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Quinidine and the non-renal elimination of digoxin

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Several studies have shown that the concomitant administration of quinidine with digoxin increases the plasma concentration of the latter almost 2-fold (Ejvinsson 1978; Hager et al 1979; Schenck-Gustafsson & Dahlqvist 1981). Although there is agreement concerning the magnitude of this interaction, several explanations have been offered to account for the phenomenon. They include a diminished distribution volume, as a result of competition for binding in the tissues (Kim et al 1981) and reduced renal clearance (Hager et al 1979; Aronson & Carver 1981). However, even in patients with normal renal function the elimination of digoxin is partly by non-renal routes. There is evidence (Schenck-Gustafsson & Dahlqvist 1981) that the non-renal elimination of digoxin is also reduced by concurrent quinidine therapy. In view of this and the recent observation (Caldwell et al 1980) that digoxin can be eliminated across the intestine, we have examined the possible interaction between these two drugs at this site.

Materials and methods

Pairs of isolated everted sacs of rat intestine were prepared as described previously (George & Gruchy 1979). [^{3}H]-Digoxin ($3{\cdot}6 \times 10^{-8}$ M) was placed on the serosal surface of the preparation and its rate of transfer into the fluid bathing the mucosal surface measured at intervals of 15 min. Radioactivity was measured in 1 ml aliquots of bath fluid by liquid scintillation counting.

The effects of potassium cyanide (10^{-3} M), gassing with nitrogen and ouabain (10^{-3} M) on one of the pair of sacs were assessed as described previously for acebutolol (George & Gruchy 1979). Finally, the effects of quinidine 10^{-4} to 10^{-3} M were assessed in a similar manner.

Results

The transfer of digoxin from serosal to mucosal surface was reduced by treatment with potassium cyanide and by gassing with nitrogen (Table 1), but ouabain was without effect. Quinidine at a concentration of 10^{-4} M reduced the rate of excretion by approximately 26% ($P < 0{\cdot}001$) and at 10^{-3} M by 35·2% ($P < 0{\cdot}01$).

Discussion

The bioavailability of digoxin tablets as assessed by comparison of the area under the concentration-time curves for intravenous and oral dosing is approximately 70%. The remainder of the dose can be recovered in the faeces, but some of this may represent material which has been excreted by non-renal routes. With a molecular weight of 780, biliary excretion is possible in most species, including man. However, in the rat there is evidence of elimination across the wall of the intestine (Caldwell et al 1980). According to the present studies it would appear that this is partly an energy-dependent process and that it can be inhibited by potassium cyanide and anoxia. It is clear also that quinidine in concentrations which are clinically relevant can affect the transfer of digoxin across the intestinal wall. Since non-renal elimination of digoxin in man (in vivo) has been demonstrated to be reduced by quinidine (Schenck-Gustafsson & Dahlqvist 1981) we propose that inhibition of secretion of digoxin across the intestinal wall by quinidine contributes to the reduction in non-renal elimination observed in man.

Table 1. Factors affecting the intestinal transfer of digoxin. [^{3}H]Digoxin solution (Radiochemical Centre) was diluted with Krebs solution to give 2 μCi; 0·036 nmol ml^{-1}. 1·0 ml of this solution was added to each sac and the treatments listed below were applied to the bath (mucosal surface).

Treatment	No. expt.	Rate of transfer of ^{3}H (d ml^{-1} min^{-1}) Control	Treated	% change
Quinidine 10^{-3}M	8	396 (159)	257 (66)	−35·2**
Quinidine 10^{-4}M	6	366 (132)	260 (126)	−26·2***
KCN 10^{-3}M	4	440 (185)	259 (145)	−41·1**
N_2 (gassed)	3	471 (36)	263 (71)	−44·3**
Ouabain 10^{-3}M	3	286 (21)	368 (50)	+28·5*
Ouabain 10^{-3} M (inside sac + bath)	3	400 (54)	421 (38)	+5·4 (NS)

The results are the mean (with s.d.).
*$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$ by Student's *t*-test for paired data.
(NS)—not statistically significant.

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