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Cigarette smoking enhances the elimination of quinine

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The pharmacokinetics of a single dose (600 mg) of quinine sulphate were examined in a group of non-smokers (n = 10) and in heavy cigarette smokers (n = 10). The mean (± s.d.) oral clearance of quinine in smokers (0.189 ± 0.075 l h^{-1} kg^{-1}) was significantly greater than in non-smokers (0.107 ± 0.045 l h^{-1} kg^{-1}, $P < 0.01$). The unbound clearance of quinine which reflects activity of the drug-metabolizing enzyme, was considerably greater (1.5-fold) in the smokers than in the non-smoker subjects. The mean elimination half-life of quinine in smokers was 7.5 ± 1.4 (s.d.) h, significantly shorter ($P < 0.005$) than the mean value in non-smokers (12.0 ± 3.1 h). These results suggest that cigarette smoking enhances the elimination of quinine. The clinical significance of these findings is unknown but they indicate the need for caution in the administration of quinine to patients who are heavy cigarette smokers.

Keywords quinine smoking drug metabolism pharmacokinetics enzyme induction

Introduction

Some 42% of the world's population live in endemic malaria areas [1]. Each year more than two million people die from malaria. Use of antimalarial drugs is still the only effective way to save the patient's life. A major problem in the drug treatment of malaria is resistance of the malarial parasite to drugs. The emergence of chloroquine-resistant malaria in many parts of the world, including South Pacific islands, Southeast Asia, South America and Africa, has necessitated the continued therapeutic use of quinine [2, 3].

It is well recognised that many factors such as genetics, age, smoking, disease states and drug interactions can influence how the individual eliminates drugs from the body. This often leads to a dosage adjustment for the patients. Chronic cigarette smoking is known to enhance the biotransformation and modify the clinical effects of several drugs in man. The elimination of certain metabolized drugs such as antipyrine, phenacetin, chlordiazepoxide and theophylline is increased in cigarette smokers [4–12]. Cytochrome P450IA2 (CYP1A2) is a major enzyme catalysing the metabolism of phenacetin [13, 14] and theophylline [15–17]. Cigarette smoking induces mainly the P450IA enzyme family [13, 18, 19]. The human P450 forms responsible for biotransformation of quinine have not been identified. There is clearly no evidence *a priori* that smoking would enhance the elimination of quinine. However, quinine is a low clearance drug with a narrow therapeutic index, significant changes in the pharmacokinetics of quinine associated with cigarette smoking might have implications with respect to dosage in patients. Therefore, we conducted this study to determine the effects of smoking on quinine pharmacokinetics after a single oral dose of quinine (600 mg).

Methods

Subjects

Ethical approval for this study was obtained from the Human Ethics Committee, Thammasat University, Thailand, and the Otago Area Health Board Ethical Committee, Dunedin, New Zealand. All subjects gave written informed consent. Our subjects were 20 otherwise healthy, Thai men, ranging in age from 24 to 35 years. Ten men were non-smokers who served as controls and ten subjects were long-term cigarette smokers (over 10 cigarettes a day). All smokers had a history of 5 years or more cigarette consumption with a reported average use of 17 cigarettes per day (Table 1). Subjects were matched for age and body weight as shown in Table 1. At the beginning of the investigation they had a full clinical examination, together with haematological and biochemical screening tests, and urinalysis to confirm that clinically significant abnormalities, particularly relating to hepatic and renal function, were absent.

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During the 2 preceding weeks and the period of study none of the subjects took alcohol or any other drugs. The consumption of alcohol, tea and coffee was normal and was similar for the two groups.

Study protocol

After an overnight fast subjects took a single dose of 600 mg quinine sulphate (497 mg quinine base). The tablets were swallowed with 200 ml tap water and no food was allowed for the following 3 h. Blood samples (4 ml each) were drawn through a heparinized intravenous catheter (Venflon®) before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 30, 36 and 48 h after dosing. Blood was collected in heparinized test-tubes and plasma was separated immediately after collection. Urine was collected over the 48 h period following the administration of the drug and the volume recorded. All plasma samples and aliquots of urine were stored at −20° C until analysis.

Analytical procedure

Quinine concentrations in plasma and urine samples were determined by h.p.l.c. [20]. The detection limit of the method is 0.02 mg l^{-1}. The inter-assay coefficient of variation was less than 8% over the concentration range of 0.02 to 10 mg l^{-1}. Blank plasma collected prior to quinine administration (i.e., blank plasma) showed no endogenous sources of interference with the assay. Plasma protein binding of quinine was measured by equilibrium dialysis [21] using the Dianorm® apparatus. Plasma was dialysed against 0.1 M phosphate buffer (pH 7.4) at 37° C for 3 h. 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 changes was necessary.

Pharmacokinetic analysis

Plasma quinine concentration *vs* time data were analyzed by noncompartment methods. The elimination rate constant (λ_z) was calculated by linear least-squares regression analysis of the terminal phase of the log plasma drug concentration *vs* time profile. At least five data points were used to estimate λ_z. The area under the plasma drug concentration-time curve from zero to infinity time (AUC 0–∞) 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. The oral clearance relative to the bioavailability (F) of quinine was estimated as CL/F = dose/AUC 0–∞. The unbound clearance relative to the bioavailability (CLu/F) of quinine was calculated using the unbound quinine concentration data, i.e. CLu/F = dose/AUC 0–∞ (unbound). The elimination half-life ($t_{½}$) was calculated from $0.693/\lambda_z$. C_{max} and t_{max} values were noted directly from the data. Renal clearance (CL_R) was calculated as (amount excreted unchanged in urine between 0 and 48 h)/AUC (0–48 h).

Statistical analysis

Results are expressed as mean ± s.d. Statistical evaluation of results was performed using Student t-test for unpaired data. When variances of data were unequal, the comparison was assessed by Welch's test. In all cases, $P < 0.05$ was considered the minimum level of statistical significance.

Results

Details of the subjects studied are given in Table 1. All volunteers were in good physical condition as assessed by medical examination and laboratory tests.

The mean plasma quinine concentration *vs* time profiles after a single-dose oral administration for the smokers and non-smokers are illustrated in Figure 1. A monoexponential decline in the log-plasma drug concentration curves was apparent in every subject. Derived mean pharmacokinetic parameters are summarized in Table 1. There were no significant differences between smokers and non-smokers in C_{max} and t_{max}. The average values of C_{max} and t_{max} obtained in this study were in accord with published data [22–24]. The other pharmacokinetic parameters found in the present study are also comparable to those reported by others [2, 3, 22–24]. The mean AUC 0–∞ in smokers was significantly less than ($P < 0.01$) from that observed in the controls, non-smokers. The 10 non-smokers exhibit the typical marked variability in quinine disposition with CL/F values ranging from 0.049 to 0.217 l h^{-1} kg^{-1}. Cigarette smoking increases quinine clearance by 77%, as compared with the non-smokers. The difference in the oral clearance of quinine between the two groups was statistically significant ($P < 0.01$). The mean unbound clearance (CLu/F) of quinine in the subjects who smoked cigarettes was significantly greater than ($P < 0.005$) that observed in the non-smokers (Table 1). The mean $t_{½}$ of quinine in smokers was 7.5 h, which is significantly shorter than the mean value of 12.0 h in the non-smokers. Plasma protein binding of quinine in the smokers was similar to that in the non-smokers. The mean 48 h recovery (% of dose) of unchanged quinine in the urine was lower in the smokers ($P < 0.01$). The mean CL_R of quinine was similar in smokers and non-smokers.

Discussion

Polycyclic aromatic hydrocarbons, and perhaps other constituents of cigarette smoke, are potent inducers of certain drug metabolizing enzymes. Therefore it is not surprising that cigarette smoking is capable of modifying the pharmacokinetics of some drugs. Chronic smoking has been reported to increase the metabolism of many drugs such as phenacetin, antipyrine, theophylline, imipramine, pentazocine and propranolol [4–12, 25, 26]. The interaction between theophylline and cigarette smoking is one of the most clinically important effects of smoking because of the low therapeutic index of

Table 1 Subject details and quinine pharmacokinetics after an oral single dose 600 mg quinine sulphate in non-smokers and smokers

	Smoker (n = *10*)	*Non-smoker* (n = *10*)	P *value*	*Difference from smoker* Mean *difference*	*95% CI*
Subject details					
Age (years)	29.6 ± 3.7 (24–35)	30 ± 3.4[a] (25–35)[b]	NS	−0.4	−3.7 to 2.9
Weight (kg)	57.3 ± 5.8 (50–67.5)	57 ± 5.3 (48–65)	NS	0.3	−4.9 to 5.5
Number of cigarettes/day	17 ± 7 (10–30)	—	—	—	—
Quinine pharmacokinetic parameters					
C_{max} (mg l^{-1})	4.1 ± 1.2 (2.6–6.1)	5.0 ± 0.8 (3.4–6.3)	NS	−0.9	−1.9 to 0.6
t_{max} (h)	2.7 ± 0.6 (1.5–4)	3.4 ± 2.5 (1.5–10.0)	NS	−0.7	−2.4 to 1.0
$t_{½}$ (h)	7.5 ± 1.4 (5.4–9.6)	12.0 ± 3.1 (8.3–19.2)	0.001	−4.5	−6.8 to −2.2
CL/*F* (1 h^{-1} kg^{-1})	0.189 ± 0.075 (0.101–0.360)	0.107 ± 0.045 (0.049–0.217)	0.008	0.082	0.024 to 0.140
CL_u/F (1 h^{-1} kg^{-1})	1.54 ± 0.32 (1.10–2.09)	1.03 ± 0.25 (0.49–1.32)	0.001	0.51	0.24 to 0.78
AUC 0–∞ (mg l^{-1} h)	52 ± 19 (27–85)	93 ± 35 (38–169)	0.006	−41	−67 to −14
AUC 0–∞ (unbound) (mg l^{-1} h)	5.9 ± 1.0 (4.7–74)	9.1 ± 3.0 (6.6–16.9)	0.005	−3.2	−5.3 to 1.1
% Unbound	12.0 ± 2.7 (8.4–17.2)	10.3 ± 2.6 (8.1–17.3)	NS	1.7	−7.9 to 4.2
% dose excreted as unchanged quinine in the urine (0–48 h)	7.1 ± 2.4 (3.6–11.2)	10.2 ± 2.4 (7.1–15.2)	0.009	−3.1	−5.4 to −0.8
CL_R (1 h^{-1} kg^{-1})	0.014 ± 0.007 (0.004–0.026)	0.011 ± 0.003 (0.006–0.018)	NS	0.003	−0.002 to 0.008

[a]Data are presented as mean ± s.d.
[b]Range of the values.
NS: Not significantly different ($P > 0.05$).
CI: Confidence intervals for the mean differences.

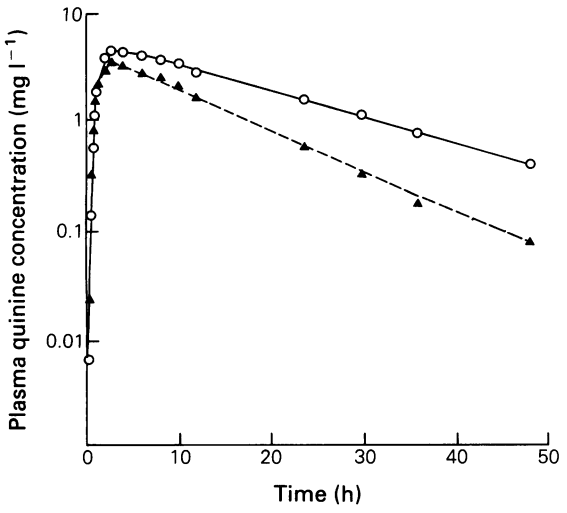

Figure 1 Mean plasma quinine concentration *vs* time profiles following administration of a single oral dose of 600 mg quinine sulphate in smokers (▲) and non-smokers (○).

theophylline [27]. The clearance of theophylline (body weight-normalized) in smokers is reported to be 1.42- to 1.66-fold greater than that observed in non-smokers [4, 6, 8]. These differences suggest that a larger theophylline daily dosage is required in patients who smoke cigarettes.

Like theophylline, quinine is extensively metabolized by hepatic oxidative biotransformation and is considered a low clearance drug with a narrow therapeutic index [2, 28]. Any significant increase in hepatic drug metabolism due to enzyme induction associated with cigarette smoking could enhance the rate of drug elimination leading to sub-therapeutic plasma drug concentrations. Our results show that the elimination of quinine is increased in cigarette smokers. The mean oral clearance in the smokers was 1.77-fold greater than in the non-smokers. This results in a shortened elimination half-life of quinine in the smokers (7.5 *vs* 12.0 h). The extent of the increase in clearance is of a similar order of magnitude to that reported for theophylline [4, 6, 8]. The higher oral

clearance in smokers indicates enhanced hepatic metabolism of quinine since the renal clearance of the drug was not altered. In addition, the unbound clearance of quinine which reflects activity of the drug-metabolizing enzyme, was considerably greater (1.5-fold) in the smokers than in the non-smoker subjects. This supports the suggestion that cigarette smoking induces the activity of hepatic enzymes that catalyse the metabolism of quinine. The increase in the clearance of quinine is possibly due to hepatic enzyme induction caused by the polycyclic aromatic hydrocarbons of cigarette smoke. It is well-known that cigarette smoking predominantly induces the P450IA enzyme family [13, 18, 19]. This is the same family responsible for theophylline metabolism and would explain the marked effects of smoking on theophylline elimination. *In vitro* hepatic microsomal studies carried out with quinine's diastereoisomer, quinidine, have shown that quinidine (and possibly quinine) is metabolized by a P450 isoenzyme that oxidizes nifedipine, *i.e.*, P450IIIA [29, 30]. Therefore one would predict that quinine metabolism would not be affected by smoking. Our results with quinine are therefore, surprising and question the validity of predictions based on results from *in vitro* hepatic microsomal studies with quinidine. The unexpected findings of this study point to caution when predictions are made from results obtained from different diastereoisomers. There is increasing evidence showing a stereoselectivity in drug metabolism [31–33].

One explanation would be that the metabolism of quinine is catalysed by P450IA enzymes which is why its elimination is enhanced by smoking. However, if the above assumption is true that quinine metabolism is mainly catalysed by P450IIIA, another explanation of our results would be that the P450IIIA enzyme in man is induced by cigarette smoking. Data from our recent experiments (unpublished) carried out using *in vitro* human liver microsomal preparations suggest that the formation of a major metabolite of quinine, likely to be 3-hydroxyquinine, is catalysed by P450IIIA isoenzyme. These results were based on experiments using quinidine metabolites as reference compounds for the identification of peaks in the h.p.l.c. analysis. The evidence indicating the major role of P450IIIA in the metabolism of quinine, was demonstrated by showing that the formation of 3-hydroxyquinine was diminished by the P450IIIA inhibitors including troleandomycin, midazolam and erythromycin [18, 19]. In addition, our results have shown that neither cDNA expressed CYP1A1 nor CYP1A2 catalyse the biotransformation of quinine, which indicate that these enzymes are not involved in the metabolism of quinine.

Previous studies with quinidine have shown that cigarette smoking does not induce any of the main pathways for quinidine metabolism [34, 35]. This gave contrasting results to our study on quinine and may be accounted for by the differences in subjects of the previous study [34]. Their subjects were patients with cardiac diseases, older age and only five smokers were examined. The possibility of differences in the metabolism of quinidine and quinine could not be ruled out. Unlike quinidine, there is little information on quinine metabolism in humans. This is probably because no authentic metabolites of quinine are available. Consequently no analytical assay has been developed to measure the various metabolites of quinine in biological samples. So, at this stage, we are unable to identify which particular metabolic pathway(s) is induced by cigarette smoking.

In conclusion, the study has shown that the elimination of quinine is enhanced in the cigarette smokers. Although there was a marked 77% increase in oral quinine clearance in the smokers compared with the subjects who do not smoke, the clinical significance of our findings remains to be reported. The enhanced drug elimination induced by cigarette smoking may produce sub-therapeutic plasma drug concentrations for antimalarial purposes. This is likely to occur upon multiple dosing of the drug in the patients, e.g. during the treatment of falciparum malaria. Sub-therapeutic drug concentrations may allow parasite survival and facilitate the development of resistance. Caution should be exercised in making decisions as to whether patients have a true drug-resistance problem. The determination of plasma quinine concentrations may be warranted to rule out a false drug-resistance.

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