The influence of β -adrenoceptor blockers with and without intrinsic sympathomimetic activity on heart rate, arrhythmias and ST-T segments, using ambulatory electrocardiography

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1 Ambulatory electrocardiography was used to compare the effects of propranolol and pindolol on symptoms, heart rate, arrhythmias and ST segments. Seventeen males (mean age 54 years) with a diagnosis of chronic stable angina pectoris (New York Heart Association Class II – III) were studied. Patients were treated on a double-blind cross-over basis with propranolol 80 mg three times daily or pindolol 5 mg three times daily for 14 days each. During the last 48 h of each treatment period ambulatory electrocardiography was performed.

2 Propranolol resulted in a significantly lower mean hourly, mean 24 h and minimum heart rate. Likewise propranolol caused a lower mean daytime and nocturnal heart rate. There was no significant difference in the frequency of angina between the treatments. The number of episodes of ST segment depression was not significantly different between the two drugs, although there was a trend in favour of propranolol.

3 Both the mean 24 h ST level and the maximum ST segment depression were lower during treatment with pindolol. Propranolol was associated with a total of 117 nocturnal pauses or episodes of asystole ranging in length from 1.5 to 2.8 s. During treatment with pindolol only one such period occurred. The number of premature ventricular contractions occurring during treatment with pindolol (1316 beats) was less than on propranolol (2010) and the mean hourly frequency of premature ventricular contractions was significantly lower during pindolol administration.

4 Pindolol is not significantly different from propranolol in the control of symptomatic and asymptomatic myocardial ischaemia and is associated with fewer premature ventricular contractions. However, there is no advantage in using pindolol in chronic stable angina.

Keywords propranolol pindolol β -adrenoceptor blocker intrinsic sympathomimetic activity arrhythmias

Introduction

β -adrenoceptor blockers are established for the symptomatic relief of angina pectoris (Thadani *et al.*, 1980) and their beneficial effects are well described (Gantz *et al.*, 1986; Gianelly *et al.*,

1967; Wolfson & Gorlin, 1969). Their effect on asymptomatic myocardial ischaemia has only recently come under scrutiny.

β -adrenoceptor blockers were introduced to

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antagonise the cardiac effects of sympathetic stimulation (Sowton & Hamer, 1966) which can, through β -adrenergic actions cause markedly increased myocardial oxygen requirements by increasing heart rate and enhancing myocardial contractility. β -adrenoceptor blockers reduce myocardial oxygen requirements mainly by reducing heart rate and blood pressure increments with exercise. In addition there is a reduction in the velocity of contraction and oxygen consumption at a given workload (Wolfson & Gorlin, 1969; Thadani *et al.*, 1973).

The anti-anginal efficacy of pindolol which possesses intrinsic sympathomimetic activity has been confirmed in several reports (Arstila *et al.*, 1973; Dwyer *et al.*, 1982; Frishman *et al.*, 1979; Harston & Friesinger, 1982; Kostis *et al.*, 1982; Sainini & Mukherjee, 1972) and comparative studies have failed to find any significant difference with β -adrenoceptor blockers not possessing intrinsic sympathomimetic activity (Arstila *et al.*, 1973; Sainini & Mukherjee, 1972). However, because of intrinsic sympathomimetic activity, pindolol produces little or no reduction in resting heart rate (Reale & Motolest, 1981) and its antagonistic effects only become apparent during periods of increased sympathetic activity (e.g. during exercise). This effect is potentially harmful in those with rest or nocturnal angina who are dependent on a reduction in resting heart rate for relief of symptoms. Quyyumi *et al.* (1984a) have recently compared the effect of pindolol and atenolol in patients with severe angina pectoris, using ambulatory electrocardiography, and showed a clear disadvantage with pindolol. The present study was undertaken to assess the effect of propranolol and pindolol on heart rate, arrhythmias and ST segments in a group of middle aged men with stable angina pectoris.

Methods

Study group

Seventeen males with a mean age of 54 ± 9.1 years (s.d.) (range 38–68 years), were recruited. Their characteristics are summarised in Table 1. All had a diagnosis of chronic stable angina pectoris (New York Heart Association Class II or III). Each subject underwent a maximal symptom limited treadmill exercise test in the run-in period using a modified Bruce Protocol, (Bruce *et al.*, 1974) on a Marquette Case II system. In all cases, ST segment depression of > 1 mm for 0.08 s after the J point developed and persisted for at least three consecutive complexes. The subjects had a mean history of angina of 30

Table 1 Pretreatment characteristics of study group ($n = 17$)

Mean age (years)	54 ± 9 (Range 38–68)
Previous myocardial infarction	7
Mean resting heart rate (beats min^{-1})	70 ± 10.1
Mean resting blood pressure (mmHg)	$134/74 \pm 21/15$

Results are expressed as mean $\pm$ s.d.

± 28.6 months (range 6–84 months), and seven had a previous history of myocardial infarction. Written informed consent was obtained from all patients and the protocol was approved by the local Ethics Committee.

Study protocol

After a diagnosis of chronic stable angina pectoris was made, all anti-anginal medication was withdrawn for at least 2 weeks before investigation. Sublingual glyceryl trinitrate was permitted for pain. Patients were randomised to treatment with propranolol 80 mg three times daily or pindolol 5 mg three times daily for a period of 14 days each, then cross-over took place onto the alternative medication for a further period of 14 days (double-blind). During the last 48 h of each treatment period, ambulatory electrocardiography was performed.

Ambulatory electrocardiography

Holter monitoring was performed using the Medilog 4000 (MARS) ambulatory ECG recorder (Oxford Medical Systems Limited, Oxford).

After careful skin preparation using an abrasive paste and shaving if necessary, five electrodes (Medicotest) were applied to the chest wall to produce a recording of lead CM5 and a modified lead II. The patient was instructed to follow his normal daily habits and to record any symptoms or activities in a diary, particular attention was paid to the occurrence of any chest pain.

Mean nocturnal heart rate was derived from the mean of the hourly rates between 24.00–06.00 h when the patients were in bed. Significant ST segment depression was defined as planar or downsloping shift of the ST segment of > 1 mm in magnitude measured 0.08 s after the J point and persisting for at least 30 s.

Maximum and minimum heart rates refer to rates recorded over the average R-R interval over four complexes. A sinus pause is defined as asystole greater than 1.5 s and 1.9 times greater

than the average R-R interval of the four previous complexes. Ventricular tachycardia is regarded as three or more consecutive premature ventricular contractions during which two R-R intervals exceed $110 \text{ beats min}^{-1}$ and if less than $110 \text{ beats min}^{-1}$ this is regarded as idioventricular rhythm.

At the end of each recording the cassette was transferred to the Medilog Mars replay system which generates a comprehensive report and offers a search or full 24 h disclosure, via a Microdot Printer.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation. Data was analysed using both Student's paired *t*-test for parametric and Wilcoxon's signed rank test for non parametric paired observations. The most conservative significance values obtained are reported.

Results

Heart rate

The 24 h trend of mean heart rate per hour is shown in Figure 1 for each drug. Propranolol resulted in a significantly lower mean hourly ($P < 0.001$), mean 24 h ($P < 0.001$), minimum ($P < 0.001$) and maximum heart rate ($P = \text{NS}$) when

compared with pindolol. Similarly propranolol caused a lower mean daytime ($P < 0.001$) and nocturnal heart rate ($P < 0.025$). These results are shown in Table 2.

Frequency of angina and ST changes

In total, fifteen episodes of angina occurred during the last 48 h of treatment with pindolol compared with 12 with propranolol ($P = \text{NS}$), and although the mean number of attacks was 1.8 ± 3.94 (range 0–14) per patient per day on propranolol and 2.1 ± 4.74 (range 0–20) on pindolol, this was also not significant.

Table 2 Heart rate response to β -adrenoceptor blockade. Results are expressed as beats min^{-1} (mean $\pm$ s.d.), and represent findings over 48 h continuous ECG monitoring

	Propranolol	Pindolol	P
24 h heart rate	62 ± 11.9 (45–79)	73 ± 8.4 (55–88)	< 0.001
Minimum heart rate	43 ± 8.1 (28–57)	52 ± 7.1 (29–63)	< 0.001
Maximum heart rate	118 ± 24.3 (83–186)	130 ± 23.1 (103–189)	NS
Daytime heart rate	66 ± 2.1 (60–69)	76 ± 1.9 (72–78)	< 0.001
Nocturnal heart rate	60 ± 1.5 (58–62)	70 ± 1.0 (69–72)	< 0.025

Figure 1 Mean heart rate over 24 h during treatment with pindolol and propranolol ($\pm$ s.d.).

Five patients developed pain during the treatment periods, and with the exception of one case, all of these subjects noted more frequent angina during treatment with pindolol. The remaining 12 patients were symptom free on both drugs. During ambulatory electrocardiography the total number of episodes of ST segment depression (> 1 mm) increased from 59 on propranolol to 85 on pindolol ($P = \text{NS}$). Both the mean 24 h ST level and the mean maximum ST segment level were lower during treatment with pindolol, but this failed to reach statistical significance, (see Table 3).

Heart rhythm

A total of 117 nocturnal pauses or episodes of asystole occurred in three patients during treatment with propranolol, ranging in length from 1.5–2.8 s. During treatment with pindolol no pause was noted in these patients, although one other patient had one episode lasting 1.7 s.

All patients exhibited premature ventricular contractions during treatment with both propranolol and pindolol although only six had more than 100 premature ventricular contractions in any one 24 h period. The total number of premature ventricular contractions occurring during treatment with pindolol (1316 beats) was less than on propranolol (2010 beats) and the mean hourly frequency of premature ventricular contractions was significantly lower during pindolol administration ($P < 0.02$) (Figure 2).

One subject developed one episode of ventricular tachycardia while on propranolol and pindolol and one subject had 42 episodes of ventri-

cular bigeminy while taking propranolol, but only five episodes occurred in the last 48 h of treatment with pindolol.

Discussion

Previous studies evaluating the use of pindolol in the treatment of angina pectoris have confirmed its efficacy in reducing anginal symptoms in 42–85% of patients and increasing exercise tolerance by 12–21%, a greater improvement being observed in short-term uncontrolled studies. However, in a double-blind cross-over comparative study with atenolol, Quyyumi *et al.* (1984a) drew attention to the deleterious effects of pindolol in subjects with severe effort angina and nocturnal angina. Their study differed substantially from the present in several ways: the patients investigated had more severe coronary artery disease; there was a very short withdrawal period for patients already on β -adrenoceptor blockers before entry into the study, which could have resulted in rebound effects in the first treatment phase; and the method of analysis of ambulant electrocardiographs was different. In the present study ambulatory electrocardiography was performed using automatic equipment, thus removing any possibility of observer error. It is likely that subjects with severe rest or nocturnal angina would require additional therapy such as nitrates or calcium antagonists. We chose to study patients with stable angina and compare the effects of pindolol with another nonselective β -adrenoceptor blocker which does not possess intrinsic sympathomimetic activity (propranolol). The withdrawal phase before entry into the study was

Table 3 Frequency of angina and number, duration and magnitude of S-T segment changes during 48 h continuous ECG monitoring. Results are expressed as mean $\pm$ s.d. with range

	Propranolol	Pindolol	P
Number of episodes of pain	12	15	NS
Mean ST level (mm)	-0.059 ± 0.719 ($-1.76-1.08$)	-0.161 ± 0.874 ($-2.24-1.08$)	NS
Maximum ST level (mm)	0.357 ± 0.929 ($-0.28-1.92$)	0.682 ± 0.775 ($-0.68-1.96$)	NS
<i>ST - segment depression</i>			
Total number of episodes	59	85	NS
Mean number of episodes	1.79 ± 3.94	2.12 ± 4.74	NS
Total duration (min)	1155	2630	NS
Maximum magnitude (mm)	-0.932 ± 1.312 ($-4.96-0.28$)	-1.297 ± 1.483 ($-4.96-0.56$)	NS

Figure 2 Frequency histogram of ventricular premature contractions occurring during 48 h of continuous ECG monitoring. Propranolol (□) vs Pindolol (■): $P = \text{NS}$.

longer, as were the treatment periods.

Using cruder methods of assessment, other workers have reported variable findings using pindolol in angina. Harston & Friesinger (1982) reported a reduction in the heart rate $\times$ blood pressure product and increased exercise tolerance in 12 patients treated with pindolol. However in the long-term, pindolol did not cause a significant reduction in attacks of angina or an enhanced exercise tolerance in comparison to placebo. Using high doses of pindolol (40 mg) against moderate daily doses of propranolol (60 mg) in patients with angina, Frishman *et al.* (1979) demonstrated a significant reduction in the frequency of angina and increased exercise tolerance with both drugs, but did not compare the difference in effect. In the present study a daily dose of 15 mg per day in three divided doses was administered. This is the dose most frequently used in clinical practice. No additional haemodynamic benefit is observed with higher doses (Dwyer *et al.*, 1982).

It appears that although pindolol is effective in terms of suppression of anginal symptoms, it is possibly inferior to other agents without intrinsic sympathomimetic activity. During exercise several investigators including Quyyumi *et al.* (1984a) have observed effective β -adrenoceptor blockade with pindolol suggesting that patients with effort angina will derive sufficient benefit from this drug.

Heart rate

The present study confirmed that pindolol suppresses resting heart rate to a lesser extent than propranolol (Figure 1), but maximum heart rate achieved during treatment with these drugs was not significantly different, suggesting a similar beta blocking effect during periods of increased sympathetic tone. The circadian rhythm of heart rate was maintained, there being no significant difference between each drugs effect on daytime and nocturnal heart rates. These findings are similar to those observed with atenolol vs pindolol previously (Quyyumi *et al.*, 1984a). The failure of β -adrenoceptor blockers with intrinsic sympathomimetic activity to effectively reduce resting heart rate has been noted by others (Frishman *et al.*, 1979; Quyyumi *et al.*, 1984a). But in stable effort angina pectoris it is probably more important to suppress exercise induced tachycardia than reduce resting heart rate.

ST segment analysis

This study found that 59 episodes of significant ST segment depression occurred during 48 h monitoring while the patients were taking propranolol, and 85 episodes while taking pindolol. Only 12 and 15 episodes respectively were accompanied by pain. This is a similar proportion to that described by Quyyumi *et al.* (1984a) but in

the present study no significant difference was observed between the number, duration or magnitude of ST depressions comparing the two drugs, although ST segment depression was more frequent, longer in duration and deeper during treatment with pindolol. In this study, ST segment depression did not correlate with elevations in heart rate. It has previously been suggested by Quyyumi *et al.* (1984b) that ST depression is usually preceded by elevation of heart rate. Under resting conditions, in those with severe coronary artery disease, nocturnal oxygen demand may still be high. However, this hypothesis has recently been refuted by Chierchia *et al.* (1984) who demonstrated that ST depression could occur irrespective of resting heart rate, and further, that tachycardia could occur in the absence of ST depression. They suggest that myocardial oxygen demand is not the only, or the most common cause of acute ischaemia in chronic stable angina. These findings suggest that a suppression of heart rate alone need not indicate an advantage to a β -adrenoceptor blocker without intrinsic sympathomimetic activity, in chronic stable effort angina.

Arrhythmias

The mean hourly frequency of premature ventricular contractions in the last 48 h of monitoring during treatment with pindolol was significantly lower than during treatment with propranolol ($P < 0.02$). The reason for such a difference is not clear. It has previously been shown that diurnal variation of premature ventricular contraction frequency occurs in patients with coronary artery

disease—with a fall in frequency during sleep (Lown *et al.*, 1975). This suggests that premature ventricular contractions are more common at times of increased neural activity with resultant high sympathetic tone. If this were true, one would expect fewer premature ventricular contractions to occur during treatment with propranolol. It is possible that the sustained, but suboptimal stimulation of β -adrenoceptors by pindolol is capable of suppressing ventricular ectopic foci already present and if a pure β -adrenoceptor blocker is administered, their suppression is lost and ectopic foci are 'released' from sympathetic influence. A number of studies have supported the hypothesis that the presence of premature ventricular contractions in patients with coronary artery disease is a risk indicator of sudden death (Hinkle *et al.*, 1969; The Coronary Drug Project Group, 1973). Thus, the 35% reduction in premature ventricular contraction frequency observed during pindolol treatment may be of some importance. However, according to Morganroth *et al.* (1978) a reduction of more than 65% would be required for 95% confidence of a drug effect and even then, 72 h periods of monitoring would be required because of the spontaneous variability in frequency of premature ventricular contractions. The reason for our finding of a fall in premature ventricular contractions during treatment with pindolol is not consistent with previous findings and may be related to spontaneous variability of frequency alone, although no formal investigation using the techniques utilised in this study has been performed.

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