EFFECTS OF KETOCONAZOLE AND ITRACONAZOLE ON PLASMA CONCENTRATIONS OF QUININE IN NORMAL HEALTHY VOLUNTEERS

Wibool Ridtitid, Malinee Wongnawa, Werawath Mahatthanatrakul, Prasit Phaipenkong, Tippawan Suvarnarak, Methi Sunbhanich

Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla 90112, Thailand.

ABSTRACT

Quinine is mainly metabolised by the cytochrome P450 3A4 isozyme (CYP3A4), whereas ketoconazole and itraconazole, potent inhibitors of CYP3A4, have been known to markedly increase plasma concentrations of various drugs which are concomitantly administered. The aims of the present study were to determine the effects of ketoconazole and itraconazole on the pharmacokinetics of quinine, and to examine a possible role of CYP3A4 on quinine metabolism in normal healthy volunteers. In a randomized crossover study with three phases and a two-week washout period, nine healthy Thai male volunteers ingested single doses of 300 mg quinine sulphate alone or after pretreatment with either 400 mg ketoconazole or 200 mg itraconazole orally once daily for 4 days. Blood samples were collected at specific time points over a 48-hour period. Plasma quinine concentrations were determined using HPLC for pharmacokinetic analysis. The results indicated that ketoconazole and itraconazole significantly increased the area under the plasma concentration-time curve (AUC_{0-48}) of quinine by 107% ($P < 0.01$) and 96% ($P < 0.01$), respectively; elimination half-life ($T_{1/2}$) by 70% ($P < 0.01$) and 71% ($P < 0.01$), respectively. Only ketoconazole significantly increased the maximum plasma concentration (C_{max}) by 29% ($P < 0.01$) and time to reach C_{max} (T_{max}) by 56% ($P < 0.01$), whereas itraconazole increased the C_{max} and T_{max} by 17% and 22%, respectively, but were not significantly different from the control phase. Therefore, the present study indicated that there was a significant interaction between ketoconazole or itraconazole and quinine in normal healthy volunteers since both ketoconazole and itraconazole elevated the AUC_{0-48} of a single oral dose of 300 mg quinine sulphate by inhibition of quinine metabolism, probably via CYP3A4 activity in the liver. Ketoconazole had a slightly greater effect on the AUC_{0-48} of quinine than that of itraconazole. Concomitant use of ketoconazole or itraconazole with quinine should be recognized in order to avoid drug interaction in malarial therapy.

Key words : quinine, ketoconazole, itraconazole, drug interaction, pharmacokinetics

Address of correspondence and reprint requests to : Wibool Ridtitid, Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla 90112, Thailand.

ผลของคีโตโคนาโซลและไอทราโคนาโซลต่อความเข้มข้นของควินีน ในพลาสมาของอาสาสมัครสุขภาพปกติ

วิบูลย์ ฤทธิทิศ, มาลินี วงศ์นาวา, วีรวัฒน์ มหัทธนตระกูล, ประสิทธิ์ ไฝเป็นคง, ทิพวัลย์ สุวรรณรักษ์, เมธี สรรพานิช

ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ อ.หาดใหญ่ จ.สงขลา 90112

บทคัดย่อ

ควินีนส่วนใหญ่ถูกแปรรูปโดยอาศัยเอนไซม์ไซโตโครม พี450 3เอ4 (CYP3A4) ในขณะที่คีโตโคนาโซลและไอทราโคนาโซลเป็นยาที่มีฤทธิ์แรงในการยับยั้งการทำงานของเอนไซม์ CYP3A4 ซึ่งจะทำให้ยาที่ถูกแปรรูปผ่านเอนไซม์ชนิดนี้มีระดับความเข้มข้นของยาในพลาสมาสูงขึ้นเมื่อใช้ยาร่วมกับคีโตโคนาโซลหรือไอทราโคนาโซล จุดประสงค์ในการวิจัยครั้งนี้เพื่อศึกษาผลของคีโตโคนาโซลและไอ-ทราโคนาโซลต่อเภสัชจลนศาสตร์ของควินีนและบทบาทของเอนไซม์ CYP3A4 ต่อการแปรรูปยาควินีนในอาสาสมัครสุขภาพปกติ ในการวิจัยครั้งนี้ได้ทำการศึกษาในอาสาสมัครชายไทยสุขภาพปกติจำนวน 9 คนแบบเปิดเผยและแบ่งช่วงของการศึกษาออกเป็น 3 ระยะ กล่าวคือในวันทำการทดลองให้อาสาสมัครทั้ง 9 คนรับประทานเฉพาะยาควินีนในขนาด 300 มก. ครั้งเดียวและรับประทานควินีนในขนาด 300 มก. ครั้งเดียวหลังจากอาสาสมัครทั้ง 9 คนได้รับประทานยาคีโตโคนาโซลวันละครั้งในขนาด 400 มก./วัน หรือไอทราโคนาโซลวันละครั้งในขนาด 200 มก./วัน มาเป็นเวลา 4 วันก่อนเจาะเลือดเพื่อเก็บตัวอย่างเลือดเป็นระยะๆ ในช่วง 48 ชั่วโมง เพื่อนำไปหาความเข้มข้นของควินีนในพลาสมาโดย HPLC เพื่อใช้ในการวิเคราะห์ทางเภสัชจลนศาสตร์ ผลการศึกษาพบว่าทั้งคีโตโคนาโซลและไอทราโคนาโซลเพิ่มพื้นที่ใต้กราฟระหว่างความเข้มข้นและเวลาของควินีนได้ 107% และ 96% ตามลำดับ และเพิ่มค่าครึ่งชีวิตของการกำจัดยาควินีนได้ 70% และ 71% ตามลำดับอย่างมีนัยสำคัญ ($P < 0.01$) เฉพาะคีโตโคนาโซลเท่านั้นที่สามารถเพิ่มความเข้มข้นสูดสุดและช่วงเวลาเกิดความเข้มข้นสูงสุดได้ 29% และ 56% ตามลำดับอย่างมีนัยสำคัญ ($P < 0.01$) แต่ไอทราโคนาโซลสามารถเพิ่มความเข้มข้นสูดสุดและช่วงเวลาเกิดความเข้มข้นสูงสุดได้ 17% และ 22% ตามลำดับ แต่ไม่มีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มควบคุม ดังนั้นจึงกล่าวได้ว่าทั้งคีโตโคนาโซลและไอทราโคนาโซลเพิ่มพื้นที่ใต้กราฟระหว่างความเข้มข้นและเวลาของควินีนในขนาด 300 มก. เมื่อให้โดยการรับประทานครั้งเดียว ซึ่งผลนี้อาจเกิดจากคีโต-โคนาโซล/ไอทราโคนาโซลยับยั้งการทำงานของเอนไซม์ CYP3A4 ที่ตับ ทำให้การแปรรูปของควินีนลดลง คีโตโคนาโซลสามารถเพิ่มพื้นที่ใต้กราฟความเข้มข้นและเวลาของควินีนได้มากกว่าไอทราโคนาโซลเล็กน้อย ดังนั้นการใช้ยาคีโตโคนาโซลหรือไอทราโคนาโซลร่วมกับควินีนจะต้องสังวรณ์อยู่เสมอว่าอาจมีโอกาสเกิดปฏิกิริยาระหว่างยาได้ในระหว่างการรักษาโรคมาเลเรีย

คำสำคัญ : ควินีน, คีโตโคนาโซล, ไอทราโคนาโซล, การเกิดปฏิกิริยาระหว่างยา, เภสัชจลนศาสตร์

INTRODUCTION

Quinine, a principal alkaloid derived from the bark of the cinchona tree, has been used in malaria suppression and treatment for more than 300 years. Despite its potential toxicity, quinine is still widely used for the suppressive treatment and cure of chloroquine-resistant and multidrug-resistant falciparum malaria[1]. Quinine has been known to be mainly metabolised in the liver via CYP3A4 isozyme both *in vitro* and *in vivo* to yield 3-hydroxyquinine, a major metabolite[2,3], but only about 20% of an administered dose is excreted unchanged in the urine.

Ketoconazole and itraconazole, broad spectrum azole antimycotics, are potent inhibitors of CYP3A4 resulting the increase in plasma concentrations of various drugs coadministered such as terfenadine, triazolam, felodipine, quinidine, nisodipine and atorvastatin[4-9], which may be life-threatening. Presently, a limit number of research articles described the effect of ketoconazole on the pharmacokinetics of quinine in humans has been reported[2,3], whereas the effect of itraconazole on quinine pharmacokinetics has not yet been published. Since quinine has a narrow thera-peutic window, coadministration of ketocona-zole or itraconazole with quinine may lead to a significant increase in plasma concentrations of quinine. Normally, treatment of fungal infection with azole antimycotics requires a long period to get rid the causative agents. Therefore, quinine is probably coadministered with ketoconazole or itraconazole in clinical practice. The aims of the present study are to demonstrate and compare the effects of ketoconazole and itraconazole on the pharmacokinetics of quinine in human subjects. Additionally, the possible roles of CYP3A4 isozyme on quinine metabolism in normal healthy volunteers would be explored.

MATERIALS AND METHODS

Chemical and drugs

Standard quinine and quinidine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, Missouri, USA). Quinine sulphate (300 mg tablet, Lot. No. 98098) was bought from General Drug House Co., Ltd., Bangkok, Thailand. Ketoconazole (Nizoral®, Lot. No. B181297) and itraconazole (Sporal®, Lot. No. 384037) were bought from Janssen Pharmaceutica Ltd., Bangkok, Thailand. An HPLC grade of acetonitrile and an analytical grade of triethylamine were purchased from J.T. Baker (Phillipsburg, New Jersy, USA) and Fluka (Messerchmittstr, Switzerland), respectively. Water was purified for HPLC by the Milli Q water purification system (Millipore, Milford, Massachusetts, USA).

Instruments and chromatographic condition

The HPLC system consisted of a Waters 515 pump and a Waters 717 autosampler (Waters Asssociates, Milford, Massachusetts, USA). The detector was the Jasco 821-FP intelligent Spectrofluorometer (Japan Spectroscopic Co., Ltd., Tokyo, Japan). The intergrator was the Jasco model 807-IT (Japan Spectroscopic Co., Ltd., Tokyo, Japan). The column was reverse phase μ-Bondapak C_{18} (30 cm x 3.9 mm i.d., particle size 10 μm, Waters Associates, Milford, Massachusetts, USA). The mobile phase consisted of deionized water, triethylamine, 85% phosphoric acid and acetonitrile (91.4: 1: 0.6: 7, v/v/v/v), which was filtered through a 0.45 μm membrane filter (Nyron 66, Millipore, Milford, Massachusetts, USA) and degassed by ultrasonication for 9 minutes before using. The mobile phase was freshly prepared in each day. The flow rate was 1.5 ml/min. The quinine concentration in plasma sample was detected using the Jasco 821-FP intelligent Spectro-fluorometer with an excitation and emission wavelengths set at 340 and 425 nm, respectively.

Subjects

Nine healthy non-smoking Thai male volunteers (16-37 years; 47-70 kg) participated in this study. All subjects were informed of the objectives of the study and gave their written consent. The study protocol was approved by the Human Ethics Committee of the Faculty of Science, Prince of Songkla University. A medical history, physical examination, and essential laboratory tests were carried out on all subjects to ensure that the subjects were in good health. All subjects were not allowed to take any medication, except drugs given by the investigators, for one month before or during the study period.

Study protocol

A randomized crossover design with three phases was used in this study. Each

phase was separated by a two-week washout period. A single oral dose of 300 mg quinine sulphate was given on the study day of each phase. *Phase one,* Quinine alone. On the study day, each subject ingested only 300 mg quinine sulphate with 150 ml water. *Phase two and three,* 400 mg ketoconazole (two 200 mg Nizoral® tablets) or 200 mg itraconazole (two 100 mg Sporal® capsules) pretreatment orally once daily for 4 days. The subjects were randomized to ingest either 400 mg ketoconazole or 200 mg itraconazole for pretreatment at 7.00 h with breakfast for 4 days. On day 4, each subject ingested a single oral dose of 300 mg quinine sulphate with 150 ml water 2 h after ketoconazole or itraconazole administration.

All subjects fasted overnight before quinine administration and received regular meals 3 h after quinine. The subjects were not allowed to have coffee, tea, cola or alcohol on the test days.

Blood sampling and determination of plasma quinine concentrations

On the day of quinine ingestion of each phase, a forearm vein of each subject was cannulated with a sterile catheter kept patent with heparinized saline solution. Blood samples (5 ml) were collected in heparinized tubes before quinine intake and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 24, and 48 h after quinine ingestion. All blood samples were centrifuged at 1000 x g for 15 min, and plasma was separated within 30 min and kept at −70 °C until analysed. Plasma quinine concentrations were determined by HPLC method[10-12] with a slight modification using quinidine hydrochloride at concentration of 25 μg/ml as an internal standard. Briefly, to 400 μl of plasma sample in a 2-ml stoppered microcentrifuge tube, a 100 μl internal standard was added and mixed for 30 sec on a vortex mixer. A 250 μl of acetonitrile was then added and shaken thoroughly on a vortex mixer for 30 sec. After 10 min the microcentrifuge tube was centrifuged at 10,000 x g for 15 min. A 40 μl of supernatant was injected into HPLC system using a reverse-phase μ-Bondapak C_{18} column with deionized water, triethylamine, 85% phosphoric acid and acetonitrile (91.4: 1: 0.6: 7, v/v/v/v) as a moblie phase, and detected by a fluorescence detector. The lower detection limit of quinine was 0.2 mg/l. The intra-day assay coefficient of variation (CV) for quinine was 1.6% at 1 mg/l, 3.5% at 2.5 mg/l, 3% at 5 mg/l and 1% at 10 mg/l (n = 8). The inter-day assay CV for quinine was 6.7% at 1 mg/l, 5.3% at 2.5 mg/l, 4.7% at 5 mg/l and 4% at 10 mg/l (n = 10). The relative recovery of standard quinine in human plasma was 90-94%. Neither ketoconazole nor itraconazole interfered with the HPLC assay of quinine.

Pharmacokinetic analysis

Plasma quinine concentrations were analysed by one-compartment model. Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained directly from the original data. The elimination rate constant (K_{el}) was determined by a linear regression analysis of the terminal phase of the plasma concentration-time profile. The elimination half-life ($T_{1/2}$) was calculated from the equation $T_{1/2} = 0.69/K_{el}$. The area under the plasma concentration-time curve from time zero to 48 h (AUC_{0-48}) was calculated by the trapezoidal rule from the origin of drug administration to the last data point.

Statistical analysis

Results were expressed as mean values ± SD. The significance of differences of pharmacokinetic variables between the study phases was analysed using ANOVA with repeated measures followed by the Newman-Keuls test where appropriate. Values of $P < 0.05$ were considered to be statistically significant.

RESULTS

All nine subjects completed the study. Any serious adverse effects were not reported during each study phase. The mean plasma concentration-time profiles of quinine after quinine ingestion alone, and pretreatment with ketoconazole or itraconazole were shown in Figure 1. The pharmacokinetic data were summarized in Table 1.

Quinine after ketoconazole

The mean C_{max}, T_{max}, $T_{1/2}$ and AUC_{0-48} of quinine significantly increased by 29% (from 2.4 ± 0.5 to 3.1 ± 0.5 mg/l; $P < 0.01$), 56% (from 1.8 ± 0.6 to 2.8 ± 0.8 h; $P < 0.01$), 70% (from 9.0 ± 2.1 to 15.3 ± 5.0 h; $P < 0.01$) and 107% (from 36.1 ± 14.0 to 74.8 ± 26.9 mg.hr/l; $P < 0.01$), respectively, after pretreatment with 400 mg ketoconazole orally once daily for 4 days compared to those of the

control phase (quinine alone) (Table 1).

Quinine after itraconazole

After pretreatment with 200 mg itraconazole orally once daily for 4 days, the mean AUC_{0-48} and $T_{1/2}$ of quinine significantly increase by 96% (from 36.1 ± 14.0 to 70.8 ± 35.8 mg.hr/l; $P< 0.01$) and 71% (from 9.0 ± 2.1 to 15.4 ± 7.2 h; $P< 0.01$), whereas the mean C_{max} and T_{max} increased by 17% (from 2.4 ± 0.5 to 2.8 ± 0.8 mg/l; $P> 0.05$) and 22% (from 1.8 ± 0.6 to 2.2 ± 0.9 h; $P> 0.05$), respectively, which were not significantly different from the control phase (quinine alone) (Table 1)

Quinine after ketoconazole phase and Quinine after itraconazole phase

There were no significant differences in the mean C_{max} (3.1 ± 0.5 mg/l versus 2.8 ± 0.8 mg/l; $P> 0.05$), T_{max} (2.8 ± 0.8 h versus 2.2 ± 0.9 h; $P> 0.05$), $T_{1/2}$ (15.3 ± 5.0 h versus 15.4 ± 7.2 h; $P> 0.05$) and AUC_{0-48} (74.8 ± 26.9 mg.hr/l versus 70.8 ± 35.8 mg.hr/l ; $P> 0.05$) of quinine after pretreatment with ketoconazole compared to those of quinine after pretreatment with itraconazole.

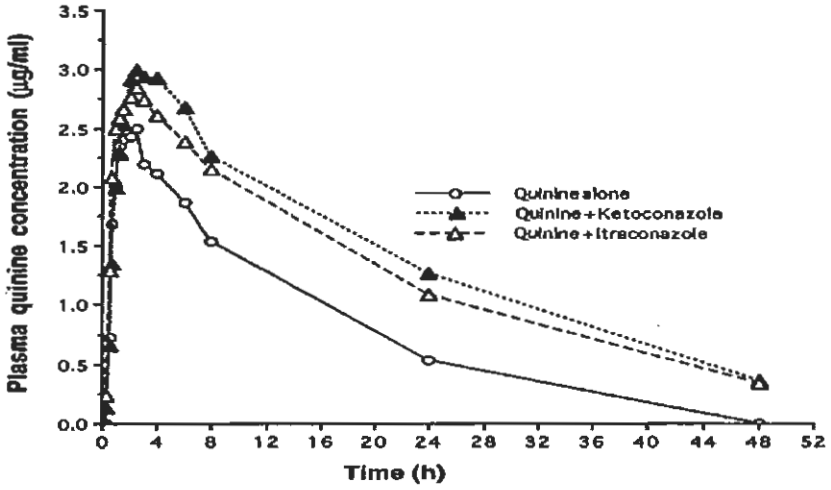

Figure 1. Mean plasma concentration-time profiles of quinine in nine normal healthy volunteers after a single oral dose of 300 mg quinine sulphate alone (O) or after pretreatment with either 400 mg ketoconazole (▲) or 200 mg itraconazole (Δ) orally once daily for 4 days. *Error bars were omitted for clarity.*

Table 1. Pharmacokinetic parameters of quinine when a single oral dose of 300 mg quinine sulphate was given alone or after pretreatment with either 400 mg ketoconazole or 200 mg itraconazole orally once daily for 4 days in nine normal healthy volunteers.

Parameter	Quinine alone (Control phase)	Quinine + Ketoconazole	Quinine + Itraconazole
C_{max} (mg/l)	2.4 ± 0.5*	3.1 ± 0.5*	2.8 ± 0.8
% of control (range)	100	129 (92-179)	117 (66-152)
T_{max} (h)	1.8 ± 0.6*	2.8 ± 0.8*	2.2 ± 0.9
% of control (range)	100	156 (96-226)	122 (68-213)
$T_{1/2}$ (h)	9.0 ± 2.1*†	15.3 ± 5.0*	15.4 ± 7.2†
% of control (range)	100	170 (113-228)	171 (96-231)
AUC_{0-48} (mg. hr/l)	36.1 ± 14.0*†	74.8 ± 26.9*	70.8 ± 35.8†
% of control (range)	100	207 (103-311)	196 (64-360)

C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; AUC, area under the plasma concentration-time curve. Data were expressed as mean ± SD. *,† $P < 0.01$, significant difference compared with the corresponding control value.

DISCUSSION

The values of C_{max}, T_{max} and $T_{1/2}$ of quinine given alone in this study were comparable to those reported for normal healthy volunteers, whereas the AUC_{0-48} found in our study was greater than that of previously reported (36.1 ± 14.0 versus 18.5 ± mg. hr/l)[13]. The difference of AUC_{0-48} values may be explained by the differences in the interindividual variations with respect to age-, sex- and race-related changes[14]. The present results also demonstrated that after pretreatment with 400 mg ketoconazole orally once daily for 4 days, the mean AUC_{0-48} increased by 107% (2-fold), C_{max} increased by 29% (1.3-fold), T_{max} increased by 56% (1.6-fold), and $T_{1/2}$ increased by 70% (1.7-fold), whereas the mean AUC_{0-48} of quinine after pretreatment with 200 mg itraconazole orally once daily for 4 days was increased by 96% (2-fold), C_{max} increased by 17% (1.2-fold), T_{max} increased by 22% (1.2-fold), and $T_{1/2}$ increased by 71% (1.7-fold) (Table 1). Interestingly, the AUC_{0-48} values of quinine were markedly increased (2-fold) after pretreatment with either ketoconazole or itraconazole. In comparison between the effects of ketoconazole and itraconazole on plasma concentrations of quinine on the basis of AUC_{0-48} values, it was found that ketoconazole had a slightly greater effect than itraconazole, but were not significantly different. Therefore, there was a markedly significant interaction between ketoconazole or itraconazole and quinine in normal healthy subjects. This was the first report described inhibitory effect of ketoconazole on quinine metabolism in human subjects compared to that of itraconazole.

Ketoconazole and itraconazole, azole antimycotics with broad spectrum antifungal activity, are potent inhibitors of many CYP3A4 drug substrates[15]. Ketoconazole and itraconazole given orally once daily for 4 days at 400 mg and 200 mg doses, respectively in normal healthy volunteers are sufficient to inhibit CYP3A4 [6,7,16]. 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[3]. In the present study, ketoconazole was likely to be a slightly stronger inhibitor of CYP3A4 in normal healthy volunteers than itraconazole. The present findings also demonstrated that both ketoconazole and itraconazole increased the $T_{1/2}$ of quinine much more than the C_{max}. Therefore, these data indicated that the interaction resulted in essence from inhibition of the hepatic CYP3A4-mediated metabolism of quinine, whereas inhibition of the intestinal metabolism had a smaller contribution. Recently, we have reported the roles of CYP3A4 in metabolism of mefloquine, a 4-quinolinemethanol compound structurally related to quinine, in humans[17], which supported the hepatic CYP3A4-mediated metabolism of quinine in this study. Additionally, quinine is rapidly absorbed from the gastrointestinal tract and the bioavailability is rather high (88%)[13], thus the effect of inhibiting CYP3A4-mediated presystemic in the small intestine of a high bioavailability drug is not much concerned[18]. However, inhibition of the intestinal P-glycoprotein transporter by ketoconazole *in vivo* should be recognized[19,20].

Our present results indicated that the mean C_{max} of quinine in nine normal healthy subjects after administration of a single oral dose of 300 mg quinine sulphate alone was 2.4 mg/l, and after pretreatment with ketoconazole and itraconazole were 3.1 and 2.8 mg/l, respectively. Our intention in this study is to observe the behavior of quinine pharmacokinetics in normal healthy subjects receiving quinine alone and after pretreatment with ketoconazole or itraconazole without producing any adverse effects. For these reasons, we used a single oral dose of 300 mg quinine sulphate as a test dose instead of 600 mg quinine dose as used in clinical practice, and expected that after pretreatment with ketoconazole or itraconazole the peak plasma concentrations of quinine would not be high enough to produce toxicity. Generally, the effective plasma quinine concentration is 8-15 mg/l, however, after administration of a 600 mg oral dose of quinine sulphate the plasma concentration may reach 15-20 mg/l. Mild toxicity usually occurred at the plasma quinine concentration above 10 mg/l and cardiovascular toxicity is observed when the plasma concentration is above 16 mg/l. The electrocardiogram may change in healthy subjects with quinine concentration around 5 mg/l after 10 mg/kg intravenous infusion[21]. If we doubled the 300 mg quinine dose to a 600 mg dose, the peak plasma quinine

concentration of quinine administered alone or after pretreatment with ketoconazole and itraconazole might be doubled that which obtained from each one which was likely to produce electrocardiogram changes. However, all subjects participated in this study did not report any adverse effects to the investigators. In clinical practice, the toxicity produced by quinine after coadministration with ketoconazole or itraconazole may occur if high doses of quinine are administered, i.e., loading dose and long-term treatment with ketoconazole or itraconazole.

CONCLUSION

In conclusion, this study clearly shows that there is a significant interaction between ketoconazole or itraconazole and quinine in human subjects. After pretreatment with either ketoconazole or itraconazole, the plasma concentrations of quinine were considerably increased as indicated by the increases in mean AUC_{0-48}, probably by inhibiting CYP3A4-mediated metabolism of quinine mainly in the liver. Therefore, concomitantly administered of quinine with the long-term treatment with ketoconazole or itraconazole should be carefully considered to avoid drug interaction. If necessary, the dose of quinine should be reduced, or the plasma concentrations of quinine should be measured regularly to prevent drug toxicity.

ACKNOWLEGEMENTS

This study was supported by grants from the Thai Government No. SC43078. We thank nurses from Songklanakarind Hospital, Faculty of Medicine, Prince of Songkla University for their expert assistance in collecting blood samples from volunteers.

REFERENCES

1. Tracy JM, Webster LT. Drugs used in the chemotherapy of protozoal infections. In: Hardman JG, et al. editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill, 1996:965-985.
2. Zhao XJ, Yokoyama H, Ciba K, et al. Identification of human cytochrome P450 involved in the 3-hydroxylation of quinine by human liver microsomes and nine recombinant human cytochrome P450. *J Pharmacol Exp Ther* 1996;279:1327-1334.
3. Mirghani RA, Hellgren U, Westerberg PA, et al. The roles of cytochrome P450 3A4 and 1A2 in the 3-hydroxylation of quinine in vivo. *Clin Pharmacol Ther* 1999;66:454-460.
4. Crane JK, Shih HT. Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. *Am J Med* 1993;95:445-446.
5. Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994;56:601-607.
6. Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effect of felodipine. *Clin Pharmacol Ther* 1997;61:410-415.
7. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 1997;62:510-517.
8. Heinig R, Adelmann HG, Ahr G. The effect of ketoconazole on the pharmacokinetics, pharmacodynamics and safety of nisoldipine. *Eur J Clin Pharmacol* 1999;55:57-60.
9. Mazzu AL, Lasseter KC, Shamblen EC, et al. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther* 2000;68:391-400.
10. Lehmann CR, Boran KJ, Pierson WP, et al. Quinine assays: Enzyme immunoassay versus high performance liquid chromatography. *Ther Drug Monit* 1986;8:336-339.
11. Edstein MD, Prasitthipayong A, Sabchareon A, et al. Simultaneous measurement of quinine and quinidine in human plasma, whole blood, and erythrocytes by high-performance liquid chromatography with fluorescence detection. *Ther Drug Monit* 1990;12:493-500.
12. Supanaranond W, Davis TME, Pukrittayakamee S, et al. Disposition of oral quinine in acute falciparum malaria. *Eur J Clin Pharmacol* 1991;40:49-52.

13. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol* 1996;49:383-386.
14. Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994;270:414-423.
15. Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998;35:361-390.
16. Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 1994;55:481-485.
17. Ridtitid W, Wongnawa M, Mahatthanatrakul W, et al. Effect of rifampin on plasma concentrations of mefloquine in healthy volunteers. *J Pharm Pharmacol* 2000;52:1265-1269.
18. Ho PC, Chalcroft SC, Coville PF, et al. Grapefruit juice has no effect on quinine pharmacokinetics. *Eur J Clin Pharmacol* 1999;55:393-398.
19. Floren LC, Bekersky L, Benet LZ, et al. Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. *Clin Pharmacol Ther* 1997;62:41-49.
20. Zhang Y, Hsieh Y, Izumi T, et al. Effect of ketoconazole on the intestinal metabolism, transport and oral bioavailability of K02, a novel vinylsulfone peptidomimetic cysteine protease inhibitor and a P450 3A, P-glycoprotein dual substrate, in male Sprague-Dawley rats. *J Pharmacol Exp Ther* 1998;287:246-252.
21. Karbwang J, Davis TME, Looareesuwan S, et al. A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males. *Br J Clin Pharmacol* 1993;35:265-271.