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Mefloquine Effect on Disposition of Halofantrine in the Isolated Perfused Rat Liver

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Abstract

Halofantrine and mefloquine are antimalarial drugs used in the treatment of malaria, including that caused by chloroquine-resistant *Plasmodium falciparum*. Reports of drug-associated adverse reactions, including sudden death in one patient, have prompted concerns over the safety of halofantrine and the potential for drug-drug interactions. We used the isolated perfused rat liver (IPRL) model to investigate a possible hepatic metabolic or pharmacokinetic drug-drug interaction between halofantrine and mefloquine.

Pharmacokinetic parameter estimates for halofantrine in the IPRL reflected the pattern seen in in-vivo studies with doses comparable with clinical doses. Halofantrine parameter estimates (mean ± s.d.) were: volume of distribution (Vd), 7·53 ± 1·45 mL (g liver)$^{-1}$; clearance (CL), 0·11 ± 0·07 mL min^{-1} (g liver)$^{-1}$; initial distribution half-life (initial t½), 14·62 ± 2·38 min; terminal half-life (terminal t½), 138·7 ± 178·8 min; AUC 606 ± 194 mg mL^{-1} min^{-1} (g liver)$^{-1}$; elimination rate constant (K_e), 0·0135 ± 0·012 min^{-1}. Prior dosing with mefloquine did not affect halofantrine perfusate pharmacokinetic parameter estimates of Vd, K_e, initial and terminal t½ ($P > 0·05$). A single dose, short term (4–6 h) interaction showed significant changes in the perfusate clearance of halofantrine in mefloquine-pretreated livers using higher doses of halofantrine. Substantial changes were seen in bile production ($P < 0·05$) and biliary clearance ($P < 0·05$) of halofantrine in mefloquine-pretreated livers.

These findings may have clinical implications in models utilizing multiple drug dosages or in patients with severe malaria who have disease-related cholestasis.

Malaria is a serious infection responsible for 100 million clinical cases and one to two million deaths each year (Oaks et al 1991). Malaria poses major health hazards to residents and travellers in endemic areas and remains a serious threat to non-immune soldiers deployed to those areas. Of the four species of *Plasmodium*, only *Plasmodium falciparum* infects erythrocytes of all ages and a high percentage of red cells can become parasitized. Thus, in contrast to other species of malaria, infection with *P. falciparum* is more likely to be fatal (Wyler 1990). Furthermore, the development of multidrug resistance in parasites and mosquito resistance to insecticides has compromised the ability to treat patients with *P. falciparum* successfully. Resistant strains of *P. falciparum* require higher doses of drugs or sequential or combination pharmacologic therapy to eradicate infection. Use of higher dose regimens and combination therapies have heightened concerns about the potential for adverse drug reactions.

Halofantrine (Halfan, 3-(dibutylamino)-1-[1,3-dichioro-6-(trifluoromethyl)-9-phenanthryl]propan-1-ol) and mefloquine (Lariam, a-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinoline-methanol) (Fig. 1) are two of the most recent antimalarial agents effective against multidrug resistant strains of *P. falciparum*. Both have advantageous pharmacologic properties that require fewer doses, thereby facilitating better compliance. Specific pharmacologic properties include long half-lives, extensive tissue and protein binding, and slow clearance (Karbwang & White 1990; Nothdruft et al 1993). The primary metabolite of halofantrine, *N*-desbutylhalofantrine (Broom 1989) (Fig. 1), has properties similar to the parent compound including schizonticidal activity (Horton 1988) and a long half-life.

It is not uncommon for patients who contract malaria while receiving mefloquine prophylaxis to subsequently receive halofantrine for curative treatment. Reports of halofantrine-induced cardiotoxicity with QT interval prolongation and rare

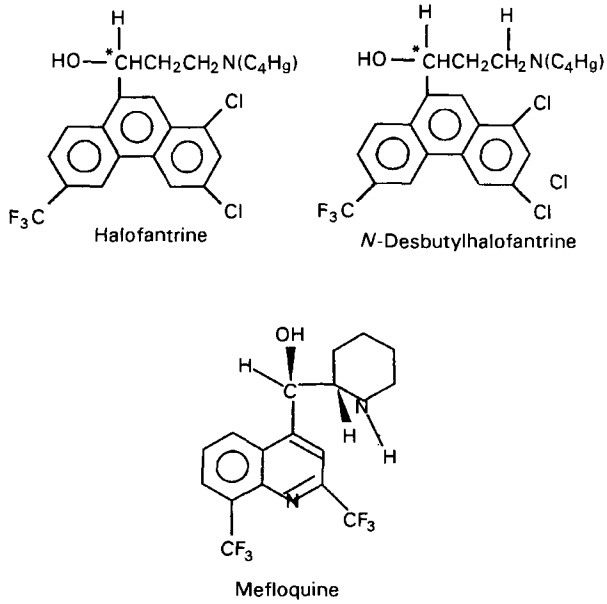

FIG. 1. Chemical structures of halofantrine, its primary metabolite, *N*-desbutylhalofantrine and mefloquine. * indicates location of ^{14}C label.

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fatalities (Nosten et al 1993) are particularly concerning. The QT interval prolongation was greater in those patients who previously had received mefloquine. The effect correlates with higher parent drug levels (Karbwang et al 1993; Karbwang & Bangchang 1994; Brueckner et al 1994). Cardiac adverse effects are highly problematic because multiple drugs may be used in some patients in attempts to treat severe or resistant malaria or for the treatment of infections after failed prophylaxis. Although adverse reactions have been reported for halofantrine and mefloquine (Panisko & Keystone 1990; Luzzi & Peto 1993), in-vitro and in-vivo data regarding drug-drug interactions are lacking.

Multiple studies have demonstrated antimalarial drug-drug interactions in-vitro (Coleman et al 1989; Bangchang et al 1992a,b; Mihaly et al 1993) but no data are available regarding metabolic or pharmacokinetic interactions between halofantrine and mefloquine, specifically the effect of mefloquine on halofantrine. Since most drugs, including antimalarials, have predominant liver metabolism and biliary disposition, the isolated perfused rat liver (IPRL) model is a useful in-vitro system to evaluate drug metabolism and disposition. It provides an in-vitro model with an intact liver architecture, bile flow, and an intravascular compartment which allows for multiple sampling, facilitating drug analysis and calculation of pharmacokinetic parameter estimates. Since the clinical evidence strongly suggests a possible interaction between halofantrine and mefloquine, we used the IPRL system to investigate changes in the metabolic and, pharmacokinetic, and dispositional properties of halofantrine due to the presence of mefloquine.

Materials and Methods

Reagents

Halofantrine hydrochloride (WR 171,669) was a gift from SmithKline Beecham Co., Philadelphia, PA. Mefloquine hydrochloride (WR 142,490) was synthesized under contract to the United States Army Medical Research and Material Command (USAMRMC) by Ash Stevens, Detroit, MI. [^{14}C]Halofantrine hydrochloride (spec. act. 14 mCi mmol^{-1}) labelled at position 1 of the propyl side chain was obtained under contract to USAMRMC from the Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, NC. Radiochemical purity was determined by HPLC and TLC to be 96% and > 98%, respectively. Liquid scintillant, Permafluor E+, and [^{14}C]carbon dioxide absorber, Carbo-sorb, were obtained from Packard Instrument Co., Inc., Meriden, CT. All other reagents were of HPLC or analytical grade.

Animals

Male Sprague–Dawley rats (n = 311, 250–300 g, Charles River, Wilmington, MA) were housed in well ventilated cages at a controlled temperature (24°C) with 12-h light:dark cycling. They were allowed free access to pelleted food (Agway Inc., C.G., Syracuse, NY) and tap water. Animals were cared for in accordance with the principles of The Guide for the Care and Use of Laboratory Animals (Department of Health, Education and Welfare, NIH).

Isolated perfused rat livers (IPRL)

Rats were anaesthetized with intraperitoneal sodium pentobarbital (40 mg kg^{-1}) and their livers were isolated using standard techniques with modifications (Mihaly et al 1982; Coleman et al 1985; Gores et al 1986). The liver was placed on a glass platform inside a thermostatically controlled (37°C) cabinet. Livers were perfused with 100 mL standard Krebs-Henseleit buffer containing 20% sheep washed red blood cells, 1% (w/v) bovine serum albumin (Sigma Chemical Co., St Louis, MO) and 0·1% glucose. Livers were perfused in a constant flow recirculating system at a rate of 1·0 mL (g liver)$^{-1}$ min^{-1} (Fig. 2). Sodium taurocholate (40 μmol h^{-1}, Sigma) was continuously infused into the perfusate reservoir to simulate enterohepatic bile acid cycling and to normalize the composition of bile (Wolkoff et al 1987). The perfusate was oxygenated with a mixture of humidified O_2–CO_2 (95%/5%).

Protocol

Perfusion experiments with halofantrine or halofantrine with mefloquine were carried out with a balanced randomization scheme with blocking. Preliminary perfusions determined that a 4-h perfusion time was adequate for accurate determination of pharmacokinetic parameter estimates for halofantrine and that longer term perfusions, up to 6 h, did not show any dif-

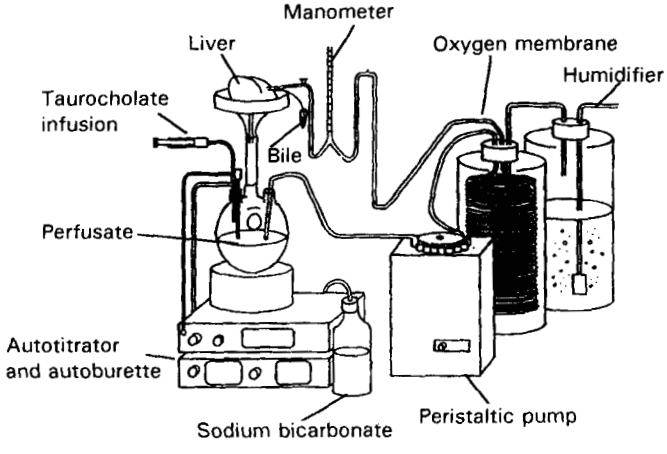

FIG. 2. Isolated perfused rat liver (IPRL) apparatus.

ferences in parameter estimates (data not shown). Doses for halofantrine and mefloquine were comparable with human doses on a mg kg^{-1} basis. A 3·8-mg bolus dose of mefloquine hydrochloride was added to the perfusate during the equilibration phase, before time 0. Bolus doses of halofantrine 2·5 or 5·0 mg were added approximately 20 min after mefloquine.

All solutions of drugs were prepared in methanol, administered in a volume of < 50 μL each, and added directly into the perfusate reservoir, thereby simulating systemic intravenous administration.

Radiochemical disposition and recovery of [^{14}C]halofantrine (n = 6) were studied in 4-h perfusions with a radiolabelled dose (2–3 μCi [^{14}C]halofantrine) sufficient to yield adequate (> 1000 d min^{-1}) counts in all fractions collected.

Perfusate was sampled from the reservoir pre-dose and at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min post-dose. An equal volume of fresh perfusate was added to the reservoir to replace the volume of samples removed. Bile was collected at hourly intervals into pre-weighed vials. Bile volume was determined by weight (assuming a density of 1·0 g mL^{-1}). The liver was weighed at the end of each experiment after all sutures, catheters, and supporting structures were removed. Perfusate, bile, and liver samples were frozen at −60°C until assayed for halofantrine, its metabolite, and radioactivity.

Analysis of liver viability

Liver viability was assessed by normal visual appearance of livers, steady oxygen consumption, sustained bile production, constant perfusing portal pressure, and steady perfusate pH (maintained at pH = 7·4 with 0·25 M $NaHCO_3$ by autotitrator (M 80, Radiometer, Copenhagen) and autoburette (ABU 80, Radiometer)). Liver viability was confirmed by visual inspection of plotted bile production-time and oxygen consumption-time data; changes in portal vein perfusing pressure; and pH stability as determined by the amount of sodium bicarbonate added to maintain a pH of 7·4. Data were prospectively excluded from analysis for significant deviation in any one of these parameters.

Drug concentration analysis

Analysis of perfusate. Halofantrine and *N*-desbutylhalofantrine concentrations in whole perfusate were quantitated using a reproducible, selective and sensitive HPLC method as described previously (Milton et al 1988). The system consisted of an SP8800 ternary HPLC pump equipped with a Rheodyne valve injection system and was coupled to a fluorescence detector (excitation at 300 nm, emission at 375 nm). Chromatographic separation was achieved at ambient temperature on a C8 (Spherisorb; 5-mm particle size) 10 × 0·6 cm reversed-phase cartridge Universal Ferruleless column. The mobile phase consisted of methanol : water (80 : 20, v/v), with final concentration of 5 mM organophosphoric acid and flow rate of 1·0 mL min^{-1}. Samples containing internal standard (procainamide HCl) were mixed with acetonitrile and extracted with methyl *t*-butyl ether.

Analysis of bile. Concentrations of halofantrine and *N*-desbutylhalofantrine were analysed by HPLC in each hourly bile sample before and after enzyme hydrolysis, to quantitate conjugated metabolites of the drug.

Analysis of liver tissue. Livers were homogenized with a Teflon-glass homogenizer in phosphate buffer (0·1 M). Concentrations of halofantrine and *N*-desbutylhalofantrine in the 25% homogenates were then determined by HPLC.

Radiochemical analysis. One hundred microlitres of perfusate, bile, and liver homogenates from radiolabelled perfusions were placed on oxidizer pads and allowed to dry. Pads were oxidized for 1 min using a Packard Tri-Carb Sample Oxidizer, and subsequently combined with 5 mL Carbosorb and 10 mL Permafluor E+. The efficiency of the oxidizer analytical process was > 95%. Disintegrations per minute were obtained using Packard 2500 (Packard Instrument Co., Inc., Meriden, CT) with quench and chemiluminescent correction on duplicate samples with appropriate control and blanks.

Pharmacokinetic analysis

Disposition kinetics were first analysed by visual inspection of plotted concentration-time or percent total radioactivity-time data and with model-independent analysis. Subsequently, more advanced and detailed approximations of apparent pharmacokinetic parameters were calculated using nonlinear regression analysis with MKMODEL (Holford 1990). Initial curve stripping or fitting routines of the data were followed by non-compartmental and compartmental pharmacokinetic analysis, where appropriate. Pharmacokinetic parameters were calculated using standard model-independent pharmacokinetic formulae (Gibaldi & Perrier 1982). Clearance (CL), elimination half-life (t½), volume of distribution (Vd), and the elimination rate constant (K_e) were determined for halofantrine when applicable. The area under the perfusate concentration-time curve (AUC) for halofantrine from time = 0 to time = 4 h was calculated using the trapezoidal rule. The AUC from 4 h to infinity was calculated from the ratio C_4/β where C_4 was the perfusate concentration at time 4 h and β was the terminal phase elimination rate constant. The area under the curve from zero to infinity ($AUC_{0-\infty}$) was obtained from the sum of the two areas. The terminal phase elimination rate constant (β) was determined using a two-compartment model via MKMODEL. Halofantrine clearance (CL_{perf}) from perfusate was calculated from the equation:

$$CL_{perf} = Dose/AUC_{0-\infty} \quad (1)$$

The apparent volume of distribution (Vd) was calculated using the equation:

$$Vd = Dose/\beta AUC_{0-\infty} \quad (2)$$

Biliary drug clearance (CL_{bile}) was calculated using the equation:

$$CL_{bile} = halofantrine_{bile}/[halofantrine]_{perf} \quad (3)$$

where $halofantrine_{bile}$ is the amount of halofantrine eliminated in the bile over each 1 h collection interval and $[halofantrine]_{perf}$ is the perfusate concentration of halofantrine at the midpoint of that time interval.

Statistical analysis

Data were tabulated and recorded on microcomputer spreadsheets for subsequent analysis using Microsoft Excel (Microsoft 1992) and Statview (Abacus Concepts 1992). All data were tabulated and graphed as mean ± s.d. In addition to

descriptive statistics, comparisons of groups means were performed with the appropriate *t*-test. Comparison of time series data was by analysis of variance. Comparison of pharmacokinetic parameters was by the unpaired Student's *t*-test for two groups and one-way analysis of variance for multiple groups. Significance was accepted for $P < 0.05$.

Results

Liver viability parameters

The halofantrine-mefloquine combination perfusions demonstrated a significant difference ($P < 0.05$) in bile production when comparing halofantrine, halofantrine-mefloquine, 2·5 mg and halofantrine-mefloquine, 5·0 mg (Fig. 3). Halofantrine alone and mefloquine alone had no effect on bile production compared with controls (data not shown). Oxygen consumption rose from baseline in all cases during the first 2 h, then steadily declined to slightly below baseline at the end of the perfusions. No other indices of variability varied with these perfusions.

HPLC results and pharmacokinetic parameters

Drug concentrations for halofantrine and *N*-desbutylhalofantrine were analysed by HPLC. Assay sensitivity was 10 ng mL^{-1} for perfusate and 20 ng mL^{-1} for bile samples. Halofantrine perfusate concentration±time curves demonstrated a rapid fall in halofantrine concentrations over the initial 90 min, followed by a second slower decrease in all perfusions (Fig. 4).

Halofantrine perfusate concentrations for halofantrine and halofantrine-mefloquine, 2·5 mg do not differ. The halofantrine-mefloquine, 5·0 mg concentration–time curve reflects higher halofantrine concentrations at all time points. A two-compartment open model was used to calculate pharmacokinetic parameters (Table 1). Clearance (CL) of halofantrine

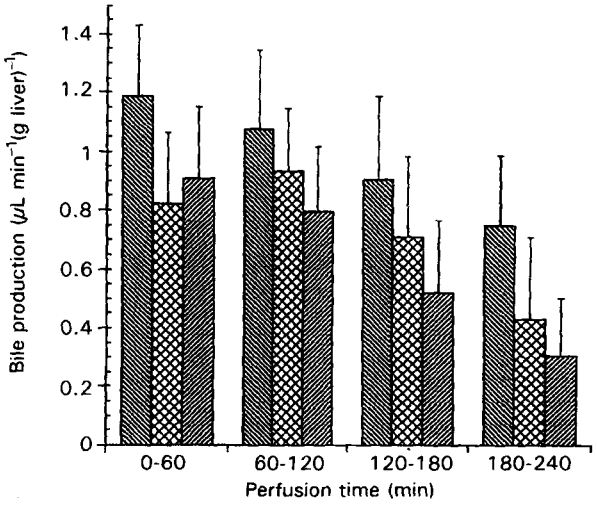

FIG. 3. Bile production for perfusions. Bile production for halofantrine-mefloquine perfusions declined over 4 h. Halofantrine-mefloquine 2·5 mg and halofantrine-mefloquine, 5·0 mg perfusions had lower bile production than halofantrine at all time intervals ($P < 0.05$, repeat measures analysis of variance). This was most evident between halofantrine and halofantrine-mefloquine, 5·0 mg. A dose-response relationship of decreased bile production with addition of mefloquine and increasing dose of halofantrine was evident (mean ± s.d.; (▨) halofantrine, n = 9; (▩) halofantrine-mefloquine, 2·5 mg and (▨) halofantrine-mefloquine, 5·0 mg, n = 6).

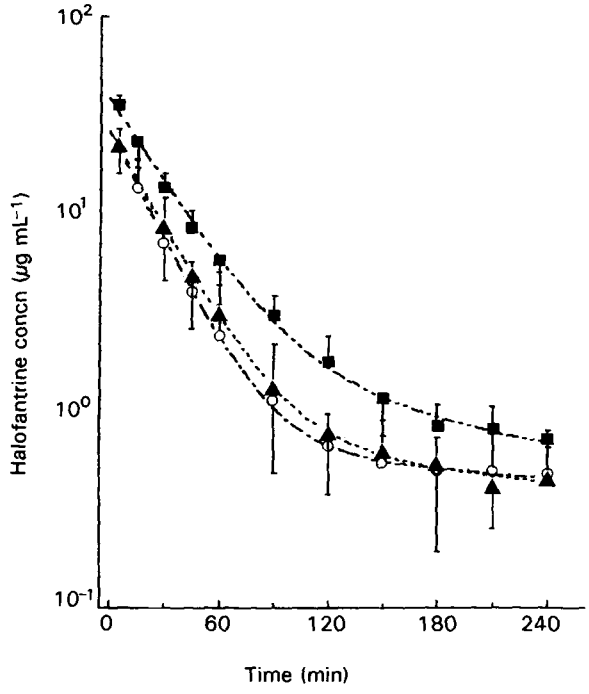

FIG. 4. Halofantrine concentration–time curves for perfusions. Concentration of halofantrine in perfusate falls rapidly over 90 min, with small changes beyond that time. Halofantrine concentrations for halofantrine and halofantrine-mefloquine, 2·5 mg do not differ. Halofantrine-mefloquine, 5·0 mg concentration–time curve reflects higher halofantrine concentrations at all time points (mean ± s.d.; (○) halofantrine, n = 9; (▲) halofantrine-mefloquine, 2·5 mg and (■) halofantrine-mefloquine, 5·0 mg, n = 6).

differed across the three groups ($P < 0.05$) with lowest CL for halofantrine perfusions at 0·11 ± 0·07 mL min^{-1} (g liver)$^{-1}$, and highest CL for halofantrine-mefloquine, 5·0 mg at 0·23 ± 0·05 mL min^{-1} (g liver)$^{-1}$. There were no other differences in any kinetic parameters. A larger area under the curve (AUC) ($P < 0.05$) was seen in halofantrine-mefloquine, 5·0 mg, as expected for the larger doses. There were no dose related differences in biliary clearance of halofantrine in the dose range studied. Prior dosing of livers with mefloquine, however, reduced biliary halofantrine clearance of both halofantrine (Fig. 5, $P < 0.05$) and *N*-desbutylhalofantrine (Fig. 6, $P < 0.05$).

Radiochemical results

Radiochemical (^{14}C) recovery (mass balance) from the perfusion system was greater than 95% (102·01 ● 11·83). The efficiency of the oxidizer analytical process was determined to be 96·1 ± 9·6% (n = 6). Larger doses of halofantrine (2·5 mg) had no effect on recovery from the system. Most of the radioactivity was associated with liver samples (70%), rather than with bile (17%) or perfusate (13%) reflecting rapid hepatic extraction of radiolabel with subsequent slower elimination of radiolabel into bile. The distribution of radioactivity was not altered by different doses of halofantrine or the addition of mefloquine.

Discussion

Pharmacokinetic parameter estimates of halofantrine were essentially unchanged by mefloquine, with the exception of

Table 1. Pharmacokinetic parameter estimates for halofantrine. Pharmacokinetic parameter estimates for halofantrine using a two-compartment open model show differences in clearance and AUC (*$P < 0.05$ compared with halofantrine alone). Clearance of halofantrine is highest for halofantrine-mefloquine, 5·0 mg, the larger dose halofantrine with mefloquine perfusion, and lowest for halofantrine, perfusions with halofantrine alone. The AUC for halofantrine-mefloquine, 5·0 mg is approximately double that for halofantrine and halofantrine-mefloquine, 2·5 mg, reflecting doubling of halofantrine concentration. (mean ± s.d.; halofantrine, n = 9; halofantrine-mefloquine, 2·5 mg and halofantrine-mefloquine, 5·0 mg, n = 6).

Parameter estimates	Halofantrine	Halofantrine-mefloquine 2·5 mg	Halofantrine-mefloquine 5 mg
Volume of distribution (Vd) (mL min^{-1} (g liver)$^{-1}$)	7·53 ± 1·45	7·20 ± 1·84	9·47 ± 1·46
Clearance (CL) (mL min^{-1} (g liver)$^{-1}$)	0·11 ± 0·07	0·17 ± 0·07*	0·23 ± 0·05*
Initial half-life (t½) (min)	14·6 ± 2·4	15·3 ± 3·1	19·3 ± 3·0
AUC (μg mL min^{-1} (g liver)$^{-1}$)	606 ± 194	668 ± 265*	1156 ± 182*
Elimination rate constant (Ke) (min^{-1})	0·014 ± 0·012	0·025 ± 0·009	0·025 ± 0·004

perfusate clearance (CL). Clearance was lowest for halofantrine, but increased significantly with the administration of mefloquine, with the greatest CL evidenced with the higher halofantrine dose (halofantrine-mefloquine, 5·0 mg), demonstrating non-linear kinetics over this dose range. Preliminary studies using radiolabelled halofantrine demonstrated more rapid clearance at higher halofantrine doses and with the addition of mefloquine. This may reflect changes in liver extraction and total drug clearance relative to changes in the fraction of unbound drug (Wilkinson & Shand 1976).

An unexpected finding of this study was the significant depression of total bile production attributable to mefloquine or a drug-drug interaction. Bile production is a highly sensitive indicator of hepatic function, as well as disease or drug-related cholestasis. Clinically, drug-induced cholestasis is known to occur with antimicrobial and antiparasitic agents such as erythromycin, nitrofurantoin, sulphonamides, sulphones, griseofulvin, and rifampicin. Drug-induced cholestasis is usually clinically insignificant; however, fatal instances reflect serious underlying disease or other systemic effects of the drug (Zimmerman & Lewis 1987).

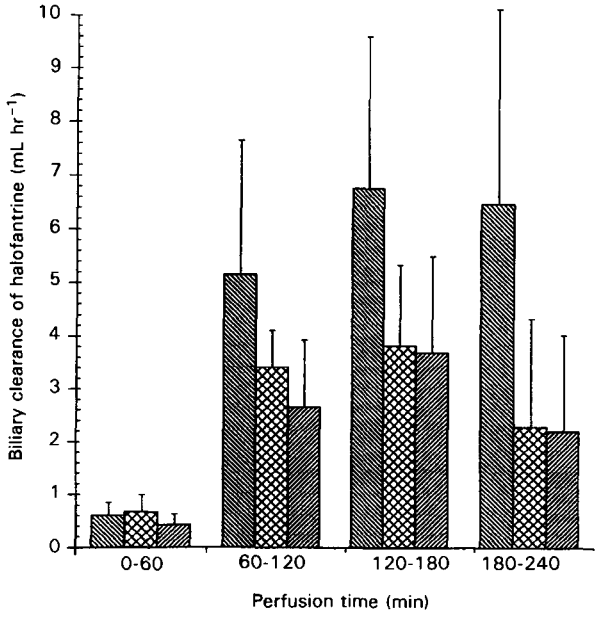

FIG. 5. Biliary clearance of halofantrine. Comparison of halofantrine-mefloquine, 2·5 mg and halofantrine-mefloquine, 5·0 mg perfusions with halofantrine shows an obvious and significant ($P < 0.05$, repeat measures analysis of variance) cholestatic effect with mefloquine treatment. No effect on biliary clearance of halofantrine ($P > 0.05$) was seen with halofantrine at two different doses. (Mean ± s.d.; (▨) halofantrine, n = 9; (▩) halofantrine-mefloquine, 2·5 mg and (▨) halofantrine-mefloquine, 5·0 mg, n = 6).

In our study, bile production was significantly impaired by combination of halofantrine with mefloquine. The halofantrine-mefloquine combination perfusions (Fig. 3) showed an inhibitory dose-response relationship associated with less bile production. A drug-drug interaction at the bile production and possibly transport level is also apparent with halofantrine demonstrating greater bile production than halofantrine-mefloquine, 2·5 mg or halofantrine-mefloquine, 5·0 mg. The cholestatic effect of mefloquine has been seen previously with primaquine in the IPRL (Coleman et al 1989). Biliary clearance of both halofantrine and *N*-desbutylhalofantrine were both significantly depressed ($P < 0.05$) with previous mefloquine administration. More changes would be expected in systems employing multiple doses (in-vivo) where the drug-induced cholestatic effect should be prominent.

Pharmacokinetic studies using rodent models may not necessarily be predictive of drug metabolism in humans. However, in-vitro rodent models can provide rapid assessment of metabolism and pharmacokinetic parameters, which provide a basic framework for subsequent investigations. The isolated perfused rat liver allows a more complete investigation of metabolism and disposition than does microsomes without the complications associated with whole animal studies. Ultimately, this study will be best performed in man to elucidate the pharmacokinetic pharmocodynamic relationship. Significant concerns about inducing QTc prolongation with risk for subsequent torsade de points have serious medical-legal implications.

Our data reveal significant changes in the perfusate clearance of high dose halofantrine after administration of mefloquine. Bile production and hence biliary clearance of both

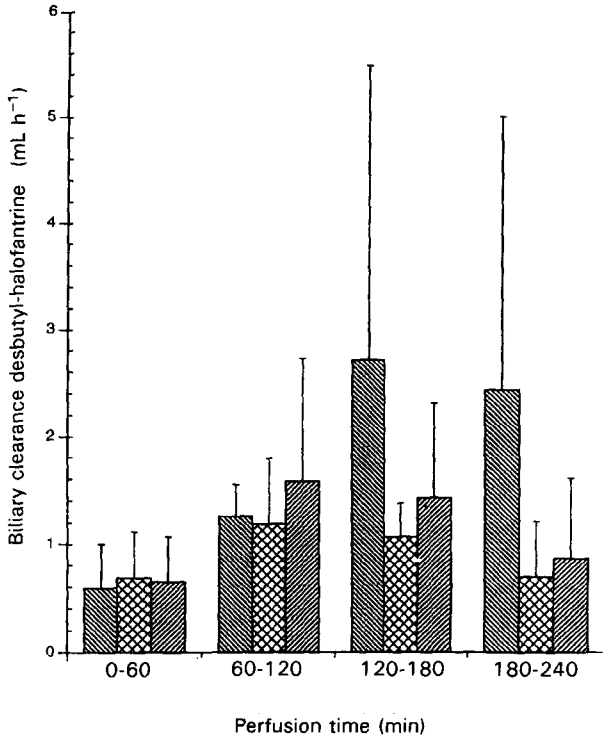

FIG. 6. Biliary clearance of *N*-desbutylhalofantrine. The biliary clearance of *N*-desbutylhalofantrine was decreased in the halofantrine-mefloquine, 2·5 mg and halofantrine-mefloquine, 5·0 mg perfusions, when compared with halofantrine perfusions ($P < 0.05$, repeat measures analysis of variance). No effect was seen with halofantrine at two doses ($P > 0.05$). (Mean ± s.d., (▧) halofantrine, n = 8; (▩) halofantrine-mefloquine, 2·5 mg, n = 6; (▨) halofantrine-mefloquine, 5·0 mg, n = 6).

halofantrine and *N*-desbutylhalofantrine were also significantly impaired by mefloquine. These pharmacokinetic and dispositional changes may have particular relevance for patients with severe malaria who already have disease-related cholestasis and hepatocellular dysfunction.

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