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Pharmacokinetic Interaction of Ketoconazole and Itraconazole with Ciprofloxacin

Hisham S. Abou-Auda[a,*], Ali A. Mustafa[b] and Mohammad S. Al-Humayyd[b]
[a] *Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451*
[b] *Department of Pharmacology, College of Pharmacy, King Saud University*

ABSTRACT: The effect of the concomitant administration of the antifungal drugs ketoconazole (KTC) and itraconazole (ITC) on the pharmacokinetics of ciprofloxacin (CIP) following short- and long-term administration in mice was investigated. Animals received either a dose of CIP (20 mg/kg, i.p.), CIP (20 mg/kg, i.p.) together with KTC (50 mg/kg, p.o.) or CIP (20 mg/kg, i.p.) and ITC (30 mg/kg, p.o.). The same treatments were repeated for 7 days. Blood samples were collected up to 4 h following drug administration and two urine samples were collected at 2 h and 4 h after drug administration. CIP plasma concentrations were significantly higher in KTC- and ITC-treated groups compared with the corresponding control groups. The concomitant administration of KTC or ITC with CIP also significantly ($p < 0.05$) increased C_{max}, $t_{1/2}$, *MRT* and $AUC_{0-\infty}$ with no change in T_{max}. CIP clearance was significantly reduced by both agents. KTC and ITC reduced CIP urinary excretion. This study suggests that an important pharmacokinetic interaction between CIP and KTC or ITC is likely to occur when either of the two antifungal drugs is administered concomitantly with CIP. The results may suggest possible reductions in total clearance of CIP, owing to inhibition of its renal tubular excretion by KTC and ITC. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: ciprofloxacin; ketoconazole; itraconazole; interaction; pharmacokinetics; mice

Introduction

Ciprofloxacin (CIP), a synthetic fluorinated 4-quinolone has a broad spectrum antimicrobial activity. CIP is effective in the treatment of a wide variety of infections, particularly those caused by Gram-negative pathogens including complicated urinary tract infections [1]. Also, it has been found to be effective in the treatment of bronchopulmonary diseases caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis [2]. CIP is mainly excreted unchanged in the urine [3]. However, dose adjustments were found to be necessary in patients with liver failure because of the significant non-renal clearance of CIP [4]. Itraconazole (ITC), a widely used antimycotic agent, is a very potent inhibitor of cytochrome P-450 and it increases the *AUC* values of certain orally administered substrates of this enzyme such as midazolam [5] and triazolam [6]. Ketoconazole (KTC), an oral antifungal agent, has been shown to be a potent inhibitor of the metabolism of a variety of drugs including cyclosporine, phenytoin and warfarin [7]. CIP is metabolized in rodents mainly by the liver microsomal enzymes and mostly by CYP 1A2 in humans [8]. In animals, it has been shown to be metabolized mainly by this isozyme of CYP 1A2 [9]. KTC and ITC, on the other hand, are mainly metabolized by CYP 3A4.

To our knowledge, studies dealing with the concomitant administration of CIP and these two

*Correspondence to: Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451. E-mail: hisham@ksu.edu.sa

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drugs are lacking. An extensive literature search using MEDLINE (English-language literature published 1985–2007, using key words interaction, ciprofloxacin, itraconazole and ketoconazole) yielded no references on the subject. There seem to be no studies on the possible interaction between ITC or KTC and CIP. Given the potential for interaction between these drugs, which may be used concomitantly in some patients, this study was conducted in order to investigate effects of ITC and KTC, if any, on the pharmacokinetics of injected CIP in mice.

Materials and Methods

Materials

CIP was obtained from Bayer (Leverkusen, Germany). KTC, ITC, heparin, phenobarbital, Tris-HCl buffer and diethyl ether were purchased from Sigma Chemical Co. (St Louis, MO, USA). Acetonitrile (HPLC grade) was obtained from Merck (Darmstadt, Germany).

Methods

Male SWR mice weighing 30–35 g were obtained from the Animal Care Center, College of Medicine, King Saud University. The animals were housed under standard laboratory conditions with free access to food and water *ad libitum*. Mice were randomly divided into six treatment groups comprising eight mice each.

Acute experiments

Animals in group I served as the control and received a dose of CIP (20 mg/kg, i.p.). The animals in group II were injected with CIP (20 mg/kg, i.p.) together with KTC (50 mg/kg) orally. The third group of animals (group III) had been injected with CIP (20 mg/kg, i.p.) and received ITC (30 mg/kg, p.o.).

Chronic experiments

Animals in group IV were injected with CIP (20 mg/kg, i.p.) for 7 days. The animals in group V were injected with CIP (20 mg/kg, i.p.) daily for 7 days together with daily oral doses of KTC (50 mg/kg, p.o.) for 7 days. The animals in group VI were injected with CIP (20 mg/kg, i.p.) daily for 7 days together with daily oral doses of ITC (30 mg/kg, p.o.) for 7 days.

Determination of plasma ciprofloxacin concentrations

In both acute and chronic treatments, 10 mice were killed at each of the following time points: 0.08, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0 and 4 h, and blood samples (0.5 ml) were collected into heparinized eppendorf tubes. The plasma concentrations of CIP were determined by modification of the method described by Bergan *et al*., 1987 [10]. Briefly, blood samples were centrifuged at 2100 × *g* for 10 min in a Gallenkamp angle head centrifuge. An aliquot (100 µl) of the plasma was precipitated with 7% perchloric acid. This was thoroughly shaken and then centrifuged at 5400 × *g* for 5 min on a Select-a-fuge 24 Biodynamics centrifuge. Twenty microliters of the perchloric acid supernatant was injected into an HPLC system consisting of a Waters (Milford, Massachusetts) M-5 10 pump and a Waters reverse phase Novapak C_{18} (3.9 mm × 150 mm) column. The column was eluted at a rate of 1.2 ml/min with a pre-filtered and degassed mobile phase consisting of 4% acetonitrile in 0.25 M phosphoric acid adjusted to pH 3 with tetrabutyl ammonium hydroxide.

CIP in plasma samples was detected by a Schimadzu RF 551 fluorescence detector. Excitation and emission wavelengths were 277 and 445 nm, respectively. The CIP retention time was 4 min. This procedure provided a detection limit of 0.01 µg/ml and 0.05 µg/ml in plasma and urine, respectively.

Determination of ciprofloxacin in urine

Two hundred microliters of urine specimens was adjusted to pH 7.5 with 400 µl phosphate buffer and extracted with 1 ml of trichlormethane for 15 min and then centrifuged for 5 min at 1300 × *g*. Five hundred microliters from the clear supernatant was taken and evaporated to dryness. This dried residue was redissolved in 100 µl mobile phase and used for CIP determination. Twenty microliters of sample was injected into the HPLC system and CIP was detected in the same way as described above under the plasma assay method.

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Pharmacokinetic analysis

CIP pharmacokinetic parameters were determined by compartmental analysis using least-square nonlinear regression analysis preformed with WinNonlin software (version 4.1, Pharsight Corporation, Palo Alto, CA, USA). The method of statistical moments [11] was also used since it has the advantage of being independent of a specific pharmacokinetic model. It gives valuable information about the overall properties of the time course of disposition process in the body. The terminal half-lives of the drug were determined by linear least squares regression analysis applied to the log-linear portions of the plasma concentration-time curves of CIP. The area under the curves from time zero to time t (AUC_{0-t}) were determined by the linear trapezoidal method with extrapolation to infinity by dividing the last measurable plasma concentration by the absolute value of the terminal slope to produce $AUC_{0-\infty}$. The areas under the curve of the first moment of CIP plasma concentration-time curve from time zero to the last measurable plasma concentration ($AUMC_{0-t}$) and from time zero to infinity ($AUMC_{0-\infty}$) were calculated by the area under the curve of a plot of the product of concentration and time vs time. The mean residence time (MRT) was calculated from the reciprocal of the absolute value of the terminal slope. The MRT was calculated by the following equation:

$$\mathbf{MRT} = \frac{\mathbf{AUMC}_{0-\infty}}{\mathbf{AUC}_{0-\infty}} \quad (1)$$

The apparent volume of distribution at steady-state (V_{ss}) was determined using the following Equation [12]:

$$\mathbf{V_{ss}} = \frac{\mathbf{D} \cdot \mathbf{AUMC}_{0-\infty}}{(\mathbf{AUC}_{0-\infty})^2} \quad (2)$$

where F is the bioavailability and D is the dose. The total body clearance of the drug was determined from the quotient of the dose and $AUC_{0-\infty}$ as follows:

$$\mathbf{CL} = \frac{\mathbf{D}}{\mathbf{AUC}_{0-\infty}} \quad (3)$$

Statistical analysis

Comparisons of pharmacokinetic parameters between ITC- or KTC-treated and control groups were carried out by the Student's t-test for independent samples assuming the homoscedastic or heteroscedastic model. The analysis of $AUC_{0-\infty}$ and C_{max} was also performed on log-transformed data. The analysis of T_{max} was carried out on ranked values using Wilcoxon rank sum test/Mann-Whitney U-test since it has been reported that the distribution of this pharmacokinetic parameter does not follow a Gaussian distribution. The remaining parameters were analysed in their original units. The CIP pharmacokinetics with or without concomitant administration of KTC or ITC were summarized and compared descriptively. The homogeneity of variances of groups was checked by Bartlett's test. The statistical level of significance was taken as 0.05 and the results were expressed as mean $\pm$ SD with the 95% confidence interval and the actual p-value. The statistical analysis was performed using the SAS statistics software package (SAS Institute, Cary, NC, USA).

Results

Acute experiments

The fluoroquinolone was not detected after 2 h in the CIP-treated group, whereas it was detectable up to 4 h in the group which had received KTC or ITC together with CIP. All CIP plasma concentrations were significantly higher in group II (CIP, 20 mg/kg, i.v., together with KTC, 50 mg/kg, p.o.) than those observed with CIP alone except at 0.5 h. The other antifungal drug ITC produced an upward shift in CIP plasma concentration-time profiles (group III). The mean plasma concentration-time profiles in mice following the administration of CIP alone (20 mg/kg, i.p.) or when given together with either KTC (50 mg/kg, p.o.) or ITC (30 mg/kg, p.o.) are depicted in Figure 1.

The pharmacokinetic data derived from the above results are summarized in Table 1. The concomitant administration of KTC significantly increased C_{max}, $t_{1/2}$, MRT and $AUC_{0-\infty}$ of CIP compared with those of CIP alone. The mean increase in C_{max} of CIP was 1.55 fold (95% CI: 1.35, 1.75; $p < 0.0001$) and 1.4 fold (95% CI: 1.24,

1.56; $p<0.0001$) with concomitant administration of KTC and ITC, respectively. Similarly, the $t_{1/2}$ and *MRT* were increased 2.58 fold (95% CI: 1.87, 3.29; $p<0.0001$) and 1.9 fold (95% CI: 1.73, 2.07; $p<0.0001$) by KTC and 2.16 fold (95% CI: 1.67, 2.65; $p<0.0001$) and 1.65 fold (95% CI: 1.52, 1.78; $p<0.0001$) by ITC, respectively. The $AUC_{0-\infty}$ of CIP was more than doubled after KTC and ITC (2.12 fold (95% CI: 1.93, 2.32; $p<0.0001$) and 2.07 fold (95% CI: 1.9, 2.25; $p<0.0001$), respectively). There were no statistically significant changes in T_{max} of CIP following the concomitant administration of any of the two antifungal drugs with CIP. Although there was a slight increase in V_{ss} (6.8% and 19.6% after KTC and ITC, respectively), these differences did not reach statistical significance ($p > 0.05$). However, the concomitant administration of either KTC or ITC with CIP produced a significant reduction in the clearance (*CL*) of CIP (52% ($p<0.0001$) and 51% ($p<0.0001$) reductions, respectively).

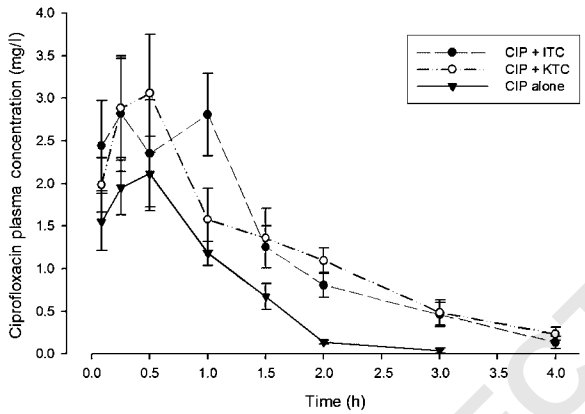

Figure 1. Mean plasma concentration-time profiles of mice following the administration of CIP alone (20 mg/kg, i.p.) or when given together with KTC (50 mg/kg, p.o.) or ITC (30 mg/kg, p.o.)

Table 1. Plasma pharmacokinetic parameters (mean ± SD) following the administration of ciprofloxacin (CIP) (20 mg/kg, i.p.) alone or together with acute administration of itraconazole (ITC) (30 mg/kg, i.p.) or ketokonazole (KTC) (50 mg/kg, i.p.) in mice ($n = 10$)

Parameter	CIP	CIP+ITC	CIP+KTC
C_{max} (μg/ml)	2.20 ± 0.41	3.01 ± 0.42[a]	3.31 ± 0.41[a]
T_{max} (h)	0.375[b]	0.375[b]	0.375[b]
$t_{1/2}$ (h)	0.39 ± 0.10	0.79 ± 0.18[a]	0.92 ± 0.23[a]
MRT (h)	0.80 ± 0.05	1.32 ± 0.16[a]	1.51 ± 0.18[a]
$AUC_{0-\infty}$ (μg h/ml)	2.48 ± 0.09	4.94 ± 0.24[a]	4.90 ± 0.17[a]
V_{ss} (l)	4.52 ± 1.14	4.56 ± 1.32	5.04 ± 0.91
CL (l/h)	8.17 ± 0.91	4.00 ± 0.63[a]	3.89 ± 0.50[a]

[a]Statistically significant compared with the values obtained for ciprofloxacin alone ($p<0.05$, independent *t*-test).
[b]Median.

Chronic experiments

Plasma determinations. Figure 2 shows the mean plasma concentration-time profiles following the administration of CIP alone (20 mg/kg, i.p.) or when it was given together with chronic treatment of KTC (50 mg/kg, p.o.) or ITC (30 mg/kg, p.o.) daily for 7 days. Similar to the findings of the acute studies, the examination of mean plasma CIP concentration-time profiles, with or without either of the two antifungal drugs, reveals that the concomitant administration of KTC or ITC caused a significant increase in the levels of CIP. The obtained pharmacokinetic parameters are summarized in Table 2. The mean C_{max} concentrations with concomitant KTC and ITC were 2.88 ± 0.21 μg/ml and 2.62 ± 0.33 μg/ml, respectively, compared with 2.20 ± 0.41 μg/ml for CIP alone. However, there were no statistically significant changes in T_{max} of CIP following the concomitant administration of any of the two antifungal drugs with CIP. The $t_{1/2}$ values of CIP were significantly longer in KTC

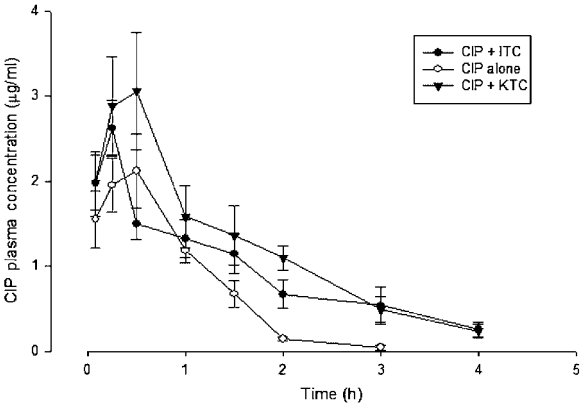

Figure 2. Mean plasma concentration-time profiles following the administration of CIP alone (20 mg/kg, i.p.) or when it was given together with chronic treatment of KTC (50 mg/kg, p.o.) or ITC (30 mg/kg, p.o.) daily for 7 days

and ITC-treated groups. The mean increase in $t_{1/2}$ following KTC and ITC was 3.85 fold (95% CI: 2.94, 4.76; $p<0.0001$) and 4.04 fold (95% CI: 2.58, 5.49; $p=0.00025$), respectively. KTC increased the *MRT* 2.39 fold (95% CI: 2.09, 2.69; $p<0.0001$) and $AUC_{0-\infty}$ 1.75 fold (95% CI: 1.53, 1.96; $p<0.0001$). On the other hand, the *MRT* and $AUC_{0-\infty}$ of CIP in the ITC-treated group increased by 2.51 fold (95% CI: 1.75, 3.27; $p=0.00064$) and 1.66 fold (95% CI: 1.32, 1.99; $p<0.00232$), respectively, compared with CIP alone. In addition, the chronic administration of KTC and ITC produced a significant decrease in clearance (CL) of CIP. The CL after concomitant administration of KTC and ITC was reduced by 40.4% ($p<0.0001$) and 35% by ITC ($p<0.0001$), respectively. Contrary to the effect of the two antifungal drugs on the volume of distribution at steady state (V_{ss}) after concomitant acute administration with CIP, V_{ss} was significantly increased 2.19 fold (95% CI: 1.76, 2.62; $p<0.0001$) by KTC and 2.31 fold (95% CI: 1.82, 2.80; $p<0.0001$) by ITC.

Determinations of ciprofloxacin in urine. The effects of the antifungal drugs, KTC and ITC on the renal elimination of CIP are shown on Table 3. The concentrations of CIP in urine of mice at 2 and 4 h following drug administration were significantly lower ($p<0.05$) in the animals that had received CIP together with either KTC or ITC than those obtained in animals that were given CIP alone (Table 3).

Table 2. Plasma pharmacokinetic parameters (mean ± SD) following the administration of ciprofloxacin (CIP) (20 mg/kg, i.p.) alone or together with chronic administration of itraconazole (ITC) (30 mg/kg, i.p.) or ketoconazole (KTC) (50 mg/kg, i.p.) in mice ($n=10$)

Parameter	CIP	CIP+ITC	CIP+KTC
C_{max} (μg/ml)	2.20 ± 0.41	2.88 ± 0.21[a]	2.62 ± 0.33[a]
T_{max} (h)	0.375[b]	0.25[b]	0.25[b]
$T_{1/2}$ (h)	0.39 ± 0.10	1.44 ± 0.73[a]	1.38 ± 0.29[a]
MRT (h)	0.80 ± 0.05	1.97 ± 0.90[a]	1.90 ± 0.36[a]
$AUC_{0-\infty}$ (μg h/ml)	2.48 ± 0.09	4.11 ± 1.44[a]	4.29 ± 0.78[a]
V_{ss} (l)	4.52 ± 1.14	9.79 ± 2.36	9.29 ± 1.22
CL (l/h)	8.17 ± 0.91	5.33 ± 1.56[a]	4.82 ± 0.94[a]

[a]Statistically significant compared with the values obtained for ciprofloxacin alone ($p<0.001$, independent *t*-test).
[b]Median.

Discussion

This study was conducted to evaluate the effect of acute and chronic administration of two antifungal drugs, KTC and ITC, on the pharmacokinetics of CIP. The results of the present study showed that the concurrent administration of the antifungal agents, KTC or ITC significantly increased the $AUC_{0-\infty}$, C_{max}, $t_{1/2}$ and *MRT* and decreased the *CL* of CIP in mice.

CIP pharmacokinetics is characterized by rapid oral absorption and 30–45% of the dose given is excreted unchanged in urine [3]. There is also significant non-renal clearance of the drug [4]. It is expected, therefore, that drugs that inhibit liver microsomal enzymes may affect the pharmacokinetics of CIP.

KTC is known to be a potent inhibitor of the metabolism of a variety of drugs such as cyclosporine, phenytoin and warfarin [13]. It is therefore, possible that the increases in $AUC_{0-\infty}$, C_{max}, $t_{1/2}$ and *MRT*, seen in this study, when CIP was given together with KTC may be due to the inhibition of cytochromes by KTC. Similarly, the fluoroquinolone antibiotics cause both class-specific and agent-specific interactions. In addition, it is well known that CIP is biotransformed by the CYP3A4 enzyme system and also inhibits CYP1A2 with varying inhibitory ability. This inhibition may lead to increases in the *AUC* values of drugs which are given concurrently with it. Based on this, an interaction at the liver microsomal level is not expected to explain the interaction of these agents with CIP. But since the results of the present study have shown that the $AUC_{0-\infty}$ of CIP was almost doubled

Table 3. Ciprofloxacin (CIP) concentration (mean ± SD) in urine following the administration of ciprofloxacin (20 mg/kg, i.p.) alone or together with chronic administration of itraconazole (ITC) (30 mg/kg, i.p.) or ketoconazole (KTC) (50 mg/kg, i.p.) in mice ($n=5$)

Time (h)	CIP urine conc. (μg/ml)		
	CIP	CIP+KTC	CIP+ITC
2	7.14 ± 1.63	3.88 ± 0.96[a]	2.77 ± 0.63[a]
4	2.40 ± 0.64	0.57 ± 0.29[a]	0.58 ± 0.24[a]

[a]Statistically significant compared with the values obtained for ciprofloxacin alone ($p<0.001$, independent *t*-test).

following the concomitant administration of KTC or ITC, it is perhaps tempting to speculate that CIP may be metabolized, at least in part, by CYP1A2 in mice. These results are similar to those of Olkkola *et al*. [5] and Varhe *et al*. [6] who have shown that ITC increases the *AUC* values of orally administered midazolam and triazolam, respectively.

In addition, it has been shown that ITC and KTC are very effective inhibitors of the active tubular flux of many drugs [14–16]. CIP is largely eliminated by renal excretion. Since the concurrent administration of CIP and KTC or ITC significantly decreased the renally eliminated fraction of the former at 2 and 4 h, it is possible that this may provide, at least in part, an explanation for the increased plasma levels of CIP observed in this study. CIP is cleared by the kidneys, and the mechanism of renal clearance is by both glomerular filtration and tubular secretion. The renal clearance of CIP in humans is approximately 300 ml/min which exceeds the normal glomerular filtration rate (GFR) of 120 ml/min. The renal clearance of CIP, in the present study, was estimated to be approximately 178 ml/min. Therefore, the active tubular secretion would seem to play a significant role in the elimination of CIP. Also, ITC has been shown to inhibit P-glycoprotein (P-gp)-mediated secretion in renal tubular cells in guinea pig model [17]. Therefore, it is likely that the interaction between these two azole antifungal agents and CIP is related to the inhibition of the ATP-dependent plasma membrane transporter P-gp. It is postulated that the observed reduction in the total body clearance of CIP could have arisen, at least in part, from the inhibition of CIP renal tubular clearance by KTC and ITC or their metabolites. This effect may serve to explain the fact that some fluoroquinolone antimicrobials including CIP may cause potentially serious forms of nephrotoxicity occurring as allergic interstitial nephritis, granulomatous interstitial nephritis, necrotising vasculitis, allergic tubular nephritis or a tubular necrosis [18]. In addition, a serious adverse effect that may be seen in patients concomitantly prescribed CIP with other drugs that inhibit its metabolism is convulsions. Therefore, if the results of animal experiments may be extrapolated to humans, it is not advisable to administer such antifungal agents together with CIP, unless dose adjustments are made.

In conclusion, the present study demonstrated that both KTC and ITC had a significant effect on the pharmacokinetics of CIP, suggesting that these two azole antifungal drugs should not be administered concomitantly with CIP. Further studies in human volunteers are warranted to explore the exact mechanism of this interaction. If serious adverse effects are to be averted, it is imperative to monitor the plasma levels of CIP when given together with KTC or ITC.

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