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Bopindolol in chronic stable angina pectoris: duration and extent of antianginal action

G. P. CARBONI, A. B. SCARDOVI, M. D'ERMO & P. L. PRATI
Divisione Cardiologia 'A', Ospedale S. Camillo, Roma

The effects of bopindolol, a new β-adrenoceptor blocker, on the exercise tolerance of 12 in-patients, mean age 57 (5 years), with stable angina pectoris and documented coronary artery disease were evaluated. All patients received on 4 different days a single oral dose of bopindolol 0.5 mg, bopindolol 1.0 mg, bopindolol 2.0 mg and placebo according to a double-blind latin square design. Treadmill symptoms-limited exercise tests were performed using a Bruce protocol, 3, 12 and 24 h after dosing. Bopindolol improved ($P < 0.05$) exercise tolerance in comparison with placebo (by a maximum of 33%, 52% and 26% after the 2.0 mg dose) with no adverse effect on ischaemia. The primary action of bopindolol appeared to be to reduce myocardial oxygen consumption (mainly by its negative chronotropic effect) for up to the 24th hour after oral administration. Eight (66%) patients were angina free at the 3rd, 12th and 24th h exercise test. The effects of bopindolol were not dose-related. A short period of inactivity due to hospitalization may have influenced the exercise performance and led us to underestimate the presence of a dose-response. The results of this report suggest that bopindolol has a long lasting effect in the treatment of patients with chronic stable angina pectoris.

Keywords bopindolol chronic stable angina pectoris exercise test

Introduction

Most episodes of transient myocardial ischaemia occur during daily life of patients with chronic stable angina pectoris with a primary peak in the morning and a secondary peak in the evening that corresponds to a similar pattern in heart rate (Carboni *et al.*, 1987). The development of β-adrenoceptor antagonists with sufficiently long duration of action may reduce the frequency of heart rate-related myocardial ischaemic episodes and improve the patient's compliance. Bopindolol is a new long-acting, non-selective β-adrenoceptor blocker with mild membrane stabilizing effects and intrinsic sympathomimetic activity (Aellig, 1985). Preliminary studies have shown the efficacy of bopindolol in the treatment of hypertension (Schiess *et al.*, 1984) but little is known of its efficacy as an antianginal drug, particularly when the drug is administered in different dosages. To clarify this point we designed a study to evaluate the extent and duration of action of the acute effects of three doses of bopindolol on exercise tolerance and electrocardiographic signs of ischaemia in 12 patients with chronic stable angina pectoris.

Methods

Twelve in-patients (age range 50–66 years, mean 57 ± 5), 10 males and two females, with confirmed chronic stable angina were selected for study. All patients had angiographically documented coronary artery disease. Eleven patients had also electrocardiographic evidence of an old myocardial infarction. After withdrawal from their current therapy all patients were maintained on sublingual isosorbide dinitrate to control anginal pain for a period of 5 days. The patients admitted to the study received a single daily oral administration (at 08.00 h) of placebo, bopindolol 0.5 mg, bopindolol 1.0 mg and bopindolol 2.0 mg on 4 different days with a 48 h interval between them, according to a double-blind latin square design. The double dummy technique was used to cause double-blindness. Exercise tests were performed 3, 12 and 24 h after the morning intake. Informed written consent was obtained from each patient before entry into the study. Treadmill exercise tests were performed with the Bruce protocol using 12 leads. Leads showing ST-segment ischaemic changes were continuously monitored. The electrocardiogram was recorded at rest

Correspondence: Dr Gian Piero Carboni, Piazza dei Re di Roma 3, 00183, Roma, Italy

and every minute, both during exercise and during recovery. Systolic blood pressure was recorded at rest, every 3 min during exercise, at peak exercise and at 3 and 6 min recovery. The exercise test was considered positive when there was > 1 mm of rectilinear or downsloping ST-segment depression or elevation for at least 80 ms as compared with the resting baseline values. Each test was terminated for symptoms-limiting exercise or > 3 mm ST-segment depression at 80 ms from the J point. Standard safety procedures as recommended by the American Heart Association were strictly observed (Ellestad *et al.*, 1979). The differences between the effects of placebo and 0.5, 1.0 and 2.0 mg doses of bopindolol at 3, 12 and 24 h after the ingestion were analysed by a two-way analysis of variance (ANOVA). Intergroup differences were analysed using a Student-Newman-Keuls test.

Results

The results are reported in Table 1. No significant differences from baseline values were observed in resting and exercise parameters measured 3, 12 and 24 h after placebo ingestion. The exercise tolerance was significantly improved ($P < 0.05$) by each of the three doses of bopindolol (by a maximum of 33%, 52% and 26% at 3, 12 and 24 h after the 2.0 mg dose). The primary effects of bopindolol appeared to be to reduce significantly ($P < 0.05$) resting and exercise double product (mainly by reduction in heart rate) for up to 24 h. The peak ST-segment depression improved ($P < 0.05$) 3 h after oral ingestion of each of the three doses of bopindolol but it remained unchanged after 12 and 24 h. Eight (66%) patients were angina free at the exercise tests performed 3, 12 and 24 h after treatment with each dose of the drug. When the intergroup differences were analysed, no dose-related effects were observed. These figures suggest an improved exercise tolerance with no adverse effect on ischaemia.

Discussion

Bopindolol improved exercise tolerance by decreasing myocardial oxygen consumption, presumably by its negative chronotropic action (Amsterdam *et al.*, 1977). These effects persisted for up to 24 h. A mean terminal half-life of bopindolol active hydrolysed metabolite between 20 and 27 h has been reported and this could justify the prolonged duration of the antianginal effect (Plazter *et al.*, 1984). β-adrenoceptor blockers with shorter half-lives (e.g. atenolol) can also suppress exercise-induced tachycardia 24 h after dosing (Balu *et al.*,

Table 1 Comparison of bopindolol, 0.5, 1.0 and 2.0 mg with placebo in 12 patients at 3, 12 and 24 h after oral ingestion

Parameters	*Time after dosing (h)*	*Placebo*	*Bopindolol 0.5 mg*	*1.0 mg*	*2.0 mg*	*Analysis of variance P values*
Rest						
Heart rate	3	83.6 (6)	68.1 (6)*	68.1 (3)*	66.7 (3)*	< 0.001
(beats min^{-1})	12	85.2 (6)	69.9 (3)*	68.9 (3)*	68.2 (3)*	< 0.001
	24	85.2 (5)	70.7 (4)*	70.9 (3)*	67.2 (3)*	< 0.001
Systolic BP	3	136.7 (7)	125.4 (4)	123.3 (5)	130.8 (5)	NS
(mm Hg)	12	148.7 (6)	134.2 (7)	133.3 (5)	133.7 (6)	NS
	24	136.2 (6)	135.8 (4)	131.7 (6)	130.8 (6)	NS
Double product/	3	11.4 (0.9)	8.5 (0.3)*	8.4 (0.6)*	8.6 (0.3)*	< 0.001
1000	12	12.7 (1.2)	9.2 (0.3)*	9.2 (0.6)*	9.1 (0.6)*	< 0.001
	24	11.7 (0.9)	9.5 (0.3)*	9.3 (0.6)*	8.8 (0.6)*	< 0.001
Peak exercise:						
Heart rate	3	116.9 (5)	103.0 (3)*	99.2 (4)*	98.5 (4)*	< 0.001
(beats min^{-1})	12	116.9 (7)	103.4 (4)*	103.7 (5)*	101.9 (4)*	< 0.001
	24	122.0 (7)	108.8 (5)*	105.5 (4)*	108.0 (5)*	< 0.001
Systolic BP	3	159.1 (9)	148.1 (3)	140.4 (6)	145.0 (7)	NS
(mm Hg)	12	166.2 (5)	154.2 (7)	152.5 (5)	149.6 (6)	NS
	24	160.0 (7)	158.3 (6)	149.2 (6)	150.4 (6)	NS
Double product/	3	18.7 (1.2)	15.1 (0.6)*	14.0 (0.9)*	14.2 (0.9)*	< 0.001
1000	12	19.6 (1.5)	15.8 (0.9)*	15.8 (0.9)*	15.4 (1.2)*	< 0.01
	24	19.8 (1.8)	17.3 (1.2)*	15.7 (0.9)*	16.2 (1.2)*	< 0.001
Exercise time	3	489 (64)	616 (48)*	595 (41)*	652 (39)*	< 0.001
(s)	12	408 (67)	599 (59)*	591 (57)*	620 (42)*	< 0.001
	24	501 (72)	629 (46)*	583 (42)*	631 (49)*	< 0.01
ST-segment depression	3	2.4 (0.3)	1.4 (0.3)*	1.5 (0.3)*	1.2 (0.3)*	< 0.001
(mm)	12	2.1 (0.4)	2.1 (0.3)	1.6 (0.3)	1.7 (0.3)	NS
	24	2.0 (0.2)	2.1 (0.3)	1.7 (0.3)	1.3 (0.3)	NS

Values are mean (s.e. mean).
* = $P < 0.05$ *vs* placebo; NS = not significant.

1983). However, while after administration of atenolol the average circadian heart rate decreases both during the day and at night, after bopindolol the heart rate decreases only during the day, without causing unnecessary depression of nocturnal heart rate (Fitscha *et al.*, 1987). The effects of bopindolol were not dose-related. However, the short period of inactivity due to hospitalization may have influenced the exercise performances and led to an underestimation of a dose-response. The results of this report are important to clinicians. Patients with diurnal heart rate-related anginal episodes would better respond to treatment with long acting β-adrenoceptor blockers. These findings have obvious practical implications in choosing treatment rationally.

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