Lack of effect of oral contraceptive use on the pharmacokinetics of quinine

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The pharmacokinetics of quinine after a single 600 mg oral dose of quinine sulphate were studied in seven female subjects who used oral contraceptives and in seven age-matched female controls who did not. There were no significant differences ($P > 0.05$) in the maximum plasma concentration ($C_{\max}$) and the time of peak concentration ($t_{\max}$) between the subjects who used oral contraceptives ($C_{\max} = 5.3 \pm 1.0$ (s.d.) mg l^{-1} ; $t_{\max} = 1.4 \pm 0.7$ h) and the control subjects ($C_{\max} = 5.6 \pm 0.9$ mg l^{-1} ; $t_{\max} = 2.1 \pm 0.9$ h). The mean elimination half-life of quinine in the oral contraceptives user group (12.5 ± 1.9 h) was similar ($P > 0.05$) to that in the control group (11.8 ± 2.7 h). The oral clearance of quinine in the oral contraceptive user group was 0.133 ± 0.055 $\text{l h}^{-1} \text{ kg}^{-1}$ (range 0.073–0.233) and was not significantly different ($P > 0.05$) from that observed in the control group (0.125 ± 0.025 $\text{l h}^{-1} \text{ kg}^{-1}$, range 0.075–0.148).

Keywords quinine pharmacokinetics oral contraceptive steroids

Introduction

A number of drug interactions have been reported involving the use of oral contraceptive steroids (OCS). Previous studies indicate that the clearance of oxidatively biotransformed drugs is impaired in OCS users (Chambers *et al.*, 1982; Meffin *et al.*, 1984; Stoehr *et al.*, 1984).

Quinine is widely used for the prevention of night cramps and has gained increasing importance in the management of chloroquine-resistant falciparum malaria (White, 1985; White *et al.*, 1983). Since it is metabolized largely by hepatic oxidative biotransformation (Barrow *et al.*, 1980; Bruce-Chwatt, 1981; White, 1985), an important interaction between OCS and quinine might occur. Such an interaction may affect a large number of people. Some 42% (2,117 million) of the world population live in endemic malaria areas (WHO, 1989). The use of OCS for family planning has been promoted in these regions. The present study was, therefore, undertaken to examine the effect of OCS on the pharmacokinetics of quinine after a single therapeutic dose.

Methods

The study was approved by the Human Experimentation Ethics Committee, the Research Institute for Health Science, Chiangmai University, Thailand.

Subjects

Fourteen healthy Thai women, aged 19–35 years, participated in the study after giving their informed consent. They were non-smokers, non-alcohol drinkers and were healthy as determined by medical history, physical examination and biochemical and haematological tests. Women taking chronic medication other than OCS or any medication in the week before the study were excluded. Seven of the women had been taking an OCS preparation for at least 6 months before the study and continued to take the contraceptive pill throughout the course of the study. The other seven subjects were not taking OCS and served as controls. The OCS used were both single and combination pills. These included

Microgynon 30 (ethinylestradiol 0.03 mg, levonorgestrel 0.15 mg) [$n = 1$], Eugynon [$n = 1$] and Eugynon ED [$n = 3$] (both ethinylestradiol 0.05 mg, norgestrel 0.5 mg), Noriday (norethisterone 0.35 mg) [$n = 1$] and Triquilar ($n = 1$). Triquilar is a combination triphasic contraceptive pill—6 brown tablets containing 0.03 mg ethinylestradiol and 0.05 mg levonorgestrel; 5 white tablets containing 0.04 mg ethinylestradiol and 0.075 mg levonorgestrel; 10 ochre tablets containing 0.03 mg ethinylestradiol and 0.125 mg levonorgestrel.

Protocol

Subjects fasted from 22.00 h the night before the study until 3 h after quinine administration. A cannula was inserted into a forearm vein for blood sampling and kept patent with heparinised saline (heparin, 5 u ml⁻¹). An oral dose of 600 mg quinine sulphate (497 mg quinine base) was administered between 07.00 and 08.00 h to each subject with approximately 200 ml of water. Venous blood samples (5 ml each) were collected before and 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 30 h post-dose. The plasma was separated by centrifugation within 2 h and stored at -20°C until assayed.

Analytical procedures

The concentration of quinine in plasma was measured by a high-performance liquid chromatographic procedure (Zoest *et al.*, 1990) using a reverse-phase column and a fluorescence detector. The coefficient of variation for this method averaged less than 8% over the concentration range of 0.02 to 10 mg l⁻¹. Blank plasma collected prior to quinine administration showed no endogenous sources of interference with the assay. Plasma protein binding of quinine was measured by equilibrium dialysis (Wanwimolruk *et al.*, 1982) using the Dianorm® apparatus. Plasma samples from each subject collected before quinine administration (i.e. blank plasma) were used to measure the protein binding. Plasma was dialysed against 0.1 M phosphate buffer (pH 7.4) at 37° C for 3 h with quinine at an initial concentration of 3 mg l⁻¹. Quinine concentrations were then estimated in the plasma and buffer sides as above. There were no significant changes in volume and pH after 3 h of dialysis, so no correction for volume shift and pH change was necessary.

Data analysis

The elimination rate constant (λ_z) was calculated by linear least-squares regression analysis of the terminal phase of the plasma drug concentration-time profile. The area under the plasma drug concentration-time curve from zero to infinity time (AUC) was calculated by the linear trapezoidal rule from the beginning of drug administration to the last datum point and with extrapolation to infinity. The area from the last datum point (C_t) to infinity was obtained as C_t/λ_z . Oral clearance was calculated from dose/AUC. The elimination half-life ($t_{1/2}$) was calculated from $0.693/\lambda_z$. $C_{\max}$ and $t_{\max}$ values were noted directly from the data.

Results are expressed as mean $\pm$ s.d. Differences between the two groups were assessed using Student's *t*-two-tailed test for unpaired data. Values of $P > 0.05$ were regarded as not significant.

Results and discussion

Side effects were noted by two subjects. One control subject was concerned about nausea which occurred at about 2.5 h after quinine administration. The plasma quinine concentration in this subject at 2.5 h post-dose was 4.3 mg l⁻¹. One (OCS user) had nausea and vomiting at 3 h after dosing. Her plasma quinine concentration at 3 h was 4.8 mg l⁻¹. These plasma quinine concentrations were within the range of those in subjects who reported no adverse reactions.

Figure 1 shows the mean plasma quinine concentration-time profile for control subjects and users of OCS. A summary of subject characteristics and kinetic variables for each group is given in Table 1. There were no significant differences ($P > 0.05$) between the OCS users and the control groups in $C_{\max}$, $t_{\max}$, AUC, oral clearance and the elimination half-life of quinine. Binding of quinine to plasma proteins was of the same order for the two groups (% unbound was 22.7% for controls and 22.4% for OCS users). These results suggest that quinine

Table 1 Quinine pharmacokinetics in control subjects and users of OCS

	Controls	Users of OCS*
<i>Subject characteristics</i>		
Number of subjects	7	7
Age (years)	26 $\pm$ 5** (19–35)***	28 $\pm$ 4 (24–34)
Weight (kg)	48 $\pm$ 5 (42–56)	49 $\pm$ 6 (41–59)
Duration of OCS use (years)	—	1.5 $\pm$ 0.7 (0.6–2.2)
Cigarette smoker	None	None
Alcohol drinker	None	None
<i>Quinine pharmacokinetic parameters</i>		
$C_{\max}$ (mg l ⁻¹)	5.6 $\pm$ 0.9 (4.8–7.0)	5.3 $\pm$ 1.0 (3.3–6.2)
$t_{\max}$ (h)	2.1 $\pm$ 0.9 (1.0–3.0)	1.4 $\pm$ 0.7 (0.75–2.5)
$t_{1/2}$ (h)	11.8 $\pm$ 2.7 (9.3–16.9)	12.5 $\pm$ 1.9 (9.6–15.1)
AUC (mg l ⁻¹ h)	88.3 $\pm$ 32.2 (64.6–159.6)	85.7 $\pm$ 24.4 (45.9–120.3)
Oral clearance (l h ⁻¹ kg ⁻¹)	0.125 $\pm$ 0.025 (0.075–0.148)	0.133 $\pm$ 0.055 (0.073–0.233)
Protein binding (% unbound)	22.7 $\pm$ 6.2 (15.1–34.0)	22.4 $\pm$ 6.1 (15.0–30.5)

* No significant difference ($P > 0.05$) between the controls and users of OCS in any derived parameters

** Data given as mean $\pm$ s.d.

*** Range of the value

Figure 1 Mean plasma quinine concentration following a single oral dose of 600 mg quinine sulphate in the control subjects (Δ) and OCS users ($\bullet$).

kinetics are not altered by co-administration of oral contraceptive steroids. A previous study has indicated that OCS had no major effect on the pharmacokinetics of mefloquine in patients with falciparum malaria (Karbwang *et al.*, 1988). The reason for the lack of interaction between OCS and quinine is unknown. It could be due to the low doses and differing steroids in the OCS preparations used which failed to inhibit metabolism of quinine. This is in spite of most steroids and quinine having been shown to be metabolized by the same isoenzyme, namely P-450_{NF} (Guengerich *et al.*, 1986a,b).

This study was supported by the Dean's Research Fund, Otago University Medical School, Dunedin, New Zealand. The authors thank Dr D. G. Ferry for his valuable discussion during preparation of this manuscript.

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(Received 27 June 1990,
accepted 2 October 1990)