Creatinine elevation in patients receiving amiodarone correlates with serum amiodarone concentration

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Serum creatinine and drug concentrations were measured at 0, 1, 2, 3, 6, 9 and 12 months in 30 consecutive patients started on amiodarone. In 28 of these patients with no obvious cause for altered renal function, mean serum creatinine increased to 11% above baseline ($P < 0.005$). Rising creatinine concentrations correlated with amiodarone concentrations ($y = 93.9 + 8.6x$, $r = 0.51$, $P < 0.0001$). When assessing elevation of serum creatinine in a patient receiving amiodarone, physicians should be aware that it may be related to this drug.

Keywords amiodarone creatinine

Introduction

Amiodarone was once considered an almost ideal antiarrhythmic agent because of its convenience, effectiveness, low incidence of acute adverse effects and lack of negative inotropic effects [1]. Following reports of serious liver and lung toxicity during long-term therapy with higher doses in the 1980s, its use had been quite restricted in North America. However, the publication of the Cardiac Arrhythmia Suppression Trial data [2] has led to a resurgence of interest in this agent. We followed a cohort of patients for adverse effects of amiodarone in a 1 year prospective trial and observed a statistically significant elevation of serum creatinine which correlated with serum drug concentrations.

Methods

Subjects

Written informed consent was obtained to study 30 consecutive patients in whom amiodarone therapy was being initiated for refractory cardiac arrhythmias. Fourteen patients had atrial and 16 had ventricular arrhythmias of which 11 were related to ischaemic disease. No patients were receiving calcium antagonists or angiotensin converting enzyme inhibitors. Of 10 patients with some degree of left ventricular dysfunction, one had symptoms requiring adjustment of frusemide dose during the study (and was excluded from analysis for this reason). Six patients were re-

ceiving hydrochlorothiazide ≤ 50 mg day⁻¹ throughout the study. Fasting glucose averaged 6.0 to 6.4 mmol l⁻¹ during the study.

Protocol

'Loading' doses of amiodarone 400 mg, 4 times daily, for 7 days were generally followed by 200 mg day⁻¹ for atrial arrhythmias or 400 mg day⁻¹ for ventricular arrhythmias. After further dosage adjustments according to response, four patients continued on 200, four on 300, 20 on 400, and two on 600 mg day⁻¹. Before and at 1, 2, 3, 6, 9 and 12 months after starting therapy, blood was drawn for biochemistry including serum creatinine done in a standardized clinical laboratory. Concentrations of amiodarone and its active metabolite, desethylamiodarone (DEA), were also measured by high performance liquid chromatography [3]. Aspects of the protocol to detect other adverse effects are described elsewhere [4].

Analysis of data

Changes from baseline measurements over time were assessed by repeated measures analysis of variance. Least squares linear regression was performed to determine the degree of correlation between drug concentrations and serum creatinine. Student's unpaired *t*-tests or contingency tables analysis were used as appropriate to compare groups in exploratory analysis. Data are presented as means $\pm$ standard errors.

Results

In 30 patients with a mean age of 56 ± 2 years, mean serum creatinine rose progressively, reaching 13% above baseline ($P < 0.001$). A search for obvious explanations for the observed increase in creatinine elevation revealed that one patient had worsening congestive heart failure which produced an increase in serum creatinine reaching 215% of baseline. This patient and one confounded by previous exposure to amiodarone were therefore excluded from analysis. No obvious causes for an increase in serum creatinine were apparent in 28 patients. The increase in mean serum creatinine in these 28 patients remained statistically significant reaching 11% above baseline ($P < 0.005$). Figure 1a illustrates the progressive rise in creatinine in these 28 patients which was statistically greater than baseline for all time points after 1 month. There was no further progression of the creatinine elevation beyond the 6 month measurement. Figure 1b demonstrates the highly statistically significant correlation between serum creatinine and amiodarone concentrations for all measurements after one month ($y = 93.9 + 8.6x$, $r =$

Figure 1 Serum creatinine in 28 patients during the first year of therapy with amiodarone. a) Plot of change in mean serum creatinine over time with standard error bars. Differences from baseline are statistically different for all time points after 1 month. b) Least squares linear regression demonstrating the correlation between serum creatinine concentrations after 1 month and corresponding amiodarone concentrations ($y = 93.9 + 8.6x$, $r = 0.51$, $P < 0.0001$).

Table 1 Exploratory analysis of characteristics for groups of patients with lesser (Group 1) and greater (Group 2) increases in serum creatinine while receiving amiodarone

	Group 1 (n = 16)	Group 2 (n = 12)	P
Age (years)	58	53	0.3
Weight (kg)	83	79	0.6
Sex (number of women)	6	2	0.3
Dose (mg day ⁻¹)	350	400	0.2
Dose (mg kg ⁻¹ day ⁻¹)	4.5	5.2	0.3
Creatinine at entry (mmol l ⁻¹)	110	99	0.6
Glucose at entry (mmol l ⁻¹)	6.1	6.8	0.4
Total cholesterol at entry (mmol l ⁻¹)	5.1	5.0	0.4
Total cholesterol at 1 year (mmol l ⁻¹)	5.3	5.9	0.2

Values are means; P is the statistical probability that the difference between groups occurred by chance.

0.51, $P < 0.0001$). Undue leverage of the correlation was avoided by excluding the earliest observations which had markedly lower concentrations. Verification of random distribution in a plot of residual vs fitted values confirmed the suitability of the data for analysis by general linear regression. Concentrations of DEA were highly correlated with those of the parent compound ($r = 0.98$) and the correlation of DEA with serum creatinine was similar to that of amiodarone.

Once the statistical relationship between serum creatinine and amiodarone concentrations was noted, some basic exploratory analyses of the data were performed to look for useful stratification criteria for future studies. The 28 patients were arbitrarily separated into two groups based on their maximum deviations in serum creatinine from baseline. Group 1 consisted of 16 patients with lesser changes in serum creatinine (< 1 s.d. for the study population), while Group 2 was 12 patients with greater changes (≥ 1 s.d.). Exploration was conducted by comparing the characteristics of the two groups to look for factors that might have influenced the rise in serum creatinine. No statistically significant differences were apparent (Table 1). Most of the women (6 of 8) were in the group with the lesser changes in creatinine. A trend toward higher dosing was seen in the group with the greater changes in creatinine.

Discussion

A correlation between administration of amiodarone and increased serum creatinine has not been reported previously. Despite the large number of clinical trials using amiodarone, only one case report of an effect on serum creatinine can be found in the literature [5]. That report verified the relationship by rechallenge with amiodarone. Amiodarone is not an obvious nephrotoxin and is not a negative inotropic agent [6], so investigators have had no reason to search for such an effect. It is understandable why changes in creatinine have not been reported, since a moderate increase in serum creatinine in a single patient from the relatively ill population usually receiving amiodarone might not be considered noteworthy in clinical practice. How-

ever, the fact that 43% of the patients analysed in this study had at least a 25% increase in serum creatinine cannot be dismissed.

This study was not designed to explore the mechanism of previously unreported effects. Repeated measurement of 24 h creatinine clearance or anthropomorphic parameters were not included in the study design and would not have determined any mechanism of toxicity. Similarly measurement of cardiac output would not have reliably reflected total daily renal perfusion. These relatively sedentary, middle aged and elderly patients would not be expected to have any increase in muscle mass over the course of the study and the effect of age on renal function would be minimal over 1 year. Thus the observed increase in serum creatinine in these patients clearly relates to a decline in creatinine clearance since this is inversely proportional to serum creatinine [7] when lean body mass and age remain constant. The observed increase could not be attributed to progressive cardiac failure, to urinary obstruction or to diabetic or hypertensive nephropathy in any of the 28 patients analysed. Had there been such chronic secondary causes responsible for the creatinine elevation, one would have expected a slow continuous increase in serum creatinine over the study period. Instead, an early rapid increase in serum creatinine was followed by a levelling off at 6 months when amiodarone reached steady state serum concentrations. This observation was corroborated by the highly statistically significant correlation between serum creatinine and amiodarone concentrations.

If amiodarone were renally excreted this correlation could have been explained by a decline in renal function leading to a reduction in amiodarone clearance. However, amiodarone is almost exclusively cleared by hepatic metabolism and excreted into the bile. The possibility that the serum creatinine was factitiously elevated by the presence of amiodarone in the serum can be discounted also since not all patients who received amiodarone had elevated creatinine concentrations. If the creatinine assay were measuring serum amiodarone or desethylamiodarone as creatinine, the

correlation between increasing creatinine and amiodarone concentrations would have been approximately 1.0. In addition, interference with the clinical assay for serum creatinine was excluded by verifying that the laboratory reported identical creatinine values for the same serum sample measured clean, spiked with amiodarone or spiked with desethylamiodarone. The possibility that amiodarone alters proximal tubular secretion of creatinine or creatinine release by muscle cannot be ruled out. Possible mechanisms of toxicity would include an amiodarone-induced imbalance in the vascular tone of the afferent and efferent arterioles of the renal glomeruli.

In most patients, the effects of amiodarone on the kidney do not appear to be clinically important, or this relationship likely would have been reported before. No patient in this series had increases in creatinine which warranted discontinuation of therapy. However, some patients in this study did have important increases in serum creatinine (up to 58% above baseline) and it is conceivable that some patients are more sensitive than others to amiodarone effects on the kidney, as in the case report by Jacobs [5]. It is important, therefore, to be aware that an unexplained increase in serum creatinine in a patient receiving amiodarone may be related to the drug therapy and may necessitate alteration in dose or discontinuation of therapy. Elevation of serum creatinine appears to occur in the first 2 months of therapy, making possible the early identification of patients at risk of the renal effects of amiodarone. It is doubtful if clinical studies using ethically feasible tests would discern the mechanism of amiodarone related effects on renal function. Animal studies with access to renal tissue will likely be needed to determine whether changes occur in proximal tubular excretion, renal perfusion, or the rate of development of atherosclerotic lesions.

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