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# Effect of itraconazole on the pharmacokinetics of ciprofloxacin in healthy volunteers

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***Abstract***

Itraconazole, a triazole antifungal agent, is a potent cytochrome P-450 inhibitor and also a P-glycoprotein (P-gp) inhibitor. Ciprofloxacin, a fluoroquinolone compound with broad spectrum antimicrobial activity, is often coadministered with an antifungal drug in HIV-infected patients. The drug-drug interaction between itraconazole and ciprofloxacin may occur in these patients. Therefore, the aim of this study was to investigate the effect of itraconazole on the pharmacokinetics of ciprofloxacin following a multiple oral dose in healthy volunteers. Two-phase crossover study with a 2 week washout period was designed to study in six healthy volunteers. In phase 1, each volunteer received 500 mg of ciprofloxacin twice daily for 7 days whereas in phase 2, they also received 500 mg ciprofloxacin and 200 mg itraconazole twice daily for 7 days. The results revealed that there was no significant difference in each ciprofloxacin pharmacokinetic parameter between 2 phases of study in six healthy volunteers. In conclusion, itraconazole co-administration with ciprofloxacin did not alter the ciprofloxacin pharmacokinetics in healthy volunteers.

***Keywords:*** Ciprofloxacin, Itraconazole, Pharmacokinetics, Drug interaction

## Introduction

Ciprofloxacin, a nalidixic acid derivatives and a fluoroquinolone drug with broad spectrum antimicrobial activity, is widely used both in human and veterinary medicine to treat infectious diseases. It is metabolized in the liver and eliminated via the kidney including tubular secretion (1).

Itraconazole, an azole derivative, has been found to be effective agents with a variety of fungal infections. It is widely used for the treatment of superficial and systemic fungal infections. Itraconazole is reported to be both an inhibitor of CYP3A4 and P-glycoprotein (P-gp) (2). Ciprofloxacin and itraconazole are usually combined together in the treatment of patients coinfected with bacteria and fungi. In previous study, it was shown that ketoconazole and itraconazole reduced ciprofloxacin urinary excretion in mice (3). So, the pharmacokinetic interaction between itraconazole and ciprofloxacin in human could be possible. The aim of this study was to investigate the effect of itraconazole on the pharmacokinetics of ciprofloxacin following a multiple oral dose in healthy volunteers.

## Materials and methods

### *Subjects and drugs*

Six healthy, nonsmoking, nonalcoholic and nonobese male volunteers were registered in this study. Their mean age and body mass index were 24.33 ± 4.46 years and 21.05 ± 2.70 $kg/m^2$, respectively. The study was approved by the ethics committee of the Faculty of Science, Prince of Songkla University and the written informed consent was obtained from each volunteer. Each subject underwent a pre-study evaluation that they had no underlying illness and were not currently on any medication. All subjects had normal biochemical and hematological laboratory profiles.

Ciprofloxacin tablet (Ciprobay®) was purchased from Bayer, Thailand and itraconazole capsules (Sporal®) was purchased from Olic, Thailand.

***Study design and sample collection***

The study was an open-labeled, randomized, two-phase crossover design with a 2 week washout period. The first phases, all subjects received 500 mg (1 tablet) of ciprofloxacin twice daily for 7 days. The second phases, all subjects received 500 mg ciprofloxacin (1 tablet) and 200 mg itraconazole (2 capsules) twice daily for 7 days. For each phase, blood samples were obtained at the following time; before (time 0), and up to 48 h after drug administration. The plasma was collected and stored at -70 ºC until analysis.

***Ciprofloxacin assay***

The concentration of ciprofloxacin was determined by the reverse-phase HPLC method which was modified from Jim *et al.*(1992) (4). Briefly, the plasma sample was deproteinized with acetonitrile. The 200 µl of supernatant was transferred to 800 µl of mobile phase. The 20 µl of the mixture was injected onto HPLC system. The mobile phase consisted of methanol, phosphate buffer adjusted to pH 3 with 85% $H_3PO_4$ and tetrahydrofuran (21.2: 78: 0.8 v/v/v). The flow rate was 1.2 $ml.min^{-1}$. The column effluent was monitored at 50 °C by fluorescence detection at $\lambda_{ex}$277 and $\lambda_{em}$440 nm. The standard curve of ciprofloxacin was done on concentrations ranging from 31.25 to 8,000 $ng.ml^{-1}$. The lower limit of quantification of ciprofloxacin was 31.25 $ng.ml^{-1}$.

***Pharmacokinetic and statistical analysis***

All pharmacokinetic parameters were analyzed by non-compartment model with the use of WinNonlin Professional Software Version 1.1. Results were expressed as mean ± SD and statistical comparisons were made using Paired *t-test.* The significance level was set at *p*-value of less than 0.05.

**Results**

The mean plasma ciprofloxacin concentration time data for phase 1 and phase 2 in healthy normal volunteers were shown in Fig. 1. The mean pharmacokinetic parameters of ciprofloxacin for phase 1 and phase 2 were shown in table 1. The results in the present study showed that there were no significant differences in each ciprofloxacin pharmacokinetic parameter when compared between phase 1 and 2.

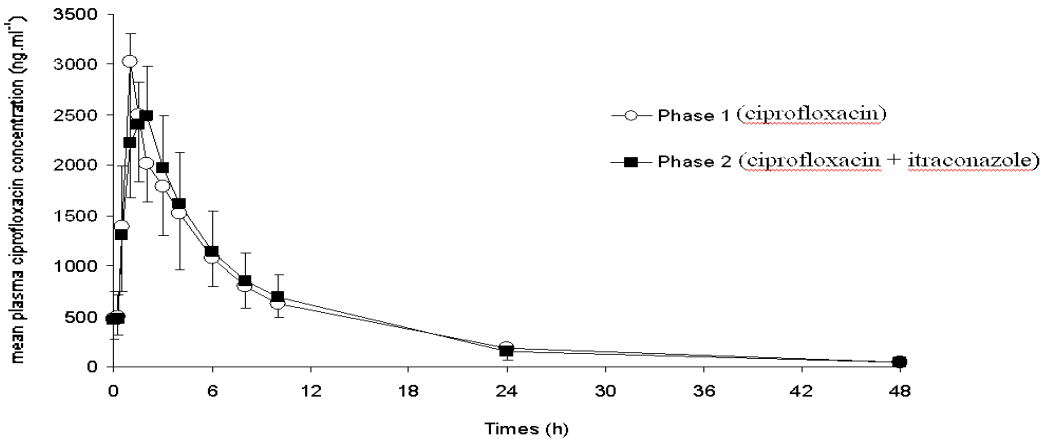


**Fig. 1** The mean plasma concentration-time curves of ciprofloxacin in six healthy male volunteers after a multiple oral dose of 500 mg ciprofloxacin alone (Phase 1), and combination with 200 mg itraconazole (Phase 2) twice daily for 7 days.

**Table 1** Pharmacokinetic parameters of ciprofloxacin in subjects after receiving a multiple oral dose of 500 mg ciprofloxacin alone (Phase 1), and combination with 200 mg itraconazole (Phase 2) twice daily for 7 days. Data are shown as mean ± SD and 95% confidence interval

| Parameter (units) | Phase 1 | Phase 2 | *P*-value |
|---|---|---|---|
| $C_{max}$ (ng.ml$^{-1}$) | 3,330.74 ± 883.95 | 2,997.40 ± 582.52 | 0.086 |
| $AUC_{0-48}$ (ng.h.ml$^{-1}$) | 21,908.08 ± 3,715.54 | 22,257.50 ± 5,033.84 | 0.875 |
| $AUC_{0-\infty}$ (ng.h.ml$^{-1}$) | 22,490.41 ± 4,010.32 | 22,912.01 ± 5,091.33 | 0.856 |
| $t_{1/2}$ (h) | 8.66 ± 2.10 | 9.02 ± 2.02 | 0.252 |
| *Cl* (L.h$^{-1}$) | 0.022 ± 0.004 | 0.023 ± 0.005 | 0.541 |

## Discussion

The pharmacokinetic drug interactions between agents used as parts of multidrug therapy are importance and may influence drug efficacy and safety. Ciprofloxacin is mainly eliminated via the kidney both glomerular filtration and tubular secretion, and trans-intestinal elimination and biliary clearance around at one-third of total ciprofloxacin clearance (1).

Itraconazole is known to be potent inhibitor of CYP3A4 and P-gp (2). Co-administration of drugs with CYP3A4 and P-gp substrates can result an increased toxicity. Measured pharmacokinetic parameters of ciprofloxacin in our study were $C_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$ and *Cl*. The results in this investigation were found that there were no significant differences of these parameters when compared between phase 1 and phase 2. Since there were not reported the metabolism pathway of ciprofloxacin via cytochrome P-450, therefore it could be implied that ciprofloxacin is not a substrate of CYP3A4. In addition, there was demonstrated that the secretion of cholic acid across the apical membrane was not inhibited by ciprofloxacin in Caco-2 and T84 monolayers, suggesting the ciprofloxacin is not a substrate of MDR1 and MRP2 in humans (5). On the contrary, some studies have reported ciprofloxacin was secreted via P-gp and other pathway. For example, Abou-Auda *et al.* (2008) found that there was a reduction of ciprofloxacin urinary excretion in mice, owing to inhibition of its P-gp at renal tubular cells by ketoconazole and itraconazole (3). Dautrey *et al.* (1999) reported ciprofloxacin intestinal elimination in rats seems to be mediated by organic anion and/or cation transporters (6). The differences of ciprofloxacin pharmacokinetics in humans, rats and mice may be explained by their different species.

In conclusion, this study indicated that itraconazole co-administration with ciprofloxacin did not alter the ciprofloxacin pharmacokinetic parameters in healthy volunteers. Further studies are needed to clarify the effect of ciprofloxacin on the pharmacokinetics of itraconazole in healthy volunteers.

## Acknowledgements

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## References

1. Davis R. Ciprofloxacin: An update Review of its Pharmacology, Therapeutic Efficacy and Tolerability. Drugs 1996; 51: 1019-74.
2. Venkatakrishnan K, υon Moltke LL, Greenblatt DJ. Effects of the Antifungal Agents on Oxidative Drug Metabolism: Clinical Relevance. Clin Pharmacokinet 2000; 38: 111-80.

3. Abou-Auda HS, Mustafa AA, Al-Humayyd MS. Pharmackinetic Interaction of Ketoconazole and Itraconazole with Ciprofloxacin. Biopharm Drug Dispos 2008; 29: 29-35.
4. Jim LK, el-Sayed N, al-Khamis KI. A simple high-performance liquid chromatographic assay for ciprofloxacin in human serum. J Clin Pharm Ther 1992; 17: 111-5.
5. Lowes S, and Simons NL. Multiple pathways for fluoroquinolone secretion by human intestinal epithelial (Caco-2) cells. British Journal of Pharmacology 2002; 135: 1263-75.
6. Dautrey S, Felice K, Petiet A, Lacour B, Carbon C, Farinotti R. Active intestinal elimination of ciprofloxacin in rats: modulation by different substrates. British Journal of Pharmacology 1999; 127: 1728-34.