J. Pharm. Pharmacol. 1990, 42: 428–432
Recieved October 17, 1990

The Effect of Malaria Infection on the Disposition of Quinine and Quinidine in the Rat Isolated Perfused Liver Preparation

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Abstract—The effect of malaria on the disposition of quinine and quinidine was studied in livers isolated from young rats infected with merozoites of *Plasmodium berghei*, a rodent malaria model, and non-infected controls. Following bolus administration of quinine (1 mg) or quinidine (1 mg) to the 100 mL recycling perfusion circuit, perfusate was sampled (0–4 h) and plasma assayed for quinine and quinidine by HPLC. Higher quinine (AUC: 6470 ± 1101 vs 3822 ± 347 ng h mL^{-1}, $P < 0.001$) and quinidine (AUC: 6642 ± 1304 vs 4808 ± 872 ng h mL^{-1}, $P < 0.05$) concentrations were observed during malaria infection (MI). MI resulted in decreased quinine clearance (CL) (0.33 ± 0.08 vs 0.64 ± 0.09 mL min^{-1} g^{-1}, $P < 0.001$) and volume of distribution (Vd) (53.0 ± 13.3 vs 81.2 ± 23.7 mL g^{-1}, $P < 0.05$) but no significant change in elimination half-life ($t_{\frac{1}{2}}$) (1.93 ± 0.6 vs 1.37 ± 0.25 h, $P > 0.05$). With quinidine, however, MI resulted in decreased CL (0.38 ± 0.16 vs 0.64 ± 0.09, $P < 0.05$) with no change in Vd and a significant increase in $t_{\frac{1}{2}}$ (1.62 ± 0.42 vs 0.88 ± 0.22, $P < 0.01$). In summary, the hepatic disposition of quinine and quinidine is altered in the malaria-infected rat.

The disposition of extensively metabolised drugs may change during malaria since there is clinical and pathological evidence of liver damage associated with infection (Boonpucknavig et al 1984; Hollingdale 1985), changes in hepatic ultrastructure (Rosen et al 1967) and perturbations in hepatic enzyme activities (Sharma et al 1978; Patwari et al 1979). With respect to hepatic drug metabolizing enzyme systems, both phase I processes as determined by hydroxylation and demethlyation (McCarthy et al 1970; Alvares et al 1984; Saxena et al 1987) and phase II conjugation reactions (Emundianughe et al 1985) are suppressed during malaria infection in rodents.

Clinical studies suggest that the pharmacokinetics of quinine and its diastereoisomer quinidine are altered during malaria (White et al 1982; Phillips et al 1985). However, the role of hepatic impairment in the pharmacokinetic changes seen clinically is unclear. Although *Plasmodium falciparum* has rapidly developed resistance to many commonly used antimalarial drugs, quinine used either singly or in combination with tetracycline still remains effective and is the drug of choice in the treatment of severe falciparum malaria. Quinidine is effective against the asexual blood stages of all forms of malaria and appears to be more potent than quinine (Phillips et al 1985). In view of reports of the emergence of quinine-resistant strains (Chongsuphajaisiddhi et al 1981; Bunnag & Harinasuta 1987), quinidine will prove an invaluable addition to the armamentarium of antimalarial drugs.

Although the pharmacokinetics of the cinchona alkaloids, including quinine and quinidine were studied extensively in the 1940's, the analytical techniques available were unsatisfactory and the effect of disease state on drug disposition was poorly understood. In this paper, we report on the effect of malaria infection on the pharmacokinetics of quinine and quinidine in normal and infected livers from rats infected with merozoites of *P. berghei*, a rodent malaria model, in the rat isolated perfused liver preparation. This experimental model enables investigation on a single organ and is suited to the study of the hepatic handling of drugs. It has been used to a limited extent to study hepatic elimination of drugs during disease states (Mihaly et al 1987a, b).

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Materials and Methods

The rat isolated perfused liver preparation

Livers were isolated by standard techniques (Pang 1984) following anaesthesia with sodium pentobarbitone (60 mg mL^{-1}; 60 mg kg^{-1} i.p.). These involved cannulation of the bile duct with polythene tubing (o.d. = 0·80 mm, i.d. = 0·40 mm) and clearance of connective tissue surrounding the liver, before cannulation of the portal vein (Argyle Medicut, 20G) which was then flushed with heparinized saline (100 u mL^{-1}). The inferior vena cava was cannulated with polythene tubing (o.d. = 2·42 mm, i.d. = 1·67 mm). The liver was then removed and placed on a glass platform inside a humidified cabinet maintained thermostatically at 37°C.

Perfusate (100 mL, pH 7·4) comprised 1% w/v bovine serum albumin (Sigma Chem, Poole, UK), 0·1% D-glucose (BDH Chem, Poole, UK) and 10% v/v washed human red-blood cells in Krebs-Henseleit buffer. Perfusate was pumped at a constant flow (5 mL min^{-1}) in a recycling system. The principal indices of liver viability were steady oxygen consumption over 4 h, sustained bile flow (over 2·5 h), perfusion back pressure (8–12 cm H_2O) and normal visual appearance.

Study design

Male Sprague-Dawley rats (100–150 g) were infected with *P. berghei* malaria by i.p. injection of a suspension of merozoites. Parasitaemia as determined by Giemsa stained thin

blood film was allowed to develop to a level of 20–50% before the removal of the livers for perfusion experiments. Control animals were non-infected age, weight and sex matched Sprague-Dawley rats.

The livers of five malaria infected rats (mean parasitaemia 38±8%) and five control livers were used to assess the disposition of quinine during malaria. The study design was essentially the same for experiments with quinidine except that the mean parasitaemia of infected livers was 29±7%.

Quinine dihydrochloride or quinidine hydrochloride monohydrate (Sigma Chem, Poole, UK) was introduced into the perfusate reservoir of both control and malaria infected liver preparations as an aqueous solution (0·1 mL; 100 mg mL^{-1}). Livers were perfused for 4 h. Samples of perfusate (1·0 mL) were removed predose and at 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min and perfusate plasma removed following centrifugation (13000 rev min^{-1}). After the removal of each sample an equal volume of drug-free perfusate was added to the reservoir. Bile was collected hourly during each experiment. Perfusate plasma and bile were frozen and stored at −20 C until analysis by HPLC.

Drug analysis

The concentration of quinine (or quinidine) in samples of perfusate were estimated by a selective and sensitive HPLC procedure adapted from Mihaly et al (1987c).

Instrumentation and chromatography

The Spectra-Physics liquid chromatograph (Spectra Physics Ltd, Hemel Hempstead, UK) consisted of an SP 8770 solvent delivery system, an SP 8750 organizer module equipped with a Rheodyne valve injection system and an LC 871 variable wavelength UV absorbance detector operating at 254 nm. Separation was achieved on an ultrasphere C_{18} (5 μm, 150 mm × 46 mm i.d.) reversed phase stainless steel column (Beckman Instruments, High Wycombe, Bucks, UK). The mobile phase consisted of water-acetonitrile (95:5 v/v) containing triethylamine (1%) adjusted to pH 2·50 with orthophosphoric acid and flowing at 1·5 mL min^{-1}.

Sample preparation

To a sample of perfusate plasma (500 μL) containing an aqueous solution of the internal standard chlorpheniramine maleate (25 μL, 1250 ng) (ICI Pharmaceuticals, Alderley Edge, UK) was added 500 μL of acetone. The mixture was centrifuged (4000 rev min^{-1}, 5 min) and following the addition of ammonia solution (500 μL), the supernatant was transferred to another set of tubes and extracted with hexane–ethyl acetate (10 mL 1:1 v/v) by mechanical tumbling for 20 min. After centrifugation (3000 rev min^{-1}, 20 min) the separated organic phase was evaporated to dryness under a gentle stream of nitrogen at 35°C. The residue was reconstituted in mobile phase (50 μL) and 20 μL injected on the column. All glassware was treated with dichlorodimethylsilane (5% v/v in toluene) to minimize drug adsorption.

Data analysis

Data in the text and tables are presented as mean ± s.d. and graphically as mean ± s.e.m. Coefficients of variation (CV) for the calculation of assay precision were obtained from the ratio of the standard deviation to the mean. Perfusate plasma elimination half-life was calculated by regression analysis of the log linear portion of the perfusate plasma concentration versus time curve. Other pharmacokinetic parameters were calculated using standard, model-independent formulae (Rowland & Tozer 1980). Statistical comparisons were made using unpaired Student's *t*-test, accepting $P < 0.05$ as significant.

Results

Liver viability

In this study, the principal physiological indices of liver viability were not significantly different between the control livers and the malaria-infected livers in both studies (Table 1).

Analysis of quinine and quinidine in perfusate plasma

In this study concentrations of either quinine or quinidine were estimated separately. Analytical recoveries for quinine, quinidine and the internal standard in spiked perfusate plasma samples were 69, 75 and 81%, respectively. Within-day and day-to-day coefficients of variation (CV) were 6–7 and 7–8%, respectively, for both quinine and quinidine. All calibration curves in the range 10–20000 ng mL^{-1} were linear (r = 0·999) for both drugs in perfusate plasma samples. The lower limit of sensitivity for the analysis of quinine and quinidine in perfusate plasma (500 μL) was 10 ng mL^{-1}.

In this analytical procedure there was no chromatographic interference from other related antimalarial drugs or derivatives of quinine or quinidine, cinchonine, cinchonidine, dihydrocinchonine and dihydrocinchonidine. A number of polar metabolites of quinine and quinidine have been identified (Brodie et al 1951; Barrow et al 1980) but under the conditions described these compounds would be expected to elute with the void volume (Mihaly et al 1987c).

Table 1. The principal indices of liver viability monitored in the IPRL preparation in both studies.

Parameter	Control	Quinine MI	Control	Quinidine MI
Oxygen consumption ($\mu mol\ O_2\ (g\ liver)^{-1} min^{-1}$)	2·1±0·7	2·3±0·5*	1·9±0·5	2·0±0·4*
Bile Flow ($mL\ h^{-1}$)	0·55±0·11	0·58±0·09*	0·46±0·08	0·47±0·07*
Back pressure (cm H_20)				
(a) initial (1 h)	8·4±1·3	8·7±1·5*	8·0±1·2	8·1±1·3*
(b) final (4 h)	12·1±1·8	12·5±1·4*	11·8±1·9	12·1±1·4*

MI: Malaria infected livers. * = $P > 0.05$.

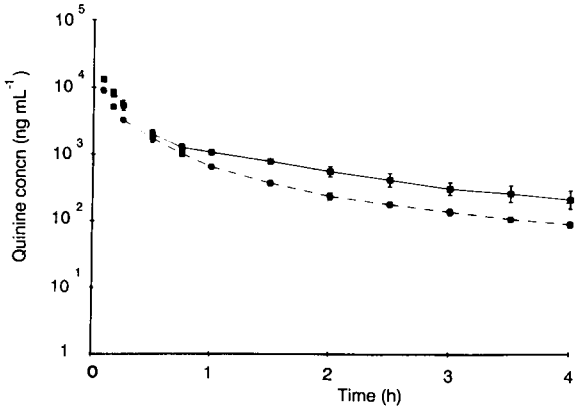

FIG. 1. Mean perfusate concentration-time profiles for quinine in control and malaria infected rat isolated perfused liver preparation. —— infected, - - - control.

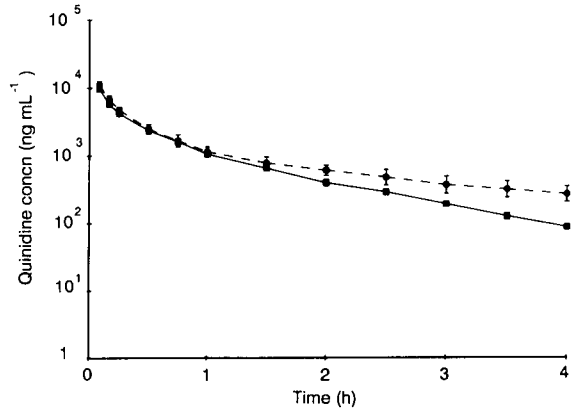

FIG. 2. Mean perfusate concentration-time profiles for quinidine in control and malaria infected rat isolated perfused liver preparation. - - - infected, —— control.

Disposition of quinine and quinidine in the isolated perfused rat liver preparation

Following the administration of either quinine or quinidine to the reservoir simulating bolus systematic dosage, perfusate plasma concentration of each drug declined biexponentially (Figs 1, 2). Initially, the decline in drug concentration is due to hepatic uptake of quinine and quinidine. Thereafter, drug concentrations declined monoexponentially, reflecting drug elimination.

Tables 2 and 3 list mean (s.d.) pharmacokinetic parameters for both quinine and quinidine. In the case of quinine, malaria infection results in a significant decrease in quinine clearance (CL) (48%) and volume of distribution (Vd) (35%). The combined effects of these changes tended to produce a prolongation of the elimination half-life ($t_{\frac{1}{2}}$) in infected livers,

Table 2. Pharmacokinetic parameters of quinine in perfused livers from control and infected groups of rats.

Parameter	Control	Infected	Significance P
AUC (ng h mL^{-1})	3822±347	6470±1101	<0·001
CL (mL min^{-1} (g liver)$^{-1}$)	0·64±0·09	0·33±0·08	<0·001
Vd (mL (g liver)$^{-1}$)	81·2±23·7	53·0±13·3	<0·05
$t_{\frac{1}{2}}$ (h)	1·37±0·25	1·93±0·60	>0·05

Table 3. Pharmacokinetic parameters of quinidine in perfused livers from control and infected groups of rats.

Parameter	Control	Infected	Significance P
AUC (ng h mL^{-1})	4808±872	6642±1304	<0·05
CL (mL min^{-1} (g liver)$^{-1}$)	0·64±0·09	0·38±0·16	<0·05
Vd (mL (g liver)$^{-1}$)	48±13·3	55±32·5	>0·05
$t_{\frac{1}{2}}$ (h)	0·88±0·22	1·62±0·42	<0·01

although this did not reach significance ($0{\cdot}1 > P > 0{\cdot}05$). A significant negative relationship ($r = -0{\cdot}898$, $P < 0{\cdot}02$) was observed when quinine CL was correlated with the severity of malaria infection (Fig. 3) although Vd ($r = -0{\cdot}493$, $P > 0{\cdot}1$) and $t_{\frac{1}{2}}$ ($r = 0{\cdot}651$, $P > 0{\cdot}1$) were not. However, with respect to quinidine, malaria infection resulted in a significant decrease in CL (41%) without any change in Vd. This resulted in a significant increase in $t_{\frac{1}{2}}$ (84%) values in the infected livers which was related linearly ($r = 0{\cdot}810$, $P = 0{\cdot}05$) to the graded effect of the severity of the parasitaemia produced (Fig. 4). There was no significant correlation between quinidine CL ($r = -0{\cdot}789$, $0{\cdot}1 < P > 0{\cdot}05$) (Fig. 5) or Vd ($r = -0{\cdot}516$, $P > 0{\cdot}1$) and severity of malaria infection.

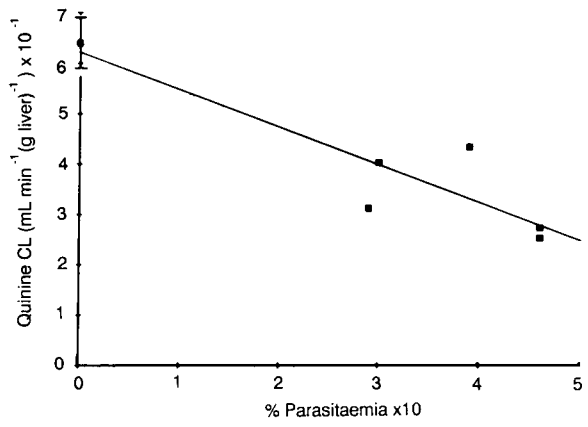

FIG. 3. Plot of quinine clearance, in malaria infected isolated perfused rat livers, against percentage parasitaemia ($r = -0{\cdot}898$, $P < 0{\cdot}02$, $n = 6$). The mean ± s.e.m. clearance in control liver is also presented.

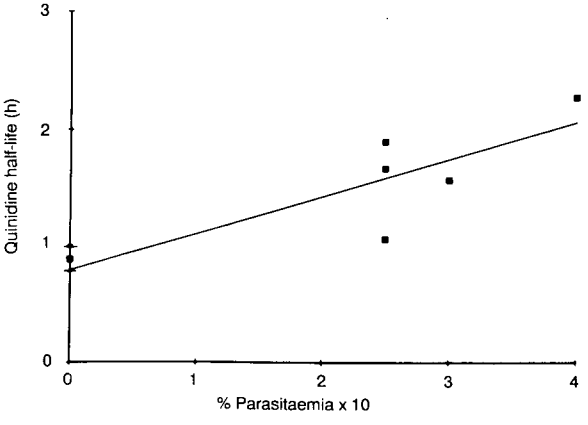

FIG. 4. Plot of the elimination half-life of quinidine, derived from malaria infected isolated perfused rat livers against percentage parasitaemia ($r = 0{\cdot}81$, $P = 0{\cdot}05$, $n = 6$). The mean ± s.e.m. elimination half-life in control liver (i.e. zero parasitaemia) is also presented.

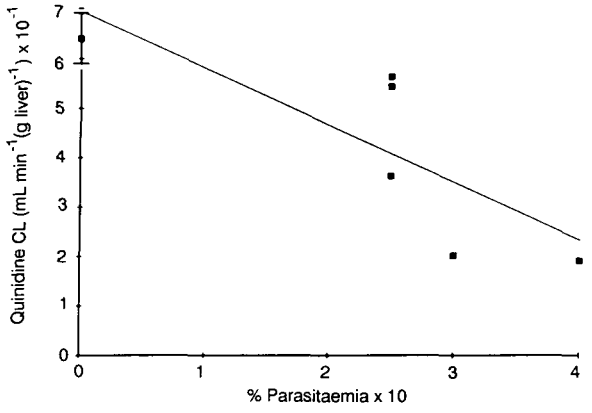

FIG. 5. Plot of quinidine clearance, in malaria infected perfused rat livers, against percentage parasitaemia. ($r = -0{\cdot}789$, $0{\cdot}05 < P < 0{\cdot}1$, $n = 6$). The mean ± s.e.m. clearance in control liver is also presented.

Discussion

The pathophysiology of malaria is complex and the liver is a major target organ during the exoerythrocytic and erythrocytic cycles of the infection. During the exoerythrocytic stage, the rupture of the hepatocyte, which results from sporozoite invasion, produces minimal damage to the liver cells. Alvares et al (1984) showed that the impairment of drug metabolizing enzymes produced in mice was not related to the exoerythrocytic stage of *Plasmodium berghei* infection and not associated with the presence of sporozoite antigen or residence of parasites in the liver. However, there is insufficient evidence to conclusively state that drug metabolism is unaffected by the exoerythrocytic stage of malaria.

The erythrocytic cycles result in severe haemolysis of the host red blood cells. The cellular and parasite materials released in the circulation are phagocytosed by Kupffer cells and ultimately cause the liver to become discoloured and enlarged. Numerous studies concerning this blood stage of the infection have demonstrated decreased hepatic cytochrome P450 and associated monoxygenase activity in *P. berghei* (McCarthy et al 1970; Sharma et al 1978; Alvares et al 1984) and in *P. yoelli nigeriensis* (Saxena et al 1987) infection. Another underlying mechanism which may disturb the microsomal mixed function oxidase system is the accumulation of haem in the form of malaria pigment, haemozoin, in hepatocytes as intravenous administration of haem or haemin in rhesus monkeys and mice decreases the activity of cytochrome P450 and associated components (Sweeney et al 1972; Muller-Eberhard et al 1983). Accumulation of iron complexes can occur during infection due to changes in host biochemistry, especially ferrokinetics, which have been reported to alter in plasmodial infection (Srichaikul et al 1976; Singh et al 1985).

In the present study, we have examined the effect of malaria infection on the hepatic handling of drugs using a rat isolated perfused liver preparation. Since quinine and quinidine are extensively metabolized by hepatic enzymes to 2- and 3-hydroxylated derivatives (Brodie et al 1951) and are low to intermediate clearance drugs, it might be expected that their hepatic clearance will be affected by changes in the hepatic enzyme activity produced by malaria infection. Impairment of microsomal drug metabolizing activities has also been reported to occur during other parasitic diseases such as filariasis (Srivastava et al 1986), amoebiasis (Kumar et al 1983) and fascioliasis (Facino & Carini 1982).

In both of the present studies, significantly higher quinine and quinidine concentrations were observed in the livers from infected rats as indicated by the increased AUC values compared to controls of 69 and 38%, respectively. In the case of quinidine, malaria infection resulted in a significant decrease in CL without any change in Vd and these changes are translated as a significant increase in $t_{\frac{1}{2}}$ in the livers from infected rats as compared to control. Since there is a linear relationship between $t_{\frac{1}{2}}$ of quinidine and the graded effect of the severity of the parasitaemia produced in the experimental livers, the higher the parasitaemia, longer $t_{\frac{1}{2}}$ of quinidine would be expected. In contrast, malaria infection resulted in a significant decrease in quinine CL and Vd without any significant changes in $t_{\frac{1}{2}}$ in the livers from infected rats. In addition, the extent to which quinine CL was impaired was related to the severity of malaria infection; the higher the parasitaemia, the greater the decrease in quinine CL. The reduction in CL presumably reflects impairment of hepatic drug metabolism via cytochrome P450 hydroxylation the principal route of quinine metabolism. The reduction in Vd is much more difficult to explain and suggests that quinine accumulation in hepatic tissue is reduced during infection; this may be related to the disposition of haem degradation products within the liver. Since, in our investigation, the albumin concentration in the perfusate mixture is kept constant, the change in Vd in the quinine study cannot be related to changes in circulating proteins. However, in clinical situations, malaria causes an increase in the concentration of serum globulin (presumably α_1-acid glycoprotein; Silamut et al 1985) to which both quinine and quinidine bind (Mihaly et al 1987d). This has been proposed to explain the contraction of Vd (White et al 1982) seen in the clinical situation.

However, haemozoin, the malaria pigment (Sherman & Hull 1960), the end product of haemoglobin digestion, consists of ferriprotoporphyrin coupled to a denatured polypeptide as yet unidentified (Sherman et al 1968; Homewood et al 1972). Recently, it has been shown that the malaria pigment of *P. lophurae* consists of haematin plus ferriprotoporphyrin coupled to a plasmodial protein, and insoluble methaemoglobin (Yamada & Sherman 1979). In our experimental malaria model, the severity of parasitaemia observed in a group of rats used to study quinine disposition was higher when compared to the quinidine group, but the difference is not significant ($P > 0{\cdot}05$). However, accumulation of malaria pigment in human liver is not related to the degree of parasitaemia, but depends on the duration or chronicity of the disease (Srichaikul 1959). It is not known to what extent this is true of the rodent malaria parasite, but it may explain the absence of a significant correlation between Vd and severity of the disease in both studies. Considerable but variable pigment accumulation might be expected to occur as peak parasitaemia levels were usually achieved between the 5th and 7th day post-injection of parasitized erythrocyte suspensions. This is supported by the observation of Taliaferro & Mulligan (1937) who noted the increasing amount of pigment within phagocytic Kupffer cells as the disease progressed. The enlargement and pigmentation of

the liver and spleen of rats in the present studies, appeared to vary with the severity of the infection produced. Since malaria pigment occupies spaces in the Kupffer cells and quinine and quinidine are reported to form complexes with ferriprotopophyrin IX to a certain extent (Fitch, 1986; Warhurst 1987) this might play a role in changing the distributional characteristic observed, especially with quinine, in this study.

In summary, we have demonstrated that the hepatic disposition of quinine and quinidine is altered during malaria infection, and emphasizes the need for a proper understanding of the pharmacokinetics of drugs in disease state before therapeutic regimens are devised. This is important from the toxicological point of view in order to minimize the serious side effects of quinine and quinidine during treatment of malaria patients as both drugs have a relatively low therapeutic index.

Acknowledgements

The authors wish to thank Miss G. Smith for technical assistance to provide malaria infected rats. SMM is supported by the Academic Staff Training Scheme of the National Drug Research Centre, Universiti Sains Malaysia. SAW is a Wolfson Lecturer.

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