Renal elimination of amiodarone and its desethyl metabolite

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Summary

Two patients in chronic renal failure receiving amiodarone for the treatment of refractory arrhythmias were commenced on dialysis, in one case, intermittent peritoneal dialysis, in the other, haemodialysis. Plasma concentrations of amiodarone and its desethyl metabolite were consistent with the dose received, whilst neither compound was recovered in the dialysate. In these patients and in 10 additional patients with normal renal function taking amiodarone, only negligible amounts of either compound were detected in urine. These findings suggest that amiodarone may be a suitable antiarrhythmic agent for use in patients with chronic renal failure.

KEY WORDS: amiodarone, renal elimination, peritoneal dialysis, haemodialysis.

Introduction

The antiarrhythmic agent amiodarone is a benzofuran derivative (mol.wt. 680) with a long duration of action. Recently, a desethyl metabolite has been noted in the plasma of patients receiving the drug (Flanagan *et al.*, 1982). Little is known about the elimination of amiodarone although work by Broekhuysen suggested that hepatic rather than renal clearance was the major route of excretion (Broek-

huysen, Laruel and Sion, 1969). A patient with polycystic kidneys who was taking amiodarone for control of atrial fibrillation, required intermittent peritoneal dialysis and we took the opportunity to measure this drug and its metabolite in plasma, urine and dialysate. Similarly, a second patient with chronic renal failure was treated by haemodialysis whilst receiving amiodarone and the two compounds were measured in plasma before and after dialysis, and samples of dialysate were analysed for their presence. The concentrations of these compounds in urine were compared with those from patients with normal or mildly impaired renal function who were also receiving amiodarone.

Patients and methods

Case 1

A 58-year-old male with a prosthetic mitral valve was admitted in atrial fibrillation and cardiac failure. The atrial fibrillation proved refractory to conventional antiarrhythmic agents but the rapid ventricular rate was controlled with amiodarone, 800 mg daily for 1 week and 200 mg daily thereafter. In addition, the patient was known to have polycystic kidneys and there had been a progressive deterioration in renal function (urea—60.4 mmol/litre, creatinine—61 µmol/litre). Intermittent peritoneal dialysis (2 hourly cycles of 2 litres dialysate, 48 hr per week) was commenced 4 months later. Blood samples were collected before, during and after 48 hr of peritoneal

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TABLE 1. Chronic peritoneal dialysis. Patient receiving 200 mg amiodarone daily. Measurements made 8 hr post-dose. (Data for 58-year-old male patient)

	Plasma		Dialysate		Urine	
	Amiodarone (mg/litre)	Desethyl-amiodarone (mg/litre)	Amiodarone (mg/litre)	Desethyl-amiodarone (mg/litre)	Amiodarone (mg/litre)	Desethyl-amiodarone (mg/litre)
24 hr after dialysis commenced	0.5	0.6	ND	ND	—	—
48 hr after dialysis commenced	0.4	0.5	ND	ND	—	—
24 hr post-dialysis	0.5	0.5	—	—	0.02	0.13
4 days post-dialysis	0.6	0.7	—	—	0.02	0.14

ND = not detected. Lower limit of detection = 0.005 mg/l.

dialysis, together with samples of dialysate and urine for the measurement of amiodarone and desethylamiodarone.

Case 2

A 54-year-old anuric woman with chronic renal failure secondary to membranous nephropathy, treated by haemodialysis, received amiodarone, 400 mg daily, for the treatment of symptomatic ventricular tachycardia. One month after starting amiodarone therapy, blood samples were collected before and after dialysis on 3 occasions (19 and 24 hr after amiodarone) together with samples of dialysate, for the measurement of amiodarone and desethylamiodarone.

In addition, samples of blood and urine were collected from 10 patients (8 male, mean age ($\pm$ s.d.) 54 ($\pm$ 10.2) years) receiving chronic amiodarone therapy, mean daily dose ($\pm$ s.d.) 359 ($\pm$ 235) mg. In all cases, the samples were collected 8–12 hr after the last dose had been administered. In 9 of these patients, the serum creatinine was within the normal limits for our laboratory whilst one patient had a modestly elevated serum creatinine of 157 μ mol/litre.

Plasma amiodarone and desethylamiodarone were measured using a specific high-performance liquid chromatographic technique (Flanagan, Storey and Holt, 1980). At the increased sensitivity required for the measurement of these compounds in dialysis fluid and urine, a modification of this method was employed (Storey and Holt, 1982).

Results

In Case 1, plasma concentrations of amiodarone and its metabolite were well within the range for the dose prescribed (Holt and Storey, 1983) (Table 1) and these did not fluctuate significantly during dialysis. Neither the parent compound nor the metabolite were detected in the dialysate, and only minimal quantities of these compounds were measured in urine.

In case 2, there was little fluctuation in mean plasma amiodarone and desethylamiodarone concentrations between pre-dialysis (1.19 ± 0.31 , 1.03 ± 0.02 mg/litre) and post-dialysis (1.00 ± 0.11 , 0.97 ± 0.04 mg/litre) samples, respectively. Neither compound could be detected in dialysate (limit of detection 0.005 mg/litre).

In the 10 additional patients receiving chronic amiodarone therapy, the mean urinary concentration of amiodarone was 0.029 ± 0.027 mg/litre and for desethylamiodarone was 0.149 ± 0.132 mg/litre; mean plasma concentrations were 2.08 ± 1.47 mg/litre (amiodarone) and 1.48 ± 0.90 mg/litre (desethylamiodarone). No correlation was found between urinary excretion of these compounds and serum creatinine or amiodarone dosage.

Discussion

Amiodarone is a class III antiarrhythmic agent, effective in the management of atrial and ventricular arrhythmias. However, its clinical use has been limited by its association with a number of unwanted effects ranging from asymptomatic corneal deposits, detectable only on slit lamp examination (Verin *et al.*, 1971), to clinical thyroid dysfunction with both hypo- and hyper-thyroidism being described (Wolff, 1969; Savoie *et al.*, 1975; Jaggarao *et al.*, 1982). More recently, amiodarone has been implicated as a possible cause of pulmonary fibrosis (Rotmensch *et al.*, 1980; Heger *et al.*, 1981). Notwithstanding these unwanted effects, amiodarone has proved sufficiently valuable in the management of refractory arrhythmias that its use in clinical practice is often required.

Despite its introduction 20 years ago, initially as an anti-anginal agent (Vastesaegeer, Gillot and Rasson, 1967), data on the pharmacokinetics of amiodarone have appeared only recently, following the development of a method to measure amiodarone and its desethyl metabolite in plasma. Both compounds have a long terminal half-life of elimination (of the order of 50 days), amiodarone having a comparatively low clearance and large volume of distribution (Holt and Storey, 1983). On a chronic oral daily dose of 400 mg

amiodarone, patients achieve a mean plasma concentration of 2.12 ± 0.80 mg/litre (amiodarone) and 1.94 ± 0.56 mg/litre (desethylamiodarone); the ratio parent compound/metabolite is approximately one (Holt and Storey, 1983). To date, desethylamiodarone is the only metabolite identified in biological fluids and tissues; its pharmacological activity is not known and the methodology employed in this study does not exclude the possibility of other, more water soluble, metabolites.

Salivary measurements of amiodarone suggest that the drug is highly protein bound (of the order of 98%) (Holt and Storey, unpublished observation) and displacement of other highly protein-bound drugs by amiodarone could be clinically important, although the marked potentiation of the action of warfarin by amiodarone is unlikely to be due to this mechanism (Serlin, Sibeon and Green, 1981).

Earlier work by Broekhuysen *et al.* (1969), using ^{131}I -labelled amiodarone suggested that the main route of elimination of the drug was via the gastrointestinal tract with little being excreted in urine. Consistent with these data, very low concentrations of parent compound and metabolite were measured in the urine of our 10 subjects with normal or mildly impaired renal function. Similarly, negligible amounts of these compounds were found in the urine of one of our patients with chronic renal failure suggesting that the renal route is not significant in the elimination of the drug. Nor were the compounds detectable in dialysis fluid, probably reflecting their very large volume of distribution and poor aqueous solubility.

In addition, our patients with chronic renal failure had plasma amiodarone and desethylamiodarone concentrations well within the normal range for the dose administered and duration of therapy, and there were minimal fluctuations between dialysis. These concentrations, coupled with a ratio of parent compound/metabolite in the range 0.8–1.2, suggest that biotransformation of amiodarone is not altered significantly in renal failure and that no dosage adjustment will be required in these patients. This would represent a definite advantage over many other antiarrhythmic agents such as digoxin, disopyramide and procainamide which are largely eliminated by the kidney (Woosley and Shand, 1978). With these

latter drugs, dosage adjustment and careful monitoring of drug plasma levels are essential in renal failure if toxicity is to be avoided.

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