The agonist activity of β-kainate was again evident from the microiontophoretic experiments in-vivo, where β-kainate produced responses very similar in profile to those of α-kainate though it was less potent. However, β-kainate showed no ability to antagonize excitation due to α-kainate, quisqualate or NMA. Indeed the application of β-kainate together with these agonists often produced merely a rising baseline. Even when β-kainate was applied at very low currents of about 5 nA, however, which was insufficient to produce an increase of baseline activity, the presence of background depolarization was seen as a rapid over-depolarization when the agonists were applied.

It may be concluded that β-kainate is *not* an antagonist of excitatory amino acids acting at the three main types of receptor currently recognized for NMA, quisqualic acid or α-kainate at least in the neocortex in-vivo or hippocampus in-vitro. The anticonvulsant properties of this isomer are presumably therefore unrelated to these receptors, or may involve a presynaptic action to reduce the release of endogenous substances mediating part of the convulsive behaviour.

The marked behavioural effects seen after β-kainate administration in-vivo (Collins et al 1984) could however, reflect the agonist properties of the compound. It is not yet clear whether these agonist effects are mediated by the α-kainate receptor, other excitatory sites, or a non-specific form of depolarization, as no selective antagonists at the α-kainate receptor are currently available. It would be of interest to examine the activity of β-kainate in kainate binding studies to help answer this question.

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Amiodarone does not affect digoxin kinetics in the rabbit

D. C. Buss*, P. A. Routledge, *Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK*

It has been reported that amiodarone may interact with digoxin in man. We investigated the effects of amiodarone pretreatment (35 mg kg^{-1} day^{-1}) on the pharmacokinetics of a single dose of digoxin (50 μg kg^{-1}) in 6 rabbits. Total body clearance of digoxin was 138·84 ± 44·67 and 147·99 ± 29·17 ml min^{-1}, serum half life 187·9 ± 60·9 and 181·34 ± 25·57 min and volume of distribution 35·4 ± 8·54 and 37·8 ± 3·9 litres before and after amiodarone treatment, respectively. None of these changes were statistically significant. We conclude that the presence of an amiodarone-induced change in digoxin pharmacokinetics in the rabbit was not evident and that other animal models will be necessary for studying this interaction.

Amiodarone is a benzofuran iodine-containing compound which has been used effectively for a wide variety of cardiac arrhythmias (Marcus et al 1981). Recent reports indicate that it may interact with digoxin (Furlanello et al 1981; Moysey et al 1981; McGovern et al 1983) although not all studies have confirmed this. Since it is technically and ethically difficult to examine the mechanism of this interaction in man, we decided to investigate the effect of amiodarone pretreatment on digoxin clearance in the rabbit.

* Correspondence.

Methods

Six New Zealand white rabbits (2·5–3·75 kg) were caged separately in metabolism cages. On day 1 the rabbits were injected slowly with digoxin (Antigen Ltd) 50 μg kg^{-1} i.v. via the left ear marginal vein over 2 min. Venous blood samples (2 ml) were obtained at 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min by incision of the right ear marginal vein and blood was collected into potassium EDTA collection tubes which were stored on ice until separation by centrifugation at 500g for 10 min. Plasma was removed and the samples were frozen at −20 °C until assayed (within 3 months).

At the end of day 1 and successively on days 2, 3 and 4, amiodarone (Cordarone-Labaz) 35 mg kg^{-1} was injected subcutaneously. On day 5, samples were collected as previously described and the animals killed by cervical dislocation.

Serum digoxin concentrations were measured using a commercially available radioimmunoassay kit (Amerlex-Amersham International). Amiodarone at a concentration of 4 mg $litre^{-1}$ showed no interference with the assay.

The decline in the post-distribution phase digoxin concentrations (pre- and post-amiodarone) was biex-

ponential. The elimination rate constant k_{el} was obtained from this data by least squares regression analysis. The area under the serum concentration time curve (AUC) was obtained by trapezoidal integration and added to the area extrapolated from time T to infinity. Total body clearance (Cl_B) was calculated using: $Cl_B = Dose/AUC^{0-\infty}$ and renal clearance ($Cl_R = A_e^{0-6h}/AUC^{0-6h}$. Where Ae^{0-6h} is the amount of unchanged drug excreted into urine between 0–6 hours.

Differences in the kinetic data between amiodarone-treated and untreated animals was determined by Student's paired *t*-test.

Results

The pharmacokinetic parameters for digoxin in each rabbit before and after amiodarone administration are shown in Table 1. There was no significant change in any pharmacokinetic parameter as a result of amiodarone administration at the dose used ($P > 0.05$ in all cases).

Table 1. Pharmacokinetic parameters for digoxin in each rabbit before and after amiodarone.

Rabbit	α min^{-1}	β min^{-1}	$t_{\frac{1}{2}\beta}$ min	AUC	Cl_B ml min^{-1}	Vdβ litres	Cl_R ml min^{-1}
				Pre-amiodarone			
1	0·0533	0·00216	320·2	1578·9	94·9	43·8	0·44
2	0·09728	0·00512	135·2	800·2	187·4	36·5	0·56
3	0·06521	0·0044	155·3	680·0	202·1	45·3	3·07
4	0·04770	0·00397	174·5	818·6	152·6	38·4	1·03
5	0·05210	0·0038	181·5	1915·5	91·3	23·9	0·92
6	0·05185	0·00430	160·8	1798·8	104·2	24·2	0·30
$\bar{x}$	0·06125	0·00397	187·9	1265·3	138·8	35·4	1·05
s.d.	0·01699	0·00091	60·9	510·6	44·6	8·5	0·94
				Post-amiodarone			
1	0·06057	0·00316	218·8	1289·1	116·36	36·7	
2	0·07768	0·00425	163·0	781·5	191·93	45·1	
3	0·38234	0·00445	155·6	772·1	178·07	39·9	
4	0·06242	0·00453	1523·9	807·1	154·87	34·2	
5	0·09936	0·00362	191·3	1442·8	121·28	33·5	
6	0·10546	0·00336	206·2	1494·5	125·46	37·3	
$\bar{x}$	0·13130	0·00390	181·3	1097·8	147·99	37·8	
s.d.	0·11353	0·00053	25·6	317·2	29·17	3·9	

Discussion

Several reports have indicated that the concomitant use of digoxin and amiodarone may result in increased plasma digoxin concentration. Moysey et al (1981) showed an increase in plasma digoxin concentrations of 69% after administration of amiodarone 200 mg t.i.d. In a study comprising 22 subjects, Oetgen et al (1982) observed a 2-fold increase whilst Nademanee et al (1982), in a study of 20 patients receiving digoxin for more than 2 months before and then after amiodarone 600–1800 mg day^{-1} for 2 weeks showed that 85% of the patients developed adverse reactions during combination treatment. Similarly Furlanello et al (1981) showed a significant interaction between plasma amiodarone and digoxin concentrations in 33 subjects, although no patient developed clinical digoxin toxicity during the study. In contrast Achilli & Serra (1981) reported no change in serum digoxin concentration in 5 patients who received digoxin at least 10 days before and during amiodarone treatment.

We have been unable to demonstrate a significant interaction in the rabbit. Several explanations for this discrepancy are possible. In man, digoxin is often excreted largely unchanged (80%) in the urine. The low renal clearance of digoxin in the rabbits in this study together with the very high total body clearance indicates that the drug is largely metabolized in the rabbit. This agrees with the work of Ochs et al (1977) which showed that digoxin was largely cleared by non-renal mechanisms and their value for average clearance (142·4 + 14·12 ml min^{-1}) corresponds closely with ours. Therefore, if the interaction in man occurs by inhibition of renal clearance of digoxin, it is unlikely that we would have detected this interaction in the rabbit.

A second possible mechanism for the interaction is through displacement of the drug from the tissues leading to increased plasma digoxin levels and a reduced apparent volume of distribution. There is no evidence of any change in this parameter in the rabbit.

We conclude that at the dose which is known to cause an interaction with warfarin in the rabbit (Rees et al 1981), amiodarone does not affect the pharmacokinetics of digoxin in this animal. The mechanisms of the interaction in man therefore remains unclear.

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