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Effect of ketoconazole on the pharmacokinetics of a single oral dose of praziquantel in healthy volunteers

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ABSTRACT

Background: Praziquantel is extensively metabolized by the hepatic cytochrome P450 enzymes. The CYP3A isoforms are likely to be major enzymes responsible for praziquantel metabolism. Ketoconazole, a potent enzyme inhibitor of CYP3A4, is known to markedly increase plasma concentrations and effects of a number coadministered drugs. The aim of the present investigation was to study the possible pharmacokinetic interaction between ketoconazole and praziquantel.

Medthods: An open, randomised two-phase crossover design was used in this study. Ten healthy Thai male volunteers ingested single doses of 20 mg/kg praziquantel alone (phase 1) or after pretreatment with 400 mg of oral ketoconazole once daily for 5 days (phase 2). Blood samples were collected at specific time points for 24-hour interval. Plasma concentrations of praziquantel were determined by the HPLC method.

Results: Ketoconazole significantly increased the mean C_{max}, AUC(0-12) and AUC(0-∞) values of praziquantel by 102% (from 183.38 ± 138.8 to 371.31 ± 141.1 ng/ml; $P < 0.01$), 97% (from 803.78 ± 905.8 to 1580.30 ± 761.5 ng/ml; $P < 0.01$) and 85% (from 962.70 ± 986.4 to 1786.30 ± 998.0 ng/ml; $P < 0.05$), respectively, whereas the mean Cl/f was significantly decreased by 58% (from 43.08 ± 30.96 to 17.90 ± 16.18 ng/ml; $P < 0.01$) after pretreatment with ketoconazole. The mean t_{max} and $t_{1/2}$ values were not significantly affected by ketoconazole.

Conclusions: Ketoconazole markedly increased the extent of praziquantel available in the circulation of single oral doses of praziquantel. Because praziquantel and ketoconazole are widely used in the treatment of liver flukes (*Opisthorchis viverrini*) and fungal infections, respectively, in Thailand and in some other countries in southeast Asia, the possibility of one drug influencing the pharmacokinetics of the other must be recognized. Therefore, simultaneous use of ketoconazole and praziquantel should be carefully considered in medical practice to avoid side effects or toxicities of praziquantel. If necessary, the doses of praziquantel must be reduced.

INTRODUCTION

Praziquantel, a synthetic pyrazinoquinoline derivative with a broadspectrum of anthelminthic activity, is effective in the treatment of schistosome infections of all species and most other trematodes (flukes) and cestodes (tapeworms), including cysticercosis, but is not effective against *Fasciola hepatica* or in hydatid disease.[1] In the treatment of schistosomiasis with praziquantel, a single oral dose of 40 mg/kg or multiple oral doses of 20 mg/kg of praziquantel (3 doses) at intervals of 4 to 6 hours produce good results in all species of schistosome infections in humans, whereas 3 doses of 25 mg/kg praziquantel taken 4 to 8 hours apart on 1 day result in high cure rates for infections with either the liver flukes, *Clonorchis sinensis* and *Opisthorchis viverrini* or the intestinal flukes *Fasciolopsis buski*, *Heterophyes heterophyes*, and *Metaonimus yokogawi*.[2] Liver fluke infection is a public health problem in the tropical region. In Thailand, human liver fluke *O. viverrini* infection is recognized as having a high prevalence.[3] The data obtained from the liver fluke control program in Thailand for year 1996 indicated the highest prevalence (32.6%) in the northern region, whereas the central region has a prevalence rate of 16.7% and the lowest prevalence (15.3%) is found in the northeastern region.[4] A single oral dose of 40 mg/kg of praziquantel for mass treatment or multiple oral doses of 25 mg/kg (3 doses on 1 day) are given to persons in an endemic area. For pharmacokinetic data in man, praziquantel is rapidly absorbed with a bioavailability of about 80% after oral admimistration and peak plasma levels of unchanged drug of 0.2 to 2.0 μg/ml are achieved in the systemic circulation 1 to 3 hours after administration of therapeutic doses.[5] It is rapidly distributed in body tissue due to its high lipid solubility. Approximately 80 to 85% of the drug is bound to plasma proteins.[6] Praziquantel crosses the blood-brain barrier, reaching CSF concentrations approximately 25% that of plasma levels.[7] In addition, small concentrations of drug (< 10% to 20% of plasma levels) have been detected in bile, feces and breast milk.[5] Praziquantel is extensively

metabolized in the liver by the cytochrome P450 (CYP) enzymes into a series of mono- and dihydroxylated products lacking anthelmintic activity.[1,2] The *trans*-4-hydroxypraziquantel is the main metabolite in humans.[8] The hydroxylated metabolites are also excreted in the urine as conjugates with glucuronic acid and sulfuric acid.[9] The elimination half-life from the serum after a single dose is 1 to 1.5 hours for praziquantel, and for praziquantel metabolites, 4 to 5 hours.[10] About 70% of an oral dose of praziquantel are recovered as metablites in the urine within 24 hours; most of the remainder is metabolized in the liver and eliminated in bile.[2] Since praziquantel undergoes extensive first pass hepatic metabolism, therefore, it is susceptible to drug interactions resulting from induction or inhibition of these enzymes. For example, the bioavailabilty of praziquantel is reduced by inducers of hepatic cytochrome P450 enzymes such as carbamazepine and phenobarbital,[11] whereas cimetidine, a CYP inhibitor, has been shown to increase praziquantel levels in a patient with neurocysticercosis being treated with anticonvulsant agents.[12]

Ketoconazole, a broad spectrum azole antimycotics, is a lipophilic with poor water solubility except at low pH (pH < 3). It is well absorbed after oral administration although there is large inter- and intraindividual variation in peak serum concentration after the same dose and absorption increased in the presence of a meal. Peak serum concentrations of ketoconazole occur within 3 hours of administration and are proportional to dose.[13] The drug is rapidly and widely distributed throughout the body in animals and humans. However, the volume of distribution of ketoconazole is only 0.36 l/kg.[14] Ketoconazole is extensively bound in human whole blood (99%), with 84% to plasma proteins, largely albumin and 15% to erythrocytes.[15] Ketoconazole is extensively metabolized in the liver, the major route of elimination being as metabolites in bile, therefore there may be enterohepatic circulation because the double peaks plasma concentrations, seen at higher doses of ketoconazole.[16] The elimination half-life appeared to be dose dependent, increasing with increasing dose and after

repeated dosing.[17] With an oral dose of 200 mg the range of mean ketoconazole half-life 1.5 to 4 hours. At higher dose (400 and 800 mg) the mean half-life were 3.7 hours (range from 1.3 to 11.6 hours).[18] Since ketoconazole is a potent inhibitor of CYP3A4 resulting the increase in plasma concentrations of various drugs coadministered such as terfenadine, triazolam, felodipine, quinidine, nisodipine, atorvastatin and quinine [19-25], which may be life-threatening. As previously mentioned, praziquantel is extensively metabolized by the hepatic cytochrome P450 enzymes, and CYP3A isoforms are considered to be a major role in metabolism of praziquantel [26], whereas ketoconazole is a potent inhibitor of CYP3A4, there is a possibility of a pharmacokinetic interaction between ketoconazole and praziquantel. To our knowledge, there are no reports on the possible interaction between ketoconazole and praziquantel in humans. We have therefore studied the effect of ketoconazole on the pharmacokinetics of praziquantel in normal healthy volunteers.

METHODS

Subjects

Ten healthy Thai male volunteers (age, 22 - 39 years; body weight; 55 - 70 kg) participated in this study (Table 1 and 2). Each subject was informed about the objectives and details of the study and gave written informed consent. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Science, Prince of Songkla University, Hat Yai, Thailand. A medical history was obtained and physical examination and essential laboratory tests (complete blood count, blood urea nitrogen, creatinine concentration, and liver function tests) were carried out in all the volunteers to evaluate the health status before they were enrolled in this study. Neither of subjects had a history of chronic smoking cigarettes, alcoholic and caffeine consumption habbits. The subjects were not allowed to take any

medications, to smoke cigarettes or to ingest alcoholic and cafeine-containing beverages for 2 weeks before starting the study and during the study period.

Study protocol

An open, convenient sampling with a simple randomized, 2-phase crossover study design was used. Each phase in this study was separated by a 2-week washout period. Single oral doses of 20 mg/kg of praziquantel (Praquantel, 600 mg/tablet, Atlantic Laboratories Corp., Ltd., Bangkok, Thailand) were given during the 2-phase study. A 5-day pretreatment period with 400 mg of oral ketoconazole (Ketazol, 200 mg/tablet, Shiwa Chemical Co., Ltd., Bangkok, Thailand) was used to evaluate the interaction between ketoconazole and praziquantel.

In phase 1, Praziquantel was given alone (control). Each subject ingested a single dose of 20 mg/kg of praziquantel with 200 mL water.

In phase 2, Praziquantel was given after ketoconazole pretreatment. Each subject received 400 mg of oral ketoconazole once daily for pretreatment at 7 am after breakfast for 5 days. On the study Day 6, a single oral dose of 20 mg/kg ketoconazole was given with 200 mL water to each subject.

On the test day of each phase, all of the subjects fasted overnight before praziquantel administration and received regular meals 3 hours after praziquantel ingestion. The subjects were not permitted to smoke or to drink coffee, tea, alcohol or cola on the test days.

Blood sampling

A forearm vein was cannulated with a sterile catheter for collection of blood samples and was kept patent with the use of 1 mL heparinized saline soluion (100 U/mL) after collection of each blood sample. Before collection of each blood sample at a specific time, 1 mL venous blood was drawn and discarded. Blood samples (5 ml) were drawn and collected in heparinized tube up to 24 hours before praziquantel intake and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8,

10, 12, and 24 hours after praziquantel dosing. Blood samples were centrifuged at 2500 rpm for 15 minutes, and plasma was separated within 30 minutes and kept at –70 °C until analyzed.

Determination of praziquantel concentrations in plasma samples

Plasma praziquantel concentrations were determined by the HPLC method with utraviolet detection, as described previously with a minor modification.[27] In brief, in a 1.5-mL stoppered microcentrifuge tube, 50 µL of diazepam internal standard solution (2700 ng/mL) and 50 µL of 0.4-mole/L zinc sulphate solution were added drop by drop to 400 µL of plasma and mixed for 30 seconds on a vortex mixer. Then 400 µL of acetonitrile was then added dropwisely and shaken thoroughly on a vortex mixer for 30 seconds. The final concentration of diazepam internal standard in the mixture was 150 ng/mL. After 15 minutes the mixture was centrifuged at 6000 rpm for 10 minutes. A 200 µL of supernatant was injected into the HPLC system by means of a reverse-phase Spherisorb octadecyl silane 2 column (5 µm, 250 x 4.6 mm internal diameter, Water Associates, Milford, Mass) with acetonitrile, methanol and water (34:10:56 v/v/v) as a mobile phase, with a flow rate of 1.5 mL/min and ultraviolet detection at 217 nm. The limit of detection of praziquantel in plasma was 12.25 ng/mL by considering a signal-to-noise ratio of 3:1. The intra- and inter-day assay coefficients of variation (CV) of praziquantel concentrations of 12.25 and 100 ng/mL in plasma were 7.5 and 10.26%, and 1.42 and 6.1%, respectively. The limit of quantitation for praziquantel was set at 100 ng/mL being the lowest concentration used in the construction of the standard curve. The standard calibration curve for praziquantel at concentration of 100 –1600 ng/ml was linear with the correlation coefficient (r) of 0.999. The equation of linear regression line was y = -4.53E-02 + 2.970E-03x with slope and intercept values of 0.00279 and 0.0453, respectively. This calibration curve was assumed to calculate the concentration of praziquantel which had lower concentration than 100 ng/ml since the linearity (r) and slopes of these calibration curves were not significantly different (12.25 - 1600 ng/ml,n = 5 vs 100 - 1600 ng/ml, n = 5 ; $P >$

0.05). The intra- and inter-day assay coefficients of variation of praziquantel in plasma were 0.7 to 2.4% and 3.3 to 6.1%, respectively, at the concentration range of 100 to 1600 ng/mL. The absolute recovery of praziquantel in human plasma was 96 – 103%.

Pharmacokinetic analysis

The pharmacokinetic parameters were analysed by noncompartment methods[28] using WinNonlin software version 1.1 (Scientific Consulting, Inc., Apex, NC). Maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were determined directly from the plasma concentration-time profiles. The terminal disposition half-lives ($t_{1/2}$) were calculated by linear regression analysis of the last data points after log transformation of the data. Elimination rate constants (λ_z) were calculated as ln 2/ $t_{1/2}$. The area under the plasma concentration-time curve values [AUC(0-12) and AUC(0-∞)] were calculated by the linear trapezoidal rule for rising phase and the log-linear trapezoidal rule for the descending phase, with extrapolation to infinity, when appropriate, by division of the last measured concentration by terminal slope. The lower detection limit of praziquantel was 12.25 ng/mL.

Statistical analysis

Results were presented as mean ± standard deviation (SD) in the text and tables, and as mean ± SEM in the figure for clarity. Statistical comparisons were performed with the use of the paired Student *t* test. $P < 0.05$ was considered to be statistically significant.

RESULTS

All of the volunteers completed the study. No adverse effects or significant symptoms and signs were observed or reported throughout the study period. The mean plasma concentration-time profiles of praziquantel in 10 healthy subjects receiving single oral doses of 20 mg/kg of praziquantel alone, and after pretreatment with 400 mg of oral ketoconazole once daily for 5 days are shown in Figure 1. The individual and mean values of C_{max}, AUC(0-12), AUC(0-∞),

t_{max}, $t_{1/2,}$ and Cl/f of praziquantel in 10 healthy subjects receiving single oral doses of 20 mg/kg of praziquantel alone, and after pretreatment with 400 mg of oral ketoconazole once daily for 5 days were summarized in Table 1 and 2, and Table 3, respectively. The mean C_{max}, AUC(0-12) and AUC(0-∞) values of praziquantel in 10 healthy subjects after ketoconazole pretreatment increased by 102% (from 183.38 ± 138.8 to 371.31 ± 141.1 ng/ml; $P < 0.01$), 97% (from 803.78 ± 905.8 to 1580.30 ± 761.5 ng/ml; $P < 0.01$) and 85% (from 962.70 ± 986.4 to 1786.30 ± 998.0 ng/ml; $P < 0.05$), respectively, whereas the Cl/f value was significantly decreased by 58% (from 43.08 ± 30.96 to 17.90 ± 16.18 ng/ml; $P < 0.01$). The mean t_{max} and $t_{1/2}$ values of praziquantel in subjects receiving praziquantel after ketoconazole pretreatment were not significantly different from the respective values after receiving praziquantel alone (Table 3).

DISCUSSION

In the present study, the mean C_{max}, AUC(0-12) and AUC(0-α), t_{max}, $t_{1/2}$ and Cl/f of praziquantel in subjects receiving a single oral dose of 20 mg/kg of praziquantel alone (Table I) could be comparable to previously published reports since the pharmacokinetics of praziquantel appear to be dose-dependent.[29-32] The wide interindividual variation in the pharmacokinetics of praziquantel has been observed in humans including of our study.[30-33] However, the overall variations in this study must be considered. This interindividual variation has been described by the wide variation in metabolism of praziquantel, a drug which undergoes an extensive first-pass metabolism.[32-33]

The difference of each pharmacokinetic parameter in each subject may be also explained by the differences in the interindividual variations with respect to age-, sex- and race-related changes[34]. The present results also demonstrated that after pretreatment with 400 mg ketoconazole orally once daily for 5 days, the mean C_{max}, AUC(0-12) and AUC(0-α) values

of praziquantel increased by 102% (2-fold; $P < 0.01$), 97% (1.97-fold; $P < 0.01$), and 85% (1.86-fold; $P < 0.05$), respectively, whereas the mean Cl/f value was significantly decreased by 58% (2.4-fold; $P < 0.01$) after pretreatment with ketoconazole. The mean t_{max} and $t_{1/2}$ values were not significantly affected by ketoconazole. These indicated a markedly significant interaction between ketoconazole and praziquantel (a single oral dose of 20 mg/kg of praziquantel after pretreatment with 400 mg of oral ketoconazole for 5 days) resulting a great increase in peak plasma praziquantel concentrations to the levels of the threshold plasma concentration of praziquantel (300 ng/mL) for therapeutic effect.[33] Ketoconazole and itraconazole, azole antimycotics with broad spectrum antifungal activity, are potent inhibitors of many CYP3A4 drug substrates.[35] Ketoconazole and itraconazole given orally once daily for 4 days as 400 mg and 200 mg doses, respectively in normal healthy volunteers are sufficient to inhibit CYP3A4.[21-22,36] One previous published report on the interaction of quinine with 100 mg ketoconazole pretreatment orally twice daily for 3 days in healthy volunteers revealed that the mean AUC and $t_{1/2}$ were increased by 45% ($P < 0.001$) and 16% ($P < 0.01$), respectively. When compared these parameters with our data, it was likely that the inhibition of CYP3A4 by ketoconazole was dependent on doses and time period of ketoconazole administration.[25] Additionally, praziquantel is rapidly absorbed from the gastrointestinal tract and the bioavailability is rather high (>80%),[37] thus the effect of inhibiting CYP3A4-mediated metabolism in the small intestine of a high bioavailability drug is not much concerned.[38] In fact, in the present study we used a local made praziquantel preparation (Praquantel) instead of an original product, therefore, the exact bioavailability was not known since the products with the same generic name have much different bioavailability. However, inhibition of the intestinal P-glycoprotein transporter by ketoconazole *in vivo* should be recognized.[39-40]

Our present results indicated that the mean C_{max} of praziquantel in 10 healthy subjects after administration of a single oral dose of 20 mg/kg alone, and after pretreatment with ketoconazole were approximately 183 ng/mL and 371 ng/mL, respectively. Our purposes in this study is to explore the pharmacokinetic interaction between ketoconazole and praziquantel and to observe the behavior of praziquantel pharmacokinetics in normal healthy subjects receiving praziquantel alone, and after pretreatment with ketoconazole with a minimal producing adverse effects. For these reasons, we used a single oral dose of 20 mg/kg of praziquantel as a test dose instead of 40 mg/kg dose as used in clinical practice, and expected that after pretreatment with ketoconazole the mean peak plasma concentrations of praziquantel would not be high enough to produce side effect or toxicity. There were evidences that oral praziquantel doses of 5, 10, 20 and 50 mg/kg produced respective serum concentrations of 0.15, 0.2, 0.8 and 4.22 ng/l, thus 2, 4 and 10 times the oral dosage produced 2, 5 and 27 times the serum concentration.[29] Therefore, if we assumed to double the 20 mg/kg dose of praziquantel to a 40 mg/kg dose as used in clinical practice, the mean peak plasma concentration of praziquantel administered alone, and after pretreatment with ketoconazole would approximately be 915 ng/mL and 1,855 ng/mL (5-folds), respectively, which would be adequate for anthelminthic efficacy. However, side effects would be increased if plasma concentrations were elevated.

Since the C_{max} and AUC of praziuantel were markedly increased by ketoconazole, with no significant change in the elimination half-life ($t_{1/2}$), it is likely that this interactions is mainly explained by inhibition of the CYP-mediated first-pass metabolism of praziquantel in the intestine and the liver. Because praziquantel is high clearance drug, its clearance is not sensitive to changes in hepatic enzyme activity, which probably explains the lack of effect on the elimination half-life of praziquantel

It is well established that praziquantel is subject to extensive first-pass metabolism by the liver. Since praziquantel has a rapid absorption and high bioavailability (>80%) after oral administration, and in the present study, the mean t_{max} of praziquantel was unaffected by ketoconazole (Table 3), it indicated that the rate of absorption of praziquantel was not altered. However, the present study did not show any evidences to exclude contribution of the intestine to decreased praziquantel first-pass metabolism. There was a report indicated that cytochromes P450 2B1 and 3A were predominantly responsible for praziquantel metabolism.[26] The CYP3A4 is the most abundant isoform, accounting for about 30% of total CYP in the liver.[41]

Clinically, praziquantel is a drug of choice in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis and used either as a single oral dose of 40 mg/kg or multiple oral doses of 25 mg/kg (3 doses in 1 day)[1-2]. Peak serum concentrations of 200 – 2000 ng/mL of the unchanged drug are reach 1-3 hours after a therapeutic dose[1]. The threshold plasma concentration of praziquantel for therapeutic effect is about 1.0 μM (approximately 300 ng/mL) and this has to prevail for about 6 hours in order to affect schistosomes lethally.[33] Furthermore, plasma concentrations of praziquantel increase when the drug is orally coadministered with a high-lipid diet and a high-carbohydrate diet in healthy volunteers.[43] Our results have shown that the mean C_{max} of praziquantel after ingestion of the single doses of 20 mg/kg praziquantel alone in 10 subjects was 183.38 ± 138.8 ng/mL, whereas the mean C_{max} of praziquantel after ketoconazole pretreatment was 371.31 ± 141.1 ng/mL (Table 3). It was seen that the therapeutic concentrations produced by 20 mg/kg dose of praziquantel given alone in this study showed levels of peak plasma praziquantel concentrations which are not sufficient to produce an efficacy for anthelminthic activity. Since the mean C_{max} values of praziquantel of subjects receiving a single oral doses after ketoconazole was 371.31 ± 141.1 ng/mL which was a small higher than that of the

minimum effective concentration of praziquantel (300 ng/mL) for anthelmintic activity, therefore, subsequently leading to the treatment successful in medical practice if the same conditions are assumed to be as in patients. Thus it could be an advantage for prescribing ketoconazole with the reduced dose of praziquantel, however, the clinical relevant should be justified.

In conclusion, results of the present study show that a 5-day 400 mg of oral ketoconazole pretreatment causes a great increase in plasma concentrations of a single oral dose of 20 mg/kg) of praziquantel, which will lead to the successful of treatment if these interactions occur in patients. In facts, the possibility of these two drugs prescribed by the physicians for the same patient is not frequent. However, in the developing countries such as Thailand, liver flukes (especially *O. viverrini*) and fugal diseases are still the important problems in most parts of the country. Praziquantel is the drug of choice and widely used in mass chemotherapy of opisthorchiasis while ketoconazole is widely prescribed to patients with fungal infections in both short- and long-term therapy. The possibility of ketoconazole influencing the pharmacokinetics of praziquantel must be considered. Thus, coadministration of ketoconazole with praziquantel must be carefully recognized in clinical practice to prevent the pharmacokinetic drug interaction and side effects. Since ketoconazole is a potent CYP3A4 inhibitor, and the present data suggested that coadministration of ketoconazole with praziquantel resulted in the increase of C_{max} and AUC of praziquantel, therefore, it could be assumed that at least CYP3A4 is most likely to play a major role in the metabolism of praziquantel.

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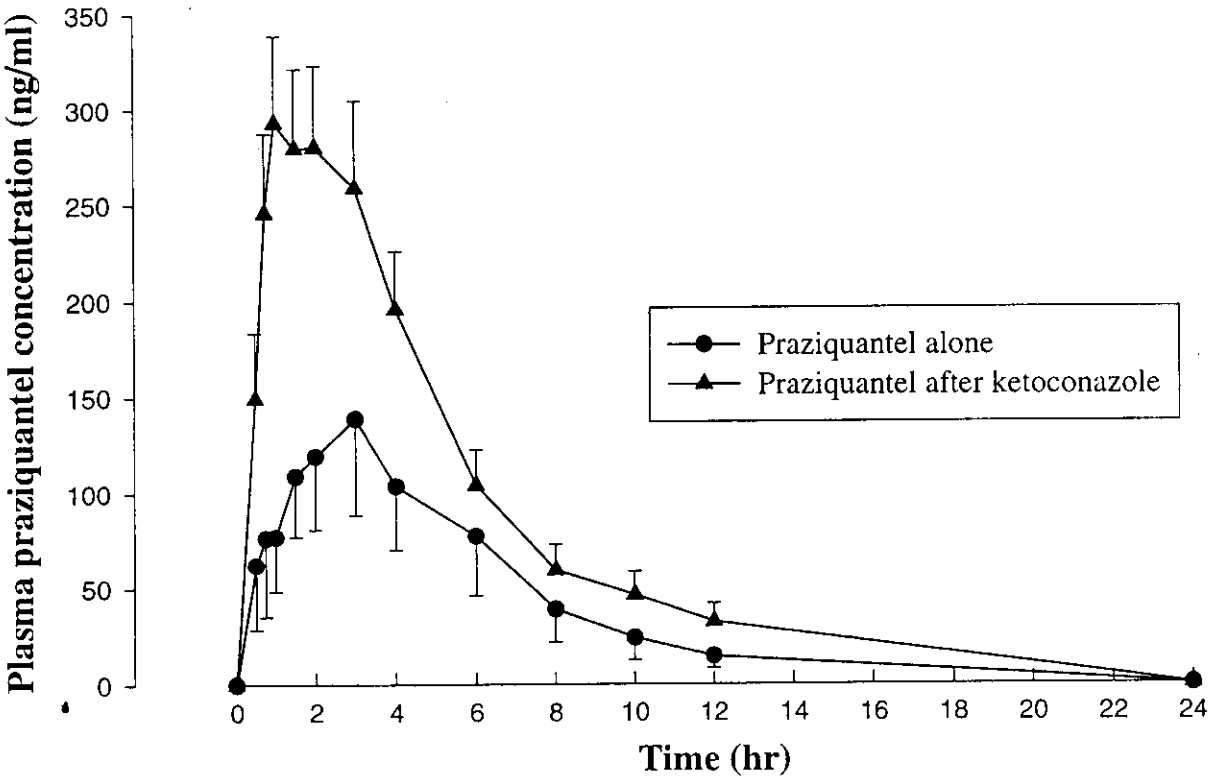

Figure 1 Plasma praziquantel concentration-time profiles in ten subjects after a single oral dose of 20 mg/kg praziquantel alone and after pretreatment with 400 mg ketoconazole orally once daily for 5 days. Each points were represented as mean and SEM for clarity.

Table 1 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a single oral dose of 20 mg/kg praziquantel alone.

Parameters	Subject number (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	24	22	37	38	30	39	30	33	29	27	30.90	5.8
Weight (kgs)	57	58	70	64	64	64	65	55	55	62	61.40	4.95
C_{max}(ng/ml)	90.6	206	528	101	288	169	48.9	152	95.3	155	183.38	138.8
$AUC_{(0-12)}$ (ng/ml.hr)	294.8	1191	3122	307.5	1262	422.6	168.90	745	318	206	803.78	905.8
$AUC_{(0-\infty)}$ (ng/ml.hr)	327.9	1337	3258	550	2000	423.7	208.8	873	420	228.6	962.70	986.4
$\lambda_Z(hr^{-1})$	0.30	0.22	0.32	0.13	0.06	0.56	0.32	0.17	0.16	0.43	0.27	0.15
$t_{1/2}$ (hr)	2.29	3.09	2.15	6.54	11.2	1.24	2.1	3.99	4.3	1.63	3.85	3.02
t_{max} (hr)	2	4	3	1	3	1.5	3	1.5	1	0.5	2.05	1.14
Cl/f (l/kg/hr)	64.20	15.47	6.58	36.36	10.00	47.20	95.78	22.90	47.60	84.70	43.08	30.96

C_{max} , Maximum plasma concentration; AUC, Area under the concentration-time curve; λ_Z , Elimination rate constant; $t_{1/2}$, Terminal disposition half-life; Cl/f, Apparent oral clearance; S1-S10, Subject No. 1 – 10; SD, Standard deviation.

Table 2 Pharmacokinetic parameters of praziquantel in each of ten subjects receiving a single oral dose of 20 mg/kg praziquantel after pretreatment with 400 mg ketoconazole orally for 5 days.

Parameters	Subject number (S1-S10)											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
Age (yrs)	24	22	37	38	30	39	30	33	29	27	30.90	5.8
Weight (kgs)	57	58	70	64	64	64	65	55	55	62	61.40	4.95
C_{max} (ng/ml)	523	320	463	446	395	524	81.1	239	444	278	371.31	141.1
$AUC_{(0-12)}$ (ng/ml.hr)	1503	1570	2528	1340	2062	2641	322	1451	1900	486	1580.30	761.5
$AUC_{(0-\infty)}$ (ng/ml.hr)	1566	1700	2870	1400	2182	3695	360	1590	2004	496	1786.30	998.0
λ_z (hr^{-1})	0.31	0.27	0.2	0.25	0.26	0.09	0.38	0.22	0.25	0.55	0.28	0.12
$t_{1/2}$ (hr)	2.21	2.5	3.43	2.77	2.62	7.55	1.82	3.18	2.8	1.25	3.01	1.71
t_{max} (hr)	1	3	1.5	0.75	3	3	2	2	1.5	0.5	1.82	0.94
Cl/f (l/kg/hr)	13.44	12.17	7.47	14.28	9.16	5.41	55.50	12.58	9.98	39.02	17.90	16.18

C_{max} , Maximum plasma concentration; AUC, Area under the concentration-time curve; λ_z , Elimination rate constant; $t_{1/2}$,Terminal disposition half-life; Cl/f, Apparent oral clearance; S1-S10, Subject No. 1 – 10; SD, Standard deviation.

Table 3 Pharmacokinetic parameters (mean ± SD) of praziquantel in ten subjects after receiving a single oral dose of 20 mg/kg praziquantel alone and after pretreatment with 400 mg ketoconazole orally for 5 days.

Parameters	Praziquantel alone (Control, n = 10)	Praziquantel *after* ketoconazole (n = 10)	*P*-value (paired Student *t* test)
C_{max} (ng/ml)	183.38 ± 138.8	371.31 ± 141.1*	$P < 0.01$ (P=0.003)
AUC_{0-12} (ng/ml.hr)	803.78 ± 905.8	1580.30 ± 761.5*	$P < 0.01$ (P=0.0065)
$AUC_{0-\infty}$ (ng/ml.hr)	962.70 ± 986.4	1786.30 ± 998.0*	$P < 0.05$ (P=0.0165)
λ_z (hr^{-1})	0.27 ± 0.15	0.28 ± 0.12	NS (P=0.429)
$t_{1/2,}$ (hr)	3.85 ± 3.02	3.01 ± 1.71	NS (P=0.2475)
t_{max} (hr)	2.05 ± 1.14	1.82 ± 0.94	NS (P=0.2285)
Cl/f (l/kg/hr)	43.08 ± 30.96	17.90 ± 16.18*	$P < 0.01$ (P=0.002)

C_{max} , Maximum plasma concentration; AUC, Area under the concentration-time curve;

λ_Z , Elimination rate constant; $t_{1/2}$,Terminal disposition half-life; Cl/f, Apparent oral clearance;

*, Significant difference from control; NS, No significant difference from control;

SD, Standard deviation.