The relative effects of digoxin and diltiazem upon ventricular ectopic activity in patients with chronic atrial fibrillation

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In eight patients with chronic atrial fibrillation, treatment with digoxin (plasma drug concentration 1.3 to 2.0 nmol l⁻¹) was associated with a significantly higher incidence of ventricular premature beats (VPBs) (mean 22.8 h⁻¹) than diltiazem 120 mg three times daily (mean 6.8 h⁻¹) ($P < 0.05$). Seven out of the eight patients showed an increase in numbers of VPBs recorded over 24 h during treatment with digoxin when compared with diltiazem. The clinical importance of these results is unclear, but atrial fibrillation and ischaemic heart disease frequently co-exist, and increases in ventricular ectopy may predispose to serious ventricular arrhythmias following myocardial infarction.

Keywords digoxin diltiazem atrial fibrillation

Introduction

Digoxin is widely used to reduce ventricular response rates in patients with atrial fibrillation. However, it fails to control exercise induced tachycardia and rate-limiting calcium antagonists such as verapamil (Lewis *et al.*, 1987) and diltiazem (Lewis *et al.*, 1988a) appear to be more effective in this respect. Furthermore, digoxin has a narrow therapeutic ratio and toxicity may be associated with ventricular arrhythmias including complex ventricular premature beats (VPBs) and ventricular tachycardia (Wellens, 1976). It is not clear whether treatment with 'therapeutic' plasma concentrations of digoxin leads to an increased incidence of ventricular ectopy. Lown and colleagues (1977) have reported that treatment with a short acting digoxin-like drug may either increase or decrease the incidence of ventricular ectopy, increases being seen more frequently in patients with higher digoxin concentrations. The threshold for glycoside toxicity varies considerably between individuals and there is some evidence to suggest that plasma digoxin concentrations as low as 0.2 ng ml⁻¹ may be associated with arrhythmias in some subjects (Shapiro, 1978).

The aim of the present study was to compare the incidence of VPBs in patients with chronic atrial fibrillation during treatment with digoxin and diltiazem.

Methods

Data derived from a study designed to examine the effects of digoxin and diltiazem upon heart rate and exercise tolerance was used in the present investigation, and details of the methodology are described elsewhere (Lewis *et al.*, 1988a).

Ten patients (mean age 61; range 52–66 years; three females) with chronic atrial fibrillation completed the study, which was conducted as a randomised, double-blind crossover trial comparing treatment with digoxin and diltiazem. Each drug was taken for 4 weeks. The dose of digoxin was adjusted so as to produce plasma drug concentrations within the range 1.3 to 2.6 nmol l⁻¹ (as measured by radioimmunoassay; Smith *et al.*, 1969) between 6 and 8 h after dosing. The dose of diltiazem was increased after 2 weeks from 60 mg to 120 mg three times daily. All patients were normokalaemic (serum potassium concentration 3.5–5.0 mmol l⁻¹).

During the last 24 h of each treatment period, two-channel ambulatory ECG monitoring was performed using Holter monitors. Technically satisfactory recordings were obtained in eight subjects. These were analysed independently for the presence of VPBs (Cardiologic (UK) Ltd, Liverpool) and printouts of representative samples of abnormal ventricular rhythm were subsequently examined by us in detail to exclude apparent VPBs resulting from aberrant conduc-

tion of supraventricular impulses. Beats with a right bundle-branch block configuration, beats without a preceding compensatory pause and those with a QRS duration of less than 0.14 s were assumed to reflect aberrancy rather than ectopy (Rapeport & Schamroth, 1985; Kastor, 1973) and were excluded from the analysis. In those patients with a large number of VPBs, printouts of all abnormal rhythms were not available. However, in only one subject were significant numbers of broad QRS complexes, identified by computer as ectopics, thought to reflect aberrancy rather than ectopy.

Results

VPBs were seen in all patients (range 3–1164 24 h^{-1}). During treatment with digoxin, four subjects had more than 25 VPBs h^{-1} and four had less than 20 VPBs h^{-1} . These two groups did not differ significantly in terms of aetiology of atrial fibrillation, presence or absence of diuretic therapy, serum potassium concentration or serum digoxin concentration. Clearly, however, a study of this size does not have the power to exclude reliably the possibility that one or more of these parameters may have influenced the prevalence of ventricular ectopy.

VPBs were significantly more frequent during treatment with digoxin (mean 22.8; range 0.13–48.5 h^{-1}) when compared with diltiazem (mean 6.8; range 0–28.4 h^{-1}) ($P < 0.05$). Seven out of the eight patients showed an increase in ventricular ectopic activity during treatment with digoxin (Figure 1). Ventricular couplets and triplets were seen in two patients during treatment with digoxin; none was seen during treatment with diltiazem.

Discussion

In the present study, treatment with digoxin was associated with a 3–4 fold increase in the prevalence of VPBs compared with diltiazem. Moreover, two patients showed ventricular couplets and triplets during treatment with digoxin and these were not seen with diltiazem. The results could be criticised on the grounds that differentiation between VPBs and aberrancy was not always possible with certainty. However, the prevalence of VPBs was compared within patients, and there is no real reason to expect that one modality of treatment as opposed to another should affect the relative incidence of ectopy as opposed to aberrancy. Nevertheless, such a possibility cannot be excluded, particularly

Figure 1 Numbers of ventricular premature beats (VPBs) h^{-1} seen in eight patients with chronic atrial fibrillation during treatment with diltiazem 120 mg three times daily and digoxin.

in view of the fact that treatment with diltiazem was associated with a small decrease in ventricular irregularity. Examination of 12 lead ECGs taken at rest and after exercise did not suggest that the two drugs differed in terms of their effect on the duration of QRS complexes.

All patients had plasma digoxin concentrations within the accepted therapeutic range and none was hypokalaemic. Hypomagnesaemia increases susceptibility to digoxin toxicity and may be seen in up to 20% of patients with atrial fibrillation (DeCarli *et al.*, 1986) although magnesium concentrations were not measured in the present study.

On the basis of this study it is not possible to say whether the relative increase in the prevalence of VPBs seen during treatment with digoxin was due to an arrhythmogenic action by digoxin or an anti-arrhythmic effect of diltiazem. Goren & Denes (1981) found that the incidence of complex VPBs was similar in three groups of patients with serum digoxin concentration of 0–1.0; 1.1–2.0 and $>2.1 \text{ ng ml}^{-1}$. Complex VPBs were seen in 68%, 63% and 73% respectively of these patients. This does not, of course, exclude the possibility that even small concentrations of digoxin may be responsible for increases in ventricular ectopy, and we have been unable to find reports comparing the prevalence of VPBs in patients taking

digoxin with those who are not. Conversely, there is little evidence to suggest that diltiazem has an important anti-arrhythmic effect in practice although verapamil, which appears to have broadly similar electrophysiological properties, has been shown to reduce the incidence of VPBs (Schamroth *et al.*, 1972).

The importance of VPBs in this context is debatable. However, many patients with atrial fibrillation have underlying ischaemic heart disease and there is concern that ventricular ectopy may predispose to potentially fatal arrhythmias following myocardial infarction (Ruberman *et al.*, 1977). Data from the MILIS study does not suggest that treatment with digoxin appears to be an independent risk factor for cardiac death in patients with coronary artery disease (Muller *et al.*, 1986). Nevertheless, it

would seem reasonable to assume that ventricular ectopy is basically an undesirable phenomenon, and that treatments which are associated with a lower prevalence of VPBs might be preferable in certain clinical situations.

Previous studies in this Department have not shown that the calcium antagonists have clear advantages over digoxin in the treatment of atrial fibrillation in terms of improvements in exercise tolerance or cardiac output (Lewis *et al.*, 1987, 1988a, b). However, if the results of the present study were to be confirmed with larger numbers of patients, diltiazem might be regarded as a more appropriate treatment than digoxin in patients with atrial fibrillation and a history of severe ventricular arrhythmias or acute myocardial infarction.

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