan FAN, and Wei ZHANG wrote the paper.

Supplementary information

Supplementary table (Table 1S) is available at the *Acta Pharmacologica Sinica* website.

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