β -adrenoceptor blockers in atrial fibrillation: the importance of partial agonist activity

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- 1 The ideal drug treatment for atrial fibrillation will control resting heart rate, blunt exercise induced tachycardia whilst not exacerbating nocturnal bradycardia. Monotherapy with digoxin may not be ideal. We have compared the effect of combining digoxin (0.25 mg daily) with atenolol 50 mg and 100 mg or pindolol 5 mg twice daily and 15 mg twice daily in a cross-over randomised single-blind trial in eight symptomatic patients (six male; mean age 62 years) with poorly controlled atrial fibrillation.
- 2 Heart rate control was measured by 24 h ECG at baseline on digoxin therapy and after 2 weeks with each treatment. Symptom scores for breathlessness and palpitation were measured using visual analogue scales.
- 3 The addition of both β -adrenoceptor blockers significantly reduced mean diurnal maximum heart rate from baseline (all $P < 0.001$ ANOVA). Atenolol at both doses caused a greater reduction than either dose of pindolol ($P < 0.001$ ANOVA). Nocturnal maximum heart rate was not significantly reduced from baseline by either β -adrenoceptor blocker, but both doses of pindolol caused increases in nocturnal maximum heart rate compared with atenolol ($P < 0.001$ ANOVA).
- 4 Atenolol caused a reduction in diurnal minimum heart rate compared with baseline and caused a reduction in nocturnal minimum heart rate whereas pindolol caused an increase ($P < 0.001$ ANOVA).
- 5 Atenolol 100 mg caused longer nocturnal pauses compared with baseline but pindolol 15 mg twice daily reduced the number of nocturnal pauses > 1.5 s ($P = 0.05$).
- 6 In conclusion both β -adrenoceptor blockers improved diurnal heart rate control but atenolol prolonged pauses and worsened nocturnal bradycardia whereas pindolol reduced pauses and nocturnal bradycardia.

Keywords atrial fibrillation β -adrenoceptor blockers partial agonist activity
atenolol pindolol

Introduction

Atrial fibrillation is a common arrhythmia especially in the elderly [1]. It is an inefficient cardiac rhythm frequently associated with impaired effort tolerance and symptoms of dyspnoea and palpitation. If cardioversion to sinus rhythm is not considered appropriate, management is aimed at reducing the ventricular response to atrial fibrillation by pharmacological block of the atrio-ventricular node. Historically, digoxin has been the principal drug used for this purpose. However, it has a low therapeutic index and it is now well established that despite apparently good heart rate control at rest, it may not blunt excessive exercise induced tachycardia [2] and may produce excessive nocturnal bradycardia [3, 4]. The ideal treatment for atrial fibrillation will therefore

stabilise resting heart rate and blunt exercise induced tachycardia whilst not exacerbating nocturnal bradycardia.

Previous studies have shown that combination treatment of digoxin with β -adrenoceptor blockers may improve ventricular rate control during exercise [3, 5, 6]. Most of these studies have concentrated on the effect on maximum heart rate or exercise-induced tachycardia without examining the effect on nocturnal bradycardia and pauses characteristic of atrial fibrillation. Pauses of up to 4 s can occur in asymptomatic patients with 'controlled atrial fibrillation' [4]. Some studies employing β -adrenoceptor blockers with marked partial agonist activity (PAA) [3, 7, 8] have shown control of exercise

induced tachycardia and a reduction in nocturnal bradycardia and pauses thus producing an overall reduction in heart rate variability. The reason for this is that the heart rate at night is principally under parasympathetic control so β -adrenoceptor blockers with PAA by virtue of their β -adrenoceptor agonist effect may reduce nocturnal bradycardia. Which β -adrenoceptor blocker is best for atrial fibrillation?

The purpose of this study was to compare the effect of a β -adrenoceptor blocker with PAA (pindolol) and one without PAA (atenolol) on heart rate control in digitalised patients with chronic atrial fibrillation to examine whether there were significant differences in heart rate control in practice. We have used two different doses of each drug to examine dose related effects on the autonomic system.

Methods

Eight patients (six male, two female of average age 62 years, range 52–70 years) with chronic atrial fibrillation inadequately controlled on digoxin alone took part in the study. All patients had good left ventricular function and no overt clinical or radiological evidence of heart failure, although four patients were taking diuretics. Six patients had mitral valve disease (five stenosis and one incompetence), one had ischaemic heart disease and one was hypertensive. All gave informed consent and the study was approved by the hospital Ethics Committee.

Heart rate control was measured by ambulatory 24 h ECG recordings which were analysed semi-automatically by a Reynolds Pathfinder II. Hourly maximum and minimum heart rates (measured over 6 s) and longest daytime (09.00–20.00 h) and night-time (21.00–08.00 h) pauses were noted. The total number of daytime and night-time pauses > 1.5 s and total ectopic count were also recorded. Hourly counts with > 300 s of artefact were discounted such that 1664/1920 (86.7%) h were included in the analysis. Recordings were made at baseline and at the end of 2 weeks of treatment with atenolol 50 mg and 100 mg daily and pindolol 5 mg twice daily and 15 mg twice daily, which were added to maintenance digoxin dosage (median 250 μ g, range 250–500 μ g a day) which was not altered during the course of the study. Treatments were given in random order. Blood digoxin concentration 6 h after the dose was median 1.1 μ g l⁻¹ (range 1.0–1.6 μ g l⁻¹) at the time of the baseline recording.

Symptom scores for breathlessness and palpitation were recorded at each visit using visual analogue scales 100 mm in length as previously described [9]. The clinic doctor interviewing the patient was unaware of the treatment.

Statistical analysis

Differences between hourly daytime (09.00–20.00 h) and nocturnal (21.00–08.00 h) maximum and minimum heart rates between treatment groups were analysed by ANOVA. The area under the maximum and minimum heart rate time curves (AUC) was calculated using the

trapezoidal rule and heart rate variability was calculated as AUCmax-AUCmin as described previously [9].

Results

Maximum heart rate

Table 1 shows the mean (and 95% confidence intervals) hourly heart rate for the day (09.00–20.00 h) and night (21.00–08.00 h). Treatment with both β -adrenoceptor blockers at both doses significantly reduced daytime maximum heart rate (Table 1; Figures 1–4; all $P <$

Table 1 Mean (95% confidence intervals) diurnal (09.00–20.00 h) and nocturnal (21.00–08.00 h) maximum heart rate during treatment with digoxin alone (baseline) and digoxin plus atenolol 50 mg, and 100 mg and pindolol 5 mg twice daily and 15 mg twice daily

	Maximum heart rate (beats min ⁻¹)	
	09.00–20.00 h mean (95% CI)	21.00–08.00 h mean (95% CI)
Baseline	121.5 (114–129)	89.6 (81.1–98.1)
Atenolol 50 mg	97.7 (92.4–103)	82.8 (75.6–90)
Atenolol 100 mg	96.3 (90.6–102)	83.3 (75.3–91.3)
Pindolol 10 mg	103.2 (100–106)	93.7 (88.9–98.5)
Pindolol 30 mg	108.8 (106–112)	95.8 (90.5–101)

Figure 1 24 h time plot of mean maximum and minimum heart rate during treatment with digoxin alone (hatched) and digoxin + pindolol 5 mg twice daily (stippled).

Figure 2 24 h time plot of mean maximum and minimum heart rate during treatment with digoxin alone (hatched) and digoxin + pindolol 15 mg twice daily (stippled).

0.001). Both doses of atenolol reduced daytime maximum heart rate significantly more than pindolol ($P < 0.01$ atenolol 50 mg vs pindolol 10 mg; all others $P < 0.005$). Low dose pindolol reduced daytime maximum heart rate significantly more than pindolol 15 mg twice daily ($P < 0.001$). Nocturnal maximum heart rate was not significantly changed compared with baseline by any treatment but both doses of pindolol caused significant increases in maximum heart rate at night compared with atenolol ($P < 0.005$). The higher dose of pindolol caused a greater increase in heart rate than the lower dose.

Minimum heart rate

Table 2 gives the mean (and 95% confidence intervals) hourly day time minimum heart rate. Daytime minimum heart rate was significantly reduced by both doses of atenolol ($P < 0.001$) whereas both doses of pindolol caused no significant change (Figures 1–4). Mean nocturnal hourly heart rate was significantly reduced by atenolol but significantly increased by pindolol in a dose related manner (all $P < 0.001$ except atenolol 100 mg vs baseline $P < 0.01$). High dose atenolol caused a significant prolongation of nocturnal pauses (Table 3) compared with both baseline and pindolol treatment. Pindolol caused significantly fewer nocturnal pauses < 1.5 s compared with digoxin alone ($P = 0.05$).

Figure 3 24 h time plot of mean maximum and minimum heart rate during treatment with digoxin alone [hatched] and digoxin + atenolol 50 mg twice daily [stippled].

Figure 4 24 h time plot of mean maximum and minimum heart rate during treatment with digoxin alone [hatched] and digoxin + atenolol 100 mg twice daily [stippled].

Heart rate variability

Table 4 shows the differences between the areas under the maximum heart rate-time curve and minimum heart rate-time curve, which is a measure of heart rate variability. Atenolol (100 mg) and pindolol (5 mg twice daily) caused significant reductions in heart rate variability compared with baseline.

Total ectopic count and symptoms of palpitation and breathlessness were not significantly affected by any additional treatment with β -adrenoceptor blockers (Table 5). No significant changes were seen in breathlessness scores with either β -adrenoceptor blocker. No patient developed heart failure during the study or was unable to tolerate the addition of a β -adrenoceptor blocker.

Discussion

This study shows that different β -adrenoceptor blockers have different effects on heart rate when combined with digoxin in patients with atrial fibrillation. Atenolol reduced daytime tachycardia but increased nocturnal bradycardia and prolonged nocturnal pauses whereas pindolol reduced daytime tachycardia without aggravating nocturnal bradycardia or pauses, but rather increased nocturnal minimum and maximum heart rate. Pindolol particularly had dose related effects; high dose pindolol caused more sympathomimetic effects with an increase in heart rate when sympathetic tone was low, at night. Both β -adrenoceptor blockers caused reductions in heart rate variability and thus improved overall ventricular rate control. Pindolol in low dosage had advantages over atenolol.

The observed differences on heart rate caused by these drugs can be explained by their different pharmacological properties. Pindolol is a β_2 non-selective blocker which not only occupies the β -receptor but also sub-maximally stimulates it, although these effects are only seen at times of low inherent sympathetic tone, for example, at night. On exercise, by occupying the receptor site the drug competitively blocks it causing a reduction in response to sympathetic activation. Atenolol, a selective β_1 -adrenoceptor antagonist, causes no stimulation and simply blocks the receptor.

Table 2 Mean (95% confidence intervals) diurnal (09.00–20.00 h) and nocturnal (21.00–08.00 h) minimum heart rate during treatment with digoxin alone (baseline) and digoxin plus atenolol 50 mg, and 100 mg and pindolol 5 mg twice daily and 15 mg twice daily

	Minimum heart rate (beats min ⁻¹)	
	09.00–20.00 h mean (95% CI)	21.00–08.00 h mean (95% CI)
Baseline	74.8 (67.9–81.7)	61.8 (59–64.9)
Atenolol 50 mg	64 (60.3–67.7)	56 (52.3–59.7)
Atenolol 100 mg	69.9 (61.1–64.7)	57.5 (53.3–61.7)
Pindolol 10 mg	71.8 (69.8–73.8)	68.5 (66.7–70.3)
Pindolol 30 mg	75.5 (74–77)	70.8 (68.6–73)

Table 3 Mean (and 95% confidence intervals) numbers of pauses (>1.5s) and longest pauses during treatment with digoxin (baseline) and digoxin and atenolol 50 mg twice daily and 100 mg and pindolol 5 mg and 15 mg twice daily

	Longest pauses (s) mean + 95% CI		
	Day	Night	
Baseline	2.0 (1.63–2.37)	2.3 (1.86–2.74)	
Atenolol 50 mg	2.7 (1.77–3.63)	2.7 (0.94–4.46)	
Atenolol 100 mg	2.3 (1.75–2.85)	2.7 (1.9–3.5)	<i>P</i> < 0.05 vs baseline
Pindolol 10 mg	2.1 (1.68–2.52)	2.0 (1.58–2.42)	<i>P</i> < 0.05 vs atenolol 100 mg
Pindolol 30 mg	2.0 (1.6–2.4)	2.3 (1.8–2.8)	<i>P</i> < 0.05 vs atenolol 100 mg

	Number of pauses (> 1.5 s) mean + 95% CI	
	Day	Night
Baseline	363 (–174, 900)	2217 (–742, 5176)
Atenolol 50 mg	1713 (–1754, 5180)	2653 (1343, 6649)
Atenolol 100 mg	1503 (–1361, 4367)	2344 (–1847, 6535)
Pindolol 10 mg	668 (–605, 1986)	845 (–350, 2040)
Pindolol 30 mg	505 (–617, 1627)	679 (–312, 1670)

Table 4 Difference between the area under the maximum heart rate-time curve and area under the minimum heart rate-time curve (AUC max and AUC min) during treatment with digoxin alone (baseline) and with digoxin and atenolol 50 mg and 100 mg and pindolol 5 mg twice daily and 15 mg twice daily

	AUC max–min (heart rate variability) mean (95% CI)	ANOVA vs Baseline
Baseline	925 (767–1083)	
Atenolol 50 mg	844 (572–1116)	<i>P</i> = NS
Atenolol 100 mg	646 (429–863)	<i>P</i> < 0.05
Pindolol 10 mg	695 (552–838)	<i>P</i> < 0.05
Pindolol 30 mg	717 (536–898)	<i>P</i> = 0.06

Table 5 Median (range) breathlessness and palpitation scores during treatment with digoxin alone (baseline) and with digoxin and atenolol 50 mg and 100 mg and pindolol 5 mg twice daily and 15 mg twice daily

	VAS (mm) median (range)	
	Breathlessness	Palpitation
Baseline	26 (0–67)	35 (0–73)
Atenolol 50 mg	34 (4–68)	6 (0–53)
Atenolol 100 mg	34 (0–79)	19 (0–47)
Pindolol 10 mg	26.5 (0–51)	25 (0–83)
Pindolol 30 mg	22 (0–83)	2 (0–49)

β -adrenoceptor blockers are used extensively and remain first line treatment in the management of hypertension and angina pectoris. In patients with atrial fibrillation, their role may be limited by their negative inotropic effects. Some patients with atrial fibrillation have impaired left ventricular function and in this setting, β -adrenoceptor blockers have induced heart failure. In some studies of patients with atrial fibrillation exercise tolerance on treadmill testing has been reduced by the addition of β -adrenoceptor blockers [10–11]. However, atrial fibrillation also occurs in patients with normal left

ventricular function when it is associated with mitral stenosis and hypertension, and can occur in the absence of apparent cardiac disease, i.e. 'lone' atrial fibrillation. In these patients improved ventricular rate control by the addition of a β -adrenoceptor blocker to digoxin therapy is not usually associated with heart failure [3]. David *et al.* [5] used timolol to improve ventricular rate control without impairment of effort tolerance but they excluded patients with heart failure and consequently had a large number of patients with lone atrial fibrillation in their study. Yahalom *et al.* [6] included patients with congestive cardiac failure and found no deterioration in patients treated with practolol. In our study we included only patients without significant left ventricular dysfunction judged by simple clinical criteria and showed no deterioration in symptoms of dyspnoea.

Thus, if patient selection is appropriate, β -adrenoceptor receptor blockers can have a beneficial effect on symptoms by controlling ventricular rate in atrial fibrillation whilst also being safe and well tolerated. Pindolol, because of its partial agonist activity is less negatively inotropic than atenolol and the symptom scores may reflect this. Xamoterol which has even more agonist activity than pindolol, has also been shown to improve ventricular rate control in atrial fibrillation and is the only additional therapy shown to improve effort tolerance [7, 8]. Since atrial fibrillation most often occurs in the elderly concomitant conduction disorders can be present and slow atrial fibrillation is an indication for cardiac pacing. Drugs which reduce the atrio-ventricular blockade at times of low sympathetic tone reduce the tendency to bradycardia in these patients. Ang *et al.* [7] studied just this group of patients and showed that xamoterol reduced pauses; pindolol has similar effects. Many patients with atrial fibrillation have concomitant hypertension or angina for which the addition of a β -adrenoceptor blocker would provide additional beneficial effects as well as improving heart rate control. β -adrenoceptor blockers may be useful in the management of patients with atrial fibrillation, and the value of drugs with partial agonist activity should not be ignored.

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