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COMMUNICATIONS

Quinine impairs quinidine clearance in rat perfused liver

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Abstract—We have examined the disposition of the cinchona alkaloids quinine and quinidine in the rat recirculating isolated perfused liver preparation. When administered as separate 1 mg doses, the hepatic clearances of quinine and quinidine were similar to the hepatic perfusate rate of 10 mL min^{-1}. When 1 mg of each was administered simultaneously, mean hepatic clearance of quinine was unchanged (9·00 ± 2·20 mL min^{-1} separate dosage, n = 7; 6·87 ± 1·77 mL min^{-1} simultaneous dosage, n = 7; $P > 0·05$). By contrast, mean hepatic clearance of quinidine was reduced significantly by concomitant quinine (10·6 ± 1·72 mL min^{-1} separate dosage, n = 7; 4·82 ± 1·25 mL min^{-1} simultaneous dosage, n = 7; $P < 0·05$). There was no significant difference in volumes of distribution when each alkaloid was administered separately (131 ± 46 mL quinine, 129 ± 21 mL quinidine; $P > 0·05$) but concomitant quinine administration increased quinidine volume of distribution to 169 ± 30 mL ($P < 0·05$). Four further experiments with simultaneous dosages of 0·5 mg of each alkaloid produced similar findings, indicating that the interactions did not derive from nonlinear drug disposition.

The cinchona alkaloid, quinine, is widely used in the treatment of malaria. It is particularly useful for the treatment of chloroquine-resistant *Plasmodium falciparum* strains, either alone or in combination with other drugs (White 1988; Panisko & Keystone 1990). Quinidine, the diastereoisomer of quinine, is at least as active an antimalarial agent as quinine, and is also useful in chloroquine-resistant falciparum strains (White 1988; Panisko & Keystone 1990). The liver is the organ mainly responsible for eliminating both of these cinchona alkaloids and the hepatic disposition of each in the rat has been defined when administered separately (Watari et al 1989; Coleman et al 1990; Mansor et al 1990, 1991a, b). With the emergence of quinine-resistant strains, there is interest in the use of quinine in combination with other cinchona alkaloids, such as quinidine and cinchonine (Merkus & Smit 1988; Bunnag et al 1989; Sowunmi et al 1990). In-vitro studies show synergism between quinine and quinidine against quinine-resistant strains of *Plasmodium falciparum* malaria, suggesting that the combination might be useful clinically (Druilhe et al 1988). To determine whether the two drugs might affect each other's metabolism, we have examined the hepatic disposition of quinine and quinidine when present together in the rat isolated perfused liver preparation.

Materials and methods

Materials. Quinine hydrochloride and quinidine hydrochloride monohydrate were obtained from Sigma Chemical Co. (St Louis, MO, USA). Bovine serum albumin was obtained from the Commonwealth Serum Laboratories (Melbourne, Australia) and sodium taurocholate was purchased from Calbiochem (San Diego, CA, USA). All other chemicals and solvents were of analytical reagent grade.

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Experimental preparation. Livers of non-fasting male Sprague-Dawley rats, 100–120 g, were isolated and perfused via the portal vein in a constant flow (10 mL min^{-1}) recycling system at 37°C, as described previously (Jones et al 1984). The perfusate (100 mL total volume) consisted of 10% v/v washed human red cells, 1% w/v bovine serum albumin and 0·1% (w/v) glucose in Krebs–Henseleit buffer. The perfusate was oxygenated by equilibration with 100% oxygen in a silastic membrane oxygenator and a constant infusion of sodium taurocholate (30 μmol h^{-1}) into the perfusate reservoir maintained perfusate bile salt concentrations. The principal indices of liver viability were steady oxygen consumption (1·5–2·0 μmol O_2 (g liver)$^{-1}$ min^{-1}), initial bile flow rates of 0·4–0·6 mL h^{-1}, initial perfusion back pressure of 7–9 cm H_2O, stable transaminase levels in perfusate and normal macroscopic appearance, which was indicative of uniform tissue perfusion (Jones et al 1984).

Experimental design. The disposition of quinine and quinidine was studied in four groups of rat isolated perfused liver preparations following separate dosage (dose = 1·0 mg; n = 7 per group) and simultaneous dosage (dose = 1·0 mg of each, n = 7; and dose = 0·5 mg of each, n = 4). Drugs were administered to perfusate reservoir as aqueous solutions (1 mg mL^{-1}). Perfusate was sampled predose and again at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min for measurement of quinine and quinidine concentrations. An equal volume of drug-free perfusate was added to the reservoir to replace that volume of perfusate removed by sampling. Bile was collected hourly into pre-weighed tubes.

Drug analysis. Perfusate concentrations of quinine and quinidine were estimated by a sensitive and selective HPLC procedure as previously described (Czuba et al 1991). This method allows for the simultaneous estimation of both diastereoisomers in perfusate plasma without interference from known metabolites, 3-hydroxyquinidine, quinidine *N*-oxide or dihydroquinidine.

Calculations and statistical assessments. Data in the text and Table 1 are presented as mean ± s.d. and in Fig. 1 as mean ± s.e.m. The elimination half-life was calculated from the slope of the terminal elimination phase, clearance from the ratio of dose to area under the curve, from the time of dosing to infinity and volume of distribution from the product of clearance and half-life divided by ln 2. Statistical comparisons were made with the Mann-Whitney U-test (two tailed) accepting $P < 0·05$ as significant.

Results

Following separate dosage, perfusate quinine and quinidine concentrations fell rapidly and monoexponentially (Fig. 1). Mean hepatic clearances of quinine (9·00 ± 2·20 mL min^{-1}) and quinidine (10·6 ± 1·72 mL min^{-1}) were not significantly different ($P > 0·05$; Table 1). The volumes of distribution of the two drugs were comparable (131 ± 46 and 129 ± 21 mL, respectively) and of similar magnitude to the physical volume of the perfusion

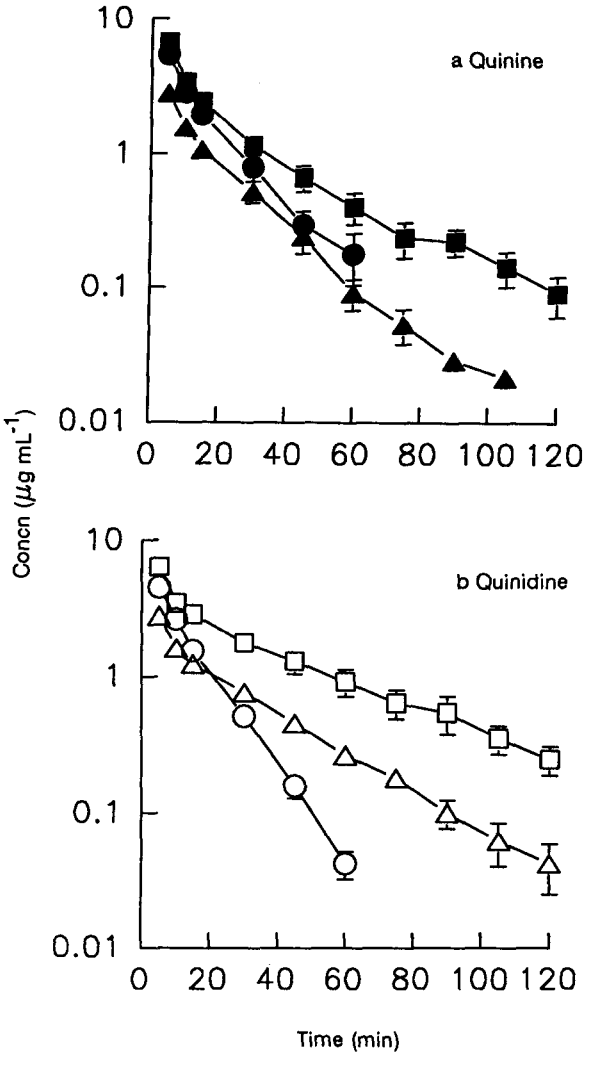

FIG. 1. a. Perfusate quinine concentrations following separate administration of 1 mg quinine (●), simultaneous administration of 1 mg quinine with 1 mg quinidine (■) and simultaneous administation of 0·5 mg quinine with 0·5 mg quinidine (▲). b. Perfusate quinidine concentrations following separate administration of 1 mg quinidine (○), simultaneous administration of 1 mg quinidine with 1 mg quinine (□) and simultaneous administration of 0·5 mg quinidine and 0·5 mg quinine (△).

system (i.e. 100 mL perfusate plus liver volume). Elimination half-lives of both drugs were also comparable (Table 1).

Following simultaneous dosage of 1 mg of each diastereoisomer, mean hepatic clearance of quinidine was reduced significantly by 55% and mean hepatic clearance of quinine was reduced by 24%; however, the latter change was not significant (Table 1). With simultaneous dosage, the volume of distribution of quinidine was increased significantly by nearly one-third, whereas volume of distribution of quinine was unchanged (Table 1). These changes in hepatic clearance and volume of distribution were manifested by an increase in the half-life of 300% for quinidine and 53% for quinine, the increase being significant in both cases (Table 1, Fig. 1).

The disposition of quinine and quinidine following simultaneous administration at a reduced dosage (0·5 mg of each) was comparable with that with simultaneous doses of 1 mg of each (Table 1, Fig. 1). This suggests that the observed changes in disposition are related to simultaneous administration rather than to nonlinear drug disposition.

Discussion

In our isolated perfused liver preparation, mean hepatic clearances of both quinine and quinidine approximated the perfusate flow rate of 10 mL min^{-1} when given separately (Table 1). In a previous study of quinine and quinidine administered separately in the isolated perfused liver preparation (Mansor et al 1990), mean clearances of quinine and quinidine were approximately one-third those observed in the present study (approx. 2 mL min^{-1} (g liver)$^{-1}$). Moreover, the half-lives were approximately 8–10 times greater than in the present study (approx. 10 min (Table 1)). In our study the duration of perfusate sampling was always about ten times the half-life (Fig. 1) so that our higher clearance values should not have been due to inadequate characterization of the time-perfusate concentration curve. Moreover, similar values to ours were obtained for quinine by Coleman et al (1990) using a perfused liver system, and hepatic clearances of both drugs in the rat, in-vivo, were found to be comparable with liver blood flow. The difference in hepatic clearance values may have been due to differences in protein binding of the drugs in the perfusate, as binding differences can have a substantial effect on hepatic clearance in the perfused liver preparation (Mansor et al 1991b).

Our results indicate that quinine inhibited the hepatic metabolism and tissue distribution of quinidine, but quinidine had no significant effect on quinine disposition. Although the hepatic clearances of both quinine and quinidine have been reported to

Table 1. Mean (±s.d.) pharmacokinetic parameters for quinine and quinidine following separate and simultaneous dosage in the isolated perfused liver of rat.

	n	Clearance (mL min^{-1})	Volume of distribution (mL)	Half-life (min)
Quinine				
Separate dosage (1 mg)	7	9·00±2·20	131±46	10·2±3·0
Simultaneous dosage (1 mg)	7	6·87±1·77	147±29	15·6±0·05*
Simultaneous dosage (0·5 mg)	4	7·88±1·72	137±10	12·6±3·0
Quinidine				
Separate dosage (1 mg)	7	10·6±1·72	129±21	8·4±1·2
Simultaneous dosage (1 mg)	7	4·82±1·25*	169±30*	25·2±4·8*
Simultaneous dosage (0·5 mg)	4	5·87±0·90*	160±15*	19·2±4·8*

*$P < 0·05$ compared with separate dose studies.

decrease with dose in the rat when administered separately (Watari et al 1989; Coleman et al 1990), dose dependence of hepatic elimination is unlikely to account for the effects of quinine on quinidine disposition in our experiments, as quinine had the same effects on quinidine disposition at both the 0·5 and 1 mg dose levels (Table 1). In the only other study that has examined the disposition of the two drugs given simultaneously, neither drug appeared to affect the hepatic clearance of the other in pregnant adult sheep. However, there was evidence of substantial mutual inhibition in foetal sheep (Czuba et al 1991).

Both quinine and quinidine are known inhibitors of the metabolism of a variety of other drugs in rats and man (Otton et al 1984; Speirs et al 1986; Lancaster et al 1990). It has been found that in man, quinidine is a specific and potent inhibitor of cytochrome P450IID6, whereas quinine causes minimal inhibition of this enzyme (Otton et al 1984; Speirs et al 1986; Kobayashi et al 1989; Ayesh et al 1991; Muralidharan et al 1991). By contrast, in rats quinine is a much more potent inhibitor of the corresponding cytochrome P450IID isoenzyme than is quinidine (Kobayashi et al 1989). Although quinidine inhibits cytochrome P450IID6 in man, it is not itself metabolized by this isoenzyme (Guengerich et al 1986; Otton et al 1988). The main isoenzyme responsible for metabolizing quinidine in man appears to be cytochrome P450IIIA4 (Brian et al 1990; Renaud et al 1990). Very little is known about the metabolism of quinine or quinidine by the rat, but if they are metabolized in the rat by the corresponding cytochrome P450IIIA isoenzyme, our study suggests that quinine may be an inhibitor of this pathway.

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