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Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria

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1 Quinine dihydrochloride (10 mg or, in two patients, a loading dose of 20 mg kg^{-1}) was infused intravenously over 4 h in ten severely ill but conscious women with falciparum malaria complicating the third trimester of pregnancy.

2 Plasma quinine concentrations, measured spectrophotofluorimetrically after benzene extraction, fitted closely a single exponential decline after the intravenous infusion. These data were therefore fitted to a one compartment model: total apparent volume of distribution, V, 0.96 ± 0.27 l kg^{-1} (± s.d.), elimination half-time ($t_{½,z}$), 11.3 ± 4.3 h, total clearance, 1.22 ± 0.77 ml min^{-1} kg^{-1}. There was no relationship between arterial blood pressure and plasma quinine concentrations.

3 Eight women delivered of live infants while taking quinine, had placental cord plasma quinine concentrations from 1.0 to 4.6 mg l^{-1} (mean 2.4) which correlated significantly with maternal plasma quinine concentrations ($r = 0.78$, $t = 3.06$, $P < 0.05$). The mean (± s.d.) ratio of cord plasma to maternal plasma quinine concentration was 0.32 ± 0.14. Heart blood from a foetus aborted at term had a plasma quinine concentration of 2.8 mg l^{-1}; simultaneous maternal plasma quinine was 7.1 mg l^{-1} (ratio 0.39).

4 Breast milk quinine concentrations and milk to plasma ratios were 0.5–3.6 mg l^{-1} (mean 2.6) and 0.11–0.53 (mean 0.31) in twenty-five women who were breast-feeding and had taken oral quinine sulphate for 1–10 days (mean 4.0). Five women with more serious infections received intravenous quinine; breast milk quinine concentrations ranged between 0.5 and 8.0 mg l^{-1} (mean 3.4). Corresponding milk to plasma ratios were 0.11 to 0.32 (mean 0.21).

Keywords quinine pregnancy lactation pharmacokinetics

Introduction

Some authorities (WHO, 1984) now recommend that all patients with severe malaria should be treated with quinine. Inevitably, some of these will be pregnant women, in whom the pharmacokinetics and toxicity of quinine are uncertain. Quinine has been used to augment labour (Stirling & Hodge, 1961) and to induce abortion (Dilling and Gemell, 1929). Therapeutic use during pregnancy has been associated with congenital deafness (Taylor, 1934; West, 1938; Mosher,

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1938; Kinney, 1953; Robinson *et al.*, 1963), hypoplasia of the optic nerve (McKinna, 1966) and acute renal failure (Terplan & Javert, 1936; Lang & Jones, 1964). Women in late pregnancy are at considerable risk of developing hyperinsulinaemia and hypoglycaemia after intravenous quinine (White *et al.*, 1983c; Looareesuwan *et al.*, 1985a).

In the absence of an alternative antimalarial, there is an urgent need to know more about the use of quinine in pregnancy.

We therefore studied the acute pharmacokinetics of quinine in pregnant women with severe falciparum malaria and also measured the concentration of quinine in foetal and cord blood and in breast milk.

Methods

Patients

Patients were selected from those admitted to the Obstetric Unit, Pra Pokklao Hospital, Chantaburi, eastern Thailand. All had asexual forms of *Plasmodium falciparum* detectable in peripheral blood smears. Three groups were studied: the first were more than 29 weeks pregnant and had malaria of sufficient severity to require treatment with intravenous quinine. The second group had received quinine shortly before or while they were in labour. The third group received quinine while breast feeding. Patients or their relatives gave written informed consent to investigation and treatment. The study was approved by the Ethics Committee, Faculty of Tropical Medicine, Mahidol University, Bangkok.

Treatment

All patients admitted to the Obstetric Unit were seen by both an obstetrician and physician. Severely ill patients were given intensive care. Fluid replacement with intravenous 0.9% saline was adjusted according to the state of hydration. Feverish patients were cooled by tepid sponging and fanning. If the oral temperature exceeded 38.5° C despite these measures 500 mg of dipyrone (Bonpyrin) was given intramuscularly. No other drugs were given during the study period.

At Pra Pokklao Hospital chloroquine resistance is well established (Phillips *et al.*, 1984; Looareesuwan *et al.*, 1985a) and quinine was the only antimalarial available to treat falciparum malaria in pregnancy. Patients who required parenteral treatment were given quinine dihydrochloride (Government Pharmaceutical Organisation, Thailand) initial dose either 10 or 20 mg of the salt kg^{-1} (equivalent to 8.3 and 16.7 mg base kg^{-1}, respectively) diluted in 500 ml of 0.9% normal saline and infused over 4 h followed by further 4 h infusions of 10 mg of the salt kg^{-1} every 8 h. Patients received a loading dose (20 mg kg^{-1}) if they were assessed clinically as having life-threatening falciparum malaria and there was no possibility of quinine treatment in the preceding 48 h. Convalescent patients and those with uncomplicated malaria took the maintenance dose as quinine sulphate tablets until a 7-day course was completed.

Pharmacokinetics

Blood was sampled through an indwelling intravenous 'Teflon' catheter, which was kept patient with heparinised saline, at 0, 0.5, 1, 2, 3, 4 h after starting the quinine infusion and 0.25, 0.5, 1, 2, 3, 4, 5, 6 h after it had finished. The blood was placed immediately in plastic lithium heparin tubes and centrifuged at 300 *g* for 10 min. Plasma was stored at −20° C until analysed. Plasma quinine elimination half time was calculated from a semilogarithmic plot of quinine concentration against time. The total apparent volume of distribution of the base (V) was calculated from the equation:

$$V = \frac{R_{inf}\,(1-e^{-kt})}{kC}$$

which describes a one compartment model for quinine disposition where R_{inf} is the rate of infusion (total dose of quinine base per kilogram body weight divided by the time of infusion), k the first order elimination rate constant (h^{-1}), C the plasma concentration (mg l^{-1}) at the end of the infusion extrapolated back from the linear plot of log plasma concentration against time and t is the duration of the infusion (h). Clearance was calculated as the product of k and V.

Cord blood and breast milk samples

Heparinised plasma was obtained from umbilical vein blood taken immediately after delivery of the placenta. Breast milk samples were obtained by either manual expression or were collected from the contralateral breast during suckling. Breast milk and plasma samples, separated from maternal blood collected simultaneously, were frozen immediately.

Quinine assay

Quinine was measured by the benzene extraction fluorescence method (Cramer & Isaaksson,

1963). After extraction, fluorescence was read with an Aminco-Bowman spectrofluorimeter which was calibrated for each run. There was a linear relationship between spectrophotofluorimetric readings and plasma quinine concentrations up to 30 mg l^{-1} and breast milk concentrations up to at least 8 mg l^{-1}. The intra-assay coefficient of variation was 3% for plasma concentrations between 5 and 15 mg l^{-1} and 6% for milk concentrations between 1 and 8 mg l^{-1}. Absolute fluorescence values of plasma compared with milk standards prepared and assayed in parallel differed by less than 3%. The lower limit of assay sensitivity for quinine was 0.5 mg l^{-1}.

Results

Quinine pharmacokinetics

Ten patients aged 17–41 years (mean 25.5) and weighing 46–75 kg (mean 54.8) were studied. All patients were severely ill but conscious. Admission temperatures ranged between 37.5 and 39.9° C (mean 38.1). Initial parasite counts were 318–365,640 (median 60,327) μl^{-1}. Calculated pharmacokinetic variables are shown in Table 1. Plasma quinine concentrations at the end of the first infusion were between 6.9 and 18.7 mg l^{-1} (mean 10.4) and followed a single exponential decline.

Toxicity

Arterial blood pressure before treatment ranged between 90/60 and 120/70 mm Hg (means 106 systolic, 69 diastolic). The maximum individual fall in systolic blood pressure ranged between 0 (four cases) and 26 mm Hg (mean 8) and occurred 30 min to 4 h after starting quinine. Blood pressure at the end of the infusion was 87/56 to 110/70 mm Hg (means 100 systolic, 67 diastolic). There was no correlation between either systolic or diastolic blood pressure and plasma quinine concentration and there was no consistent change in pulse rate. No patient developed painful uterine contractions or went into labour during the intravenous infusion of quinine. Clinical details and cardiotocographic and glucose-insulin changes are reported elsewhere (Looareesuwan *et al.*, 1985a).

Cord blood quinine concentrations

Eight women aged 16–32 years who were delivered of live infants 1–6 days after starting quinine therapy had placental cord plasma quinine concentrations between 1.0 and 4.6 mg l^{-1} (mean 2.4). Corresponding maternal plasma quinine concentrations are shown in Figure 1. Mean ± s.d. ratio of cord plasma to maternal plasma quinine concentration was 0.32 ± 0.14. There was a significant correlation ($r = 0.78, t = 3.06, P < 0.05$) between cord blood and maternal plasma quinine concentrations. Plasma quinine concentration in heart blood sampled from a foetus aborted at term during an attack of malaria was 2.8 mg l^{-1}. Simultaneous plasma quinine concentration in the mother, who had received intravenous quinine for 24 h, was 7.1 mg l^{-1} (ratio 0.39).

Breast milk quinine concentrations

Breast milk was collected from 30 women aged 16–39 years who began lactating during the previous 24 h (three cases) and up to 10 days previously. Five patients requiring parenteral

Table 1 Quinine pharmacokinetics in pregnancy

Patient	*Dose (mg kg^{-1})*	$t_{½,z}$	V *(l kg^{-1})*	*CL (ml min^{-1} kg^{-1})*
1	10	10.1	0.80	0.92
2	10	9.3	1.22	1.52
3	10	6.8	1.04	1.76
4	10	12.4	0.90	0.84
5	20	9.7	0.94	1.12
6	10	15.5	0.76	0.57
7	10	9.6	1.38	1.67
8	10	4.9	1.24	2.91
9	10	18.3	0.85	0.54
10	20	16.1	0.46	0.33
Mean ± s.d.		11.3 ± 4.3	0.96 ± 0.27	1.22 ± 0.77

$t_{½,z}$ = plasma half-time
V = total apparent volume of distribution
CL = total clearance

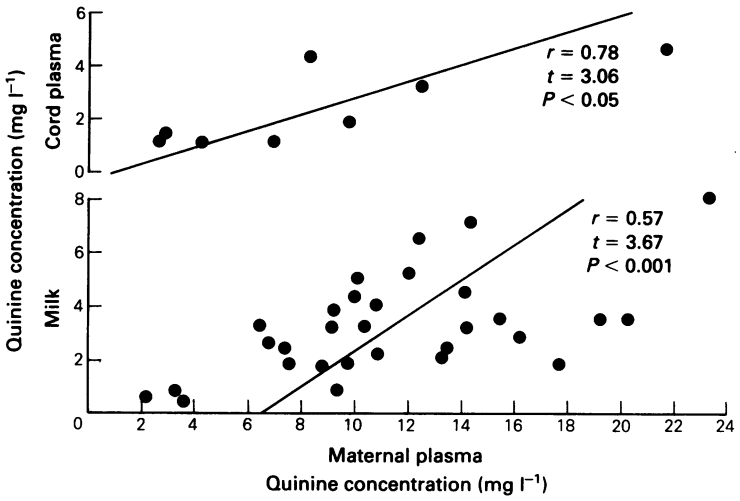

Figure 1 Simultaneous umbilical vein (cord) plasma and maternal plasma, and milk and maternal plasma concentrations in patients with falciparum malaria.

therapy, in whom breast milk concentrations were 0.5–3.6 mg l^{-1} (mean 2.6) and milk to plasma ratios were 0.11–0.32 (mean 0.21), had received 2–7 doses of quinine intravenously by the time samples were collected.

Breast milk concentrations in the rest, who had taken oral quinine sulphate for 1–10 days (mean 4.0) were 0.5–8.0 mg l^{-1} (mean 3.4); milk to plasma ratios were 0.11–0.53 (mean 0.31). Breast milk pH in 14 patients ranged between 7.0 and 8.1 (mean 7.5). There was no correlation between breast milk quinine concentration and pH. Three patients who had just started lactating produced colostrum containing 0.4, 0.9 and 1.9 mg l^{-1} of quinine with colostrum to maternal plasma ratios of 0.11, 0.26 and 0.25, respectively.

Discussion

Quinine was used successfully to cure malignant tertian fever in pregnancy when no other drugs were available (Maxwell, 1908). Most early workers agreed that the danger of untreated malaria exceeded the risk of giving quinine, although the drug was traditionally regarded as an abortifacient. However the doses of quinine used to induce or augment labour were 2–3 times greater than those used to treat malaria (Dilling & Gemmell, 1929; Stirling & Hodge, 1961). Since chloroquine-resistant falciparum malaria still responds to quinine there has been a major revival in the use of this drug throughout the malarious regions. In most of Asia and South America quinine is the mainstay of therapy while in Thailand, where chloroquine resistance is intense, there is no other effective drug available for the parenteral treatment of severe infections.

The pharmacokinetics of quinine in the pregnant women from this study differed significantly from those previously reported in adults with cerebral malaria (White *et al.*, 1982) (Table 2). Compared with uncomplicated infections in non pregnant adults, total apparent volumes of distribution were generally smaller and elimination was more rapid in the pregnant women. Systemic clearance was approximately the same. Physiological changes of pregnancy, including expansion of total body water and plasma volume are thought to account for an increase in the V of some drugs (Cummings, 1983). However, alterations in plasma protein and tissue binding associated with plasmodial infection (Silamut *et al.*, 1985) and pregnancy itself (Perucca & Crema, 1982) may have been responsible for the reduction in V observed in these pregnant women with malaria. Similar quinine kinetics have been reported during acute attacks of malaria in children (Sabcharoen *et al.*, 1982). Patients with cerebral malaria have a smaller V for quinine and lower systemic clearance compared with those with less severe infections but elimination is unchanged (Table 2). The pregnant women reported here were severely ill but conscious and so are not strictly comparable to patients studied previously (White *et al.*, 1982). However it is possible that further contraction of the V for quinine could occur in pregnant women with cerebral malaria.

Table 2 Comparison of quinine pharmacokinetics in *Plasmodium falciparum* malaria

	1	*Uncomplicated*	*2*	*Cerebral*	*1* vs *2*	*3*	*Pregnancy*	*1* vs *3*
	n	*Mean* ± *s.d.*	n	*Mean* ± *s.d.*	P	n	*Mean* ± *s.d.*	P
$t_{½,z}$ (h)	13	16.0 ± 7.0	25	18.2 ± 9.7	NS	10	11.3 ± 4.3	< 0.02
V (l kg^{-1})	11	1.67 ± 0.34	18	1.18 ± 0.37	< 0.002	10	0.96 ± 0.27	< 0.001
CL (ml min^{-1} kg^{-1})	11	1.35 ± 0.60	18	0.92 ± 0.42	< 0.05	10	1.22 ± 0.77	NS

Data in columns (1) and (2) are from White *et al.* (1982).
n = number of patients
P = significance (two tailed *t*-test)
NS = not significant

These pharmacokinetic data have several important implications for the intravenous therapy of falciparum malaria complicating pregnancy. Quinine should be infused slowly over at least 4 h. Used in this way cardiovascular toxicity even with a loading dose of 20 mg kg^{-1} is minimal. Slow distribution from a contracted central compartment (Chantavanich *et al.*, unpublished observations) will result in toxic blood concentrations if quinine is infused too rapidly. For the same reason rapid injection over 10–15 min is particularly dangerous (White *et al.*, 1983a). Yet this potentially lethal practice is still recommended by some, although its dangers were recognised over 60 years ago (Brahmachari, 1922). Hall (1982, 1985) has advocated reducing quinine dosage in severe malaria and increasing the dosing interval to 12 or 24 h. Our pharmacokinetic data indicate that such regimens would produce unsatisfactory plasma quinine profiles. If doses of 5 mg salt kg^{-1} are given at 8 h intervals or less frequently (Hall, 1982), peak concentrations will not exceed the minimum inhibitory concentration of quinine for Thai strains of *P. falciparum* for more than 48 h in many patients (White *et al.*, 1983b). This could have disastrous consequences for pregnant women who already have a substantial risk of dying (Looareesuwan *et al.*, 1985a). Where *P. falciparum* is more sensitive to quinine, lower doses than those used here may be adequate therapy but this remains to be proved. In pregnant women with severe falciparum malaria, as in cerebral malaria, it may be necessary to reduce the dose of quinine after 3 days of treatment if there is no clinical improvement in order to prevent a continued rise in blood concentrations (White *et al.*, 1982). In this case the dose, but not the frequency of administration, should be reduced.

Symptoms of cinchonism (variable degrees of tinnitus, deafness, dysphoria, nausea and sometimes vomiting) are common whenever plasma quinine concentrations exceed 5 mg l^{-1} (White *et al.*, 1982). This predictable, dose related toxicity is acceptable during treatment of a life threatening infection and should not limit treatment.

Death from cerebral malaria usually occurs within 48 h of admission to hospital and many patients die on the first day (Warrell *et al.*, 1982). Cerebral malaria complicating pregnancy has a particularly grave prognosis both for the mother and the foetus (Looareesuwan *et al.*, 1985b). Since antimalarials are the only treatment of proven benefit, dosage regimens should aim to achieve therapeutic drug concentrations as quickly and safely as possible. Intravenous quinine fusions should be given slowly but if the minimum inhibitory concentration of quinine for Southeast Asian strains of *P. falciparum* (Chongsuphajaisiddhi *et al.*, 1981) is to be reached and sustained during the early critical phase of treatment, a loading dose, without reduction in maintenance doses, is necessary. Fears that in late pregnancy these quinine doses would start uterine contraction or kill the foetus have not been substantiated (Looareesuwan *et al.*, 1985a). Although quinine stimulated insulin release is an important toxic effect, the benefits of chemotherapy with quinine clearly overshadow the risks of malaria treated inadequately.

In experimental animals, quinine damages the cochlea and auditory nerve (West, 1938; Mosher, 1938) but the risk of congenital deafness in the children of mothers given therapeutic doses of quinine is uncertain (Taylor, 1934; Kinney, 1953). Recent epidemiological observations did not show a teratogenic effect (Heinonen *et al.*, 1977) although in late pregnancy quinine is definitely distributed to the foetus. By the third trimester, the foetal pancreatic beta cell is functional (Bassett & Fletcher, 1982) so quinine, if present in sufficient concentrations, could trigger insulin release thus causing or exacerbating foetal hypoglycaemia. In malaria patients the teratogenic consequences of hypoglycaemia (Wickes, 1954) and the infection itself are unknown.

Quinine was present in breast milk at concentrations of 0.5–8.0 mg l^{-1}, considerably higher

than those cited in two recent reviews (O'Brien, 1974); Chow & Jewesson, 1985). The partition of drugs between plasma and breast milk is influenced in part by pH differences (Berlin, 1981). Weakly basic drugs tend to be concentrated in acid milk but no effect of pH on breast milk quinine concentrations could be detected in this study. Our results show that the total dose of quinine excreted in breast milk will usually be less than 2–3 mg day^{-1}. Hypersensitivity reactions such as thrombocytopenia (Bottiger & Westerholm, 1973) could be triggered by such doses. Other toxic effects are unlikely although the metabolic capacity of the liver in neonates, particularly those who are premature, may be limited.

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