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Factors affecting the clinical response to treatment with digoxin and two calcium antagonists in patients with atrial fibrillation

R.V. LEWIS & D.G. McDEVITT
Department of Pharmacology and Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee DD1 9SY, Tayside

It has been suggested that patients in whom atrial fibrillation (AF) is associated with poor exercise tolerance respond better to treatment with xamoterol plus digoxin than to digoxin alone; this may be attributable to better control of exercise induced tachycardia. We have examined data obtained during studies comparing digoxin and two calcium antagonists in the treatment of AF to see whether subgroups of patients with particularly poor exercise tolerance, rheumatic heart disease or rapid post-exercise heart rates might derive particular benefit from one modality of treatment as opposed to another. The results do not indicate that calcium antagonists improve exercise tolerance compared with digoxin in any of these subgroups despite achieving consistently better control of exercise induced tachycardia.

Keywords digoxin calcium channel antagonists

Introduction

Rate-limiting calcium antagonists such as verapamil and diltiazem achieve better control of exercise induced tachycardia than digoxin in patients with atrial fibrillation (AF) (Lang *et al.*, 1983; Lewis *et al.*, 1987, 1988a,b). However, we have found that the lower ventricular rates seen with the calcium antagonists are not generally associated with improved symptom control, exercise tolerance or cardiac output. Molajo *et al.*, (1984) have reported that xamoterol improves exercise capacity in patients with limited exercise tolerance (NYHA classes II and III) but not in those in NYHA class I. This suggests that there may be subgroups of patients with AF who may benefit from one form of treatment as opposed to another. We have examined data derived from studies described elsewhere (Lewis *et al.*, 1987, 1988a,b) comparing verapamil, diltiazem and digoxin in the treatment of AF, to try and identify any subgroups of patients who may benefit from one form of treatment as opposed to another. Comparisons were made between individuals with limited exercise tolerance and good exercise tolerance, and between subjects with rheumatic heart disease (RHD) and non-rheumatic heart disease (non-RHD) as prolongation of diastolic filling time might be of benefit in patients with mitral stenosis where ventricular filling may be particularly slow. Comparisons were also made between patients with rapid post-exercise heart rates (> 175 beats min^{-1}) and the remainder.

Methods

All studies were conducted as randomised, double-blind crossover comparisons of the effects of digoxin and calcium antagonists upon heart rate and maximum exercise tolerance in patients with chronic AF. In each case, therefore, comparisons were made between digoxin and either verapamil or diltiazem within the same subject. In study 1 (Lewis *et al.*, 1987) 12 subjects took varying doses of verapamil (40 mg, 80 mg and 120 mg, each given three times daily for 2 weeks) or digoxin (plasma drug concentration 1.3 to 2.6 $nmol^{-1}$) for 6 weeks. Maximum exercise tolerance was estimated using a treadmill according to a modified Bruce protocol. In study 2 (Lewis

et al., 1988b) 14 patients took diltiazem (60 mg, increased after 2 weeks to 120 mg, three times daily) or digoxin, for 4 weeks each. Maximum exercise tolerance was estimated using a 6 min walking test. In study 3, (Lewis *et al.*, 1988a) six patients took single varying doses of verapamil, diltiazem and digoxin, and maximum exercise tolerance was determined 3 h after dosing using a treadmill, according to a modified Bruce protocol. In all studies, resting and post-exercise heart rates were determined from 20 s ECG strips.

Results obtained during treatment with digoxin, verapamil 120 mg three times daily and diltiazem 120 mg three times daily were included in the present analysis. These dose levels of verapamil and diltiazem achieved similar reductions in exercise-induced tachycardia and results obtained during treatment with each of the calcium antagonists was therefore combined. Data derived from 25 different patients who completed all relevant treatment periods were examined in the present analysis.

Results

Results for all of the subjects showed that the calcium antagonists achieved a highly significant reduction in exercise induced tachycardia compared with digoxin (134.5 *vs* 147.6 beats min^{-1}; $P < 0.003$). However, there was no evidence that the improved control of exercise induced tachycardia seen with calcium antagonists was associated with increases in exercise tolerance. Mean walking distances were similar with both treatments (digoxin: 428 m, calcium antagonist: 455 m, NS). Twelve patients were better with digoxin, 11 were better with a calcium antagonist and two were unchanged.

The relative effects of digoxin and a calcium antagonist in subgroups of patients with good and poor exercise tolerance, rheumatic and non-rheumatic heart disease and post-exercise heart rates of more than or less than 175 beats min^{-1} were examined in two ways. Firstly, the numbers of subjects who showed increases or decreases in maximum walking distance during treatment with a calcium antagonist as compared with digoxin were noted. Secondly, walking distances seen during treatment with a calcium antagonist were expressed as a percentage of those seen during treatment with digoxin, and mean percentage changes were compared between the subgroups. Thus, values of >100% indicate that the calcium antagonist improved maximum exercise tolerance compared with digoxin.

Subgroup comparisons

Comparisons between subjects with good exercise tolerance and poor exercise tolerance. For each of the three studies, patients were divided into (approximate) quintiles according to their maximum walking distances. On this basis, six patients in the lowest 'quintile' were defined as having poor exercise tolerance, and six in the upper 'quintile' as having good exercise tolerance. Mean walking distances varied widely between the two groups (259 *vs* 630 m). The relative effects of digoxin and a calcium antagonist were examined as described above and the results (shown in Table 1) indicate that both subgroups responded similarly to each modality of treatment.

Comparisons between subjects with RHD and non-RHD. Twelve of the 25 subjects had rheumatic heart disease and the remainder had AF

Table 1 The results of the study

	Exercise tolerance		*Aetiology of AF*		*Post-exercise HR*	
	Poor	*Good*	*RHD*	*non-RHD*	*>175 beats min^{-1}*	*>175 beats min^{-1}*
Number of patients	6	6	12	13	6	19
Maximum walking distance						
Digoxin > calcium antagonist	2	3	6	6	2	10
Calcium antagonist > digoxin	3	2	5	6	3	8
Unchanged	1	1	1	1	1	1
Percentage change in walking distance seen with a calcium antagonist (compared with digoxin)	99.7	100.3	94.4	101.2	100.5	97.0

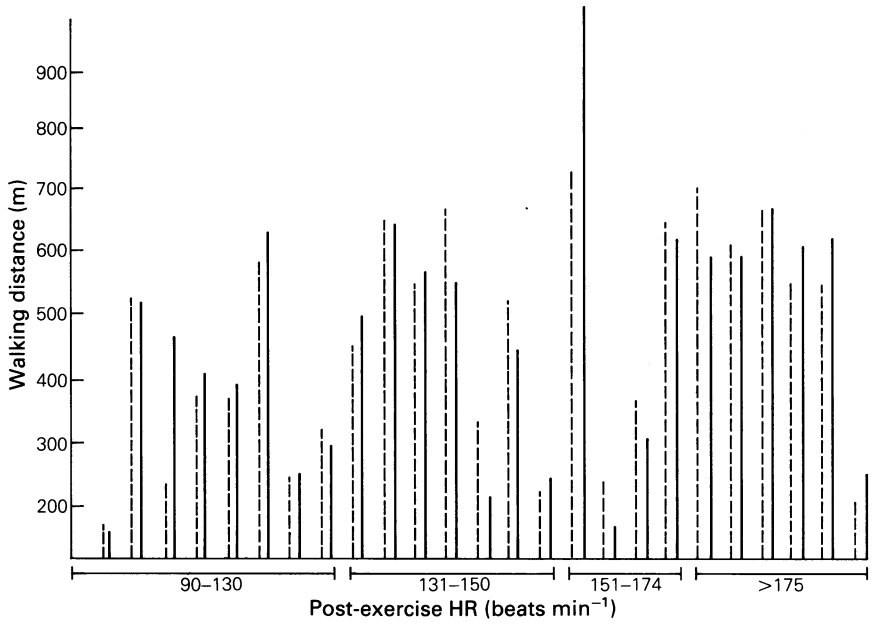

Figure 1 The relative effects of digoxin (---) and a calcium antagonist (——) upon maximum walking distance in 25 patients with chronic atrial fibrillation. Divisions based on post exercise heart rate refer to the digitalized state of the patients.

secondary to ischaemic heart disease, idiopathic fibrosis or treated thyrotoxicosis. These subgroups were compared as described above and the results (shown in Table 1) indicate that digoxin and a calcium antagonist had similar effects upon maximum walking distance in patients with RHD and in those with non-RHD.

Comparisons between subjects with post-exercise heart rates of more than or less than 175 beats min^{-1}. An (approximate) upper quintile of post-exercise heart rates was defined and six subjects were found to have rates of >175 (mean 180.3) beats min^{-1} during treatment with digoxin. Treatment with a calcium antagonist reduced the mean post-exercise heart rate in this upper quintile to 142 beats min^{-1}, but failed to improve exercise tolerance when compared with digoxin (Table 1); similar relative effects were seen in the 19 patients with lower post-exercise heart rates (Figure 1).

Discussion

Reduction of the rapid post-exercise heart rates, seen in digitalised patients with AF when they are treated with a calcium antagonist does not improve exercise tolerance. This may be because the negative inotropism of the calcium antagonists outweighs any benefit brought about by prolongation of ventricular filling times, or because the improvement in stroke volume seen with the calcium antagonists (Lewis *et al.*, 1988b) is offset by a rate-related reduction in cardiac output. Subgroups of patients with poor exercise tolerance, rheumatic heart disease or particularly rapid ventricular rates during exercise do not appear to derive any particular benefit from treatment with a calcium antagonist as opposed to digoxin. The benefits of xamoterol reported in patients with poor exercise tolerance (Molajo *et al.*, 1984) may be due to mechanisms other than reduction of the ventricular rate.

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