PAPERS AND SHORT REPORTS

Effect of partial agonist activity in β blockers in severe angina pectoris: a double blind comparison of pindolol and atenolol

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Abstract

The use of β adrenoceptor blockade in the treatment of rest angina is controversial, and the effects on severe angina of partial agonist activity in β blockers are unknown. Eight patients with effort angina and seven with effort and nocturnal angina and severe coronary artery disease were studied initially when they were not taking any antianginal drugs. Pindolol 5 mg thrice daily (with partial agonist activity) and atenolol 100 mg daily (without partial agonist activity) were given for five days each in a double blind randomised manner. Diaries of angina were kept and treadmill exercise testing and ambulatory ST monitoring performed during the last 48 hours of each period of treatment. Daytime and nocturnal resting heart rates and the frequency of angina were significantly reduced by atenolol compared with pindolol ($p < 0.01$). The duration of exercise was significantly increased and the frequency, duration, and magnitude of daytime and nocturnal episodes of ST segment depression on ambulatory monitoring were reduced by atenolol.

Reduction in resting heart rate is important in the treatment of both effort and nocturnal angina. Partial agonist activity in β adrenoceptor antagonists may be deleterious in patients with severe angina pectoris.

Introduction

β Adrenoceptor antagonists are now established in the treatment of angina pectoris.[1] Patients with angina vary widely in their clinical and pathophysiological symptoms: some have purely exertional pain and others develop angina mainly at rest and at night, when primary reduction in myocardial oxygen supply is considered to be important.[2,3] β Adrenoceptor antagonists reduce myocardial oxygen consumption and would therefore be expected to be effective in patients with exertional angina, but their role in patients with nocturnal and rest angina is controversial.[4]

Partial agonist activity in certain β adrenoceptor antagonists such as pindolol, oxprenolol, and practolol results in a higher resting heart rate, but the rate of increase in heart rate on exercise is claimed to be similar to that during treatment with other agents such as propranolol and atenolol that do not possess partial agonist activity.[5] We carried out a study to investigate, firstly, the influence of partial agonist activity in β blockers in the treatment of severe angina pectoris and, secondly, the effects of such treatment on the frequency and severity of nocturnal angina. We compared the effects of pindolol (with partial agonist activity) and atenolol (without partial agonist activity) in patients with severe angina pectoris.

Methods

We studied 15 patients (11 men, four women; mean age 60·5 years) with chronic stable severe angina pectoris; eight had angina of effort alone, and seven had effort and rest (nocturnal) angina (table I). A further patient began the study but was withdrawn after developing severe hypotension induced by exercise. All patients had angiographically proved coronary artery disease, and two had poor left ventricular function (table I). Thirteen patients developed chest pain and ST segment depression on exercise testing. The two other patients had frequent rest angina with ST segment depression and were not exercised. All patients had multiple episodes of ST segment depression, with or without pain, during ambulatory electrocardiographic monitoring in the run in period (table II). None had episodes of ST segment elevation.

Protocol—All antianginal medication was stopped 48 hours before the study (run in period), but sublingual glyceryl trinitrate was given for pain. A detailed clinical history was obtained and exercise testing and 48 hour ambulatory monitoring performed. Nocturnal angina and ST segment changes were considered to be present if they occurred between midnight and 0600 while the patients were in bed.

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TABLE I—*Characteristics of patients studied*

	Effort angina only	Effort plus nocturnal angina
No of patients	8	7
No with coronary artery disease of:		
Two vessels	4	
Three vessels	4	7
No with angiographic ejection fraction:		
<50%	1	1
>50%	7	6
No who had received β blockers previously	3	7

TABLE II—*Mean (SD) frequency of angina, exercise tolerance, and frequency, duration, and magnitude of ST segment depression during ambulatory monitoring in patients during run in period (when not receiving any antianginal drugs)*

	Effort angina (n = 8)	Effort plus nocturnal angina (n = 7)	Total (n = 15)
No of episodes of pain/24 h	8 (1·1)	7 (2·4)	15 (1·8)
Duration of ST segment depression on exercise testing (min)	4·9 (1·8)	2·9 (2·5)*	4·3 (2·2)
ST segment depression on ambulatory monitoring:			
No of episodes	3·8 (2·6)	12·9 (8)	8 (7·3)
Duration of episodes (min)	81 (97)	397 (436)	228 (366)
Maximum magnitude (mm)	2·5 (1·7)	3·4 (1·5)	2·9 (1·6)

*Measured in only five patients.

The patients then underwent two treatment periods of five days each with atenolol 100 mg once daily and pindolol 5 mg three times a day in a double blind, double dummy randomised study. Patients with only daytime angina and those with daytime and nocturnal angina were randomised separately. All gave their informed consent, and the protocol was approved by the hospital ethical committee.

Diaries of angina—A detailed record of pain was kept by the patients during each 48 hour period of ambulatory monitoring.

Exercise testing—Thirteen patients underwent maximal, symptom limited treadmill exercise during the initial run in period and at the end of each five day treatment period. A 12 lead electrocardiogram was recorded at rest and at the end of each minute of exercise, during which the workload was increased according to the modified Bruce protocol. Appreciable ST segment depression was defined as depression of 1 mm or more occurring 0·08 second after the J point and persisting for three consecutive beats.

Ambulatory monitoring—Forty eight hour ambulatory electrocardiographic recordings were made with a frequency modulated recorder (Oxford Medilog II, frequency response 0·05-40 Hz) to obtain a two channel recording of lead CM5 and modified lead II, and the magnetic tapes were read visually at 60 times normal speed; the number, magnitude, and duration of the episodes of appreciable ST segment depression were noted.

Statistical analysis—Results are expressed as means (SD). Discrete data were analysed with Wilcoxon's signed rank test for paired observations.

Results

Heart rate and blood pressure—Resting heart rate and blood pressure during the day were measured before the exercise test. The mean nocturnal heart rate was derived from the mean of the hourly heart rates from 2400 to 0600 during ambulatory monitoring. The mean resting heart rate during the day and the mean nocturnal heart rate were significantly lower during treatment with atenolol than with pindolol ($p<0·01$) (table III, figure). The resting blood pressure was similar with both drugs. There were no significant differences between the daytime resting and nocturnal heart rates during treatment with pindolol and the run in period, but both these variables were significantly lower during treatment with atenolol ($p<0·01$).

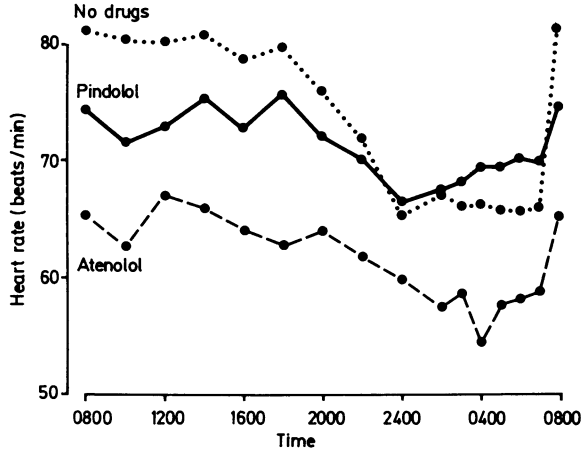
Frequency of angina—The mean daily number of attacks of angina during the last two days of each assessment period, during which the patients' activities were comparable, was significantly lower with atenolol (0·36/day) than with pindolol (1·16/day) ($p<0·01$). Six patients had fewer episodes of pain during treatment with atenolol, two had the same number of episodes, and the nine other patients had no pain with either drug.

Exercise test—All 13 patients exercised during the run in period developed appreciable ST segment depression and chest pain that caused them to stop the exercise. Three patients did not develop appreciable ST segment depression while taking atenolol or pindolol; exercise was stopped owing to tiredness or dyspnoea. In the 10 patients whose exercise was stopped by chest pain and appreciable ST segment depression the duration of exercise was significantly longer during treatment with atenolol (mean 5·95 minutes) than with pindolol (mean 4·0 minutes) ($p<0·01$). When the data were analysed for all 13 patients there was also a significant difference between the duration of exercise with atenolol (6·4 (2·3) min) compared with pindolol (4·6 (2·6) min) ($p<0·01$) (table III). Six patients exercised for six minutes or longer during the two treatment periods, and all patients exercised for at least three minutes. Table IV shows the heart rate and rate-pressure product achieved at the same workload. β Blockade was evident during both treatment periods when compared with the run in period, and the rates of increase in heart rate and rate-pressure product were similar with the two agents.

Ambulatory electrocardiography—The total number of episodes of ST segment depression and their duration and severity were greater during treatment with pindolol compared with atenolol (table V). Although only 23 of the total of 160 episodes of ST segment depression were associated with chest pain, painful episodes were more common with pindolol than with atenolol ($p<0·01$). Separate analysis of the patients in whom ST segment depression occurred only during the day and those in whom it occurred both during the day and at night

TABLE III—*Differences in heart rates, blood pressure, and duration of exercise with atenolol and pindolol (figures are means (SD))*

	Run in period	Atenolol	Pindolol	Atenolol *v* pindolol
Heart rate (beats/min):				
At night	68 (12)	59 (10)	68 (9)	p<0·01
During day, resting	73 (10)	60 (9)	73 (8)	p<0·01
At end of exercise	111 (13)	91 (19)	96 (13)	NS
Resting blood pressure (mm Hg)	135 (20)	125 (23)	127 (16)	NS
Heart rate × blood pressure	15 600 (4500)	12 400 (3400)	13 500 (2500)	NS
Duration of exercise (min)	4·3 (2·2)	6·4 (2·3)	4·6 (2·6)	p<0·01



Mean heart rate over 24 hours during treatment with atenolol and pindolol during run in period.

TABLE IV—*Heart rates and products of heart rates and systolic blood pressure at rest and after three and six minutes' exercise during run in period and treatment with atenolol and pindolol*

	Run in period	Atenolol	Pindolol
Heart rate (beats/min):			
Resting	79 (9)	63 (7)	69 (7)
At 3 minutes (n = 10)	95 (14)	78 (9)	83 (7)
At 6 minutes (n = 6)	112 (12)	91 (10)	98 (10)
Heart rate × systolic blood pressure:			
Resting	10 600 (2700)	8 100 (1400)	8 800 (1400)
At 3 minutes (n = 10)	14 300 (4500)	10 100 (2400)	11 600 (2000)
At 6 minutes (n = 6)	19 100 (4000)	12 700 (1900)	14 300 (1800)

showed that atenolol was associated with a reduced frequency of both daytime and nocturnal episodes, which were of shorter duration ($p<0.05$) (table V). The improvement with atenolol was of similar magnitude in the two patients with poor left ventricular function (ejection fraction $<50\%$) compared with the 13 other patients and was not associated with any adverse effects.

Adverse effects—Worsening of angina did not occur during either period of treatment. One patient complained of dizziness and paraesthesia during treatment with pindolol but not with atenolol.

TABLE V—*Number, duration, and magnitude of episodes of ST segment depression with atenolol and pindolol observed during ambulatory monitoring (figures are means (SD))*

	Run in period	Atenolol	Pindolol	Atenolol v pindolol
No of painful episodes	1·8 (1·8)	0·36 (0·41)	1·16 (1·4)	$p<0.01$
No of daytime episodes (n = 15)	8 (7·3)	3·6 (4·1)	5·1 (5·4)	$p<0.01$
No of nocturnal episodes (n = 7)	2·9 (1·2)	1·6 (1·4)	2·6 (1·2)	$p<0.05$
Duration of daytime episodes (min) (n = 15)	228 (366)	66 (90)	102 (132)	$p<0.01$
Duration of nocturnal episodes (min) (n = 7)	88 (100)	45 (60)	117 (96)	$p<0.01$
Maximum magnitude of depression (mm)	2·9	1·72	2·41	$p<0.05$

Discussion

Pindolol, a structural analogue of isoprenaline, is suboptimally bound to adrenergic receptors; this causes only partial stimulation,[6] which results in a higher resting heart rate than that induced by agents that do not possess such activity.[7] Binding of the drug to the receptor, however, blocks the effects of endogenous sympathetic stimulation, and β blockade is evident only on exercise or when the heart rate is high. Partial agonist activity has been claimed to be beneficial in patients with compromised myocardial function,[8 9] bronchospasm, and Raynaud's phenomenon,[6] in whom conventional β receptor antagonists are contraindicated. We did not, however, observe any adverse effects with atenolol in two patients with poor left ventricular function in this study.

Several studies with pindolol[9-15] and atenolol[16 17] have confirmed the efficacy of these drugs in the treatment of angina pectoris, and comparative studies[10 14 18] have not shown any significant differences. This study differs substantially from others in the type of patients investigated. During the short run in period, when the patients did not receive any treatment, it was obvious that they had severe angina pectoris; indeed, seven had angina at rest and the remaining eight were able to achieve only a very low workload before the onset of chest pain. For this reason we thought it unethical to randomise them to a placebo group, and so we made a straight comparison between the two drugs. Ten patients had previously been treated with various β adrenoceptor antagonists (table I), and withdrawal of antianginal drugs may have resulted in rebound effects during the run in period. Comparisons between the results of exercise tests and ambulatory monitoring and the frequency of angina were therefore confined to the two periods of drug treatment, which were randomly allocated.

The higher daytime and nocturnal resting heart rates during treatment with pindolol reflect the drug's partial agonist activity. β Receptor blockade was, however, evident with exercise as the peak exercise heart rate was significantly lower during treatment with pindolol compared with the run in period (table III). Equipotent β blockade with atenolol and pindolol was observed with the doses of the drugs used in this study, the rates of increase in the heart rate and blood pressure being similar with both atenolol and pindolol (table IV), but the heart rate reached with atenolol was lower at the same workload because the basal heart rate was significantly lower. At peak exercise the heart rates with both drugs were similar and significantly lower than during the run in period. As patients had a higher resting heart rate when taking pindolol they reached their threshold of angina sooner than when they were taking atenolol. Previous studies have shown adequate β blockade with 15 mg pindolol daily; no haemodynamic change was observed with higher doses.[15]

In such severely ill patients control of heart rate is of paramount importance not only for exertional angina but also for rest angina. Ambulatory monitoring of ST segment changes showed that the frequency and magnitude of both painless and painful episodes of ST segment depression were reduced with atenolol compared with pindolol, both during the day and during the night (table V). ST segment changes have been recorded in healthy ambulatory volunteers,[19] but there is no doubt that ST segment depression, often of 2 mm or more, occurring at relatively low heart rates and often accompanied with chest pain in patients with proved coronary disease represents myocardial ischaemia.

Coronary artery spasm has been suggested as the mechanism underlying angina at rest and at night.[2 12 20] β Adrenoceptor antagonists would therefore be expected either to have no influence or even to exacerbate coronary spasm by exposing the heart to unopposed α stimulation. As evidence suggests that coronary vasodilatation is mediated by β_1 receptors[21] it is unlikely that the differences in effect on nocturnal angina seen between atenolol and pindolol are due to differences in β blockade. All patients in this study, however, had considerable limitation of coronary reserve, and higher nocturnal heart rates induced by the partial agonist activity in pindolol may be expected to be detrimental.

In conclusion, this study shows that in patients with severe angina pectoris the reduction of resting heart rate with β blockade is an important factor in reducing the frequency and severity of myocardial ischaemia occurring not only during the day but also at rest in the night. Hence, β adrenoceptor antagonists with partial agonist activity may be of less benefit in patients with severe angina.

We are indebted to the British Heart Foundation for its support.

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(*Accepted 20 July 1984*)