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Antianginal effects of atenolol and pindolol in patients with stable effort angina pectoris

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Abstract A double blind, randomised crossover study with 20 patients was performed to compare the antianginal effects of atenolol 100 mg once daily and pindolol 5 mg thrice daily. After a placebo run-in period, 2 treatments were given for 2 wk each. The number of anginal attacks and the nitroglycerin (NTG) consumption were determined. During bicycle exercise testing, the systolic blood pressure (BP), heart rate (HR), double product and exercise tolerance were measured. Both drugs reduced the number of anginal attacks and NTG consumption relative to the placebo, with atenolol being more effective than pindolol. During exercise, both β-blockers produced a slight increase in BP and HR compared to the placebo. HR attained with atenolol was lower than pindolol at the same workload. The total duration of exercise and the maximal tolerated workload were greater in atenolol than pindolol experiment. The special properties of β-blockers, such as cardioselectivity or intrinsic sympathomimetic activity (ISA), may have clinical importance in the treatment of angina pectoris.

Key words atenolol; pindolol; angina pectoris; exercise test; clinical trials; blood pressure; heart rate; electrocardiography; sympathomimetics

Beta-blockers with marked ISA produce a higher resting HR, however, the level of increase in HR on exercise is similar to that during treatment with other β-blockers with no ISA. It has been demonstrated that in patients with severe angina pectoris, the reduction in resting HR is an important factor in reducing the frequency and severity of myocardial ischemia and it may raise the question of risk-benefit consideration of the ISA[1-3]. The aim of this study was to compare the antianginal and circulatory effects of 2 β-blockers having different pharmacological properties——pindolol, a non-cardioselective drug with strong ISA and atenolol, a cardioselective drug with no ISA.

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Materials and methods

Patients Twenty patients (5 female, 15 male; aged 24-70 yr) were studied. They had had chronic, stable effort angina pectoris for at least 6 months and 5 attacks/wk without any treatment or nitrates. There were no changes in their symptoms for the 6 wk prior to the study.

The resting ECGs were normal. During exercise, an ST segment depression of 0.1 mV which lasted 80 ms after point J was seen in all patients. There were no spontaneous anginal attacks and none developed angina or ST segment depression after prolonged hyperventilation.

Significant coronary artery disease was confirmed by coronarography except for 2 patients in whom the localized perfusion defects were verified by thallium 201 exercise scintigraphy.

Study design A double blind, randomized crossover, fixed dose study was organized on an outpatient basis. After a washout period (1 wk) during which all medications were discontinued, the patients were given placebo for 2 wk (run-in period). At the start and end of this period, the patients underwent a clinical examina-

tion, BP and HR measurements and an exercise test was performed. No significant differences between these 2 evaluations were observed. After assuming that the entry criteria were satisfied, the patient were given at random either atenolol 100 mg once a day at 8:00 AM or pindolol 5 mg tid at 7:00 AM, 1:00 and 8:00 PM. The first treatment period lasted for 14 d. Patients then entered a wash-out period (1 wk) prior to being crossed over to the alternative treatment period (2 nd period). 1) placebo-pindolol-placebo-atenolol: 2) placebo-atenolol-placebo-pindolol.

Clinical examinations and exercise tests were performed at the end of each period. All examinations were performed about 3 h after the last dose. At each examination, the number of anginal attacks, NTG tablets, drug tolerance and side effects were recorded. Subjective assessment of any anginal episodes and NTG consumption were analysed by a special 'angina diary' in which the patients wrote their experiences.

The exercise test was performed on an electrically breaked bicycle ergometer (Medicor ER 32) beginning at 30 W and progressively increasing the workload by 30 W every 3 min to the following end points: anginal pain, dyspnea, fatigue, maximal HR.

During exercise the maximal tolerated workload, total duration of exercise duration to chest pain, to significant ST depression (1 mm or more occuring 80 ms after point J and lasting for at least 3 consecutive beats) and to the end of exercise were analysed. HR and systolic BP were recorded just prior to exercise, at the onsets of ST segment depression, chest pain and cessation of exercise, and immediately after the completion of exercise.

Statistical analysis Data are presented as $\bar{x} \pm SD$. Linear regression and *t*-tests were used for statistical evaluation. Data and parameter changes in the treatment and placebo periods were compared.

Results

Effects of treatment on anginal attacks and nitroglycerin consumption All 20 patients completed the crossover trial. Both atenolol and pindolol significantly reduced the number of anginal attacks and NTG tablets after 14 d of treatment. Compared with pindolol, atenolol resulted in a greater reduction in the number of anginal attacks and in NTG consumption at the end of each treatment period (Fig 1).

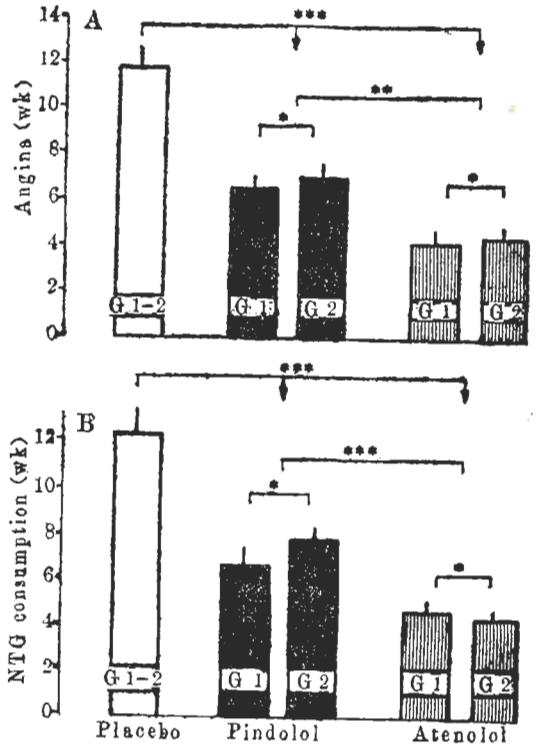

Fig 1. A) Number of anginal attacks with placebo and the two β-blockers. B) Consumption of nitroglycerin (NTG) tablets on placebo and the two β-blockers. *$P>0.05$, **$P<0.05$, ***$P<0.01$. G 1 = group 1, G 2 = group 2.

Circulatory changes at rest

1 Atenolol slightly reduced systolic BP when compared to the placebo. Pindolol did not cause significant changes in systolic BP. There were no differences in the effects of the drugs on BP measured in

standing and supine positions.

2 Atenolol significantly reduced the HR with respect to placebo, while pindolol showed no such effect (Fig 2).

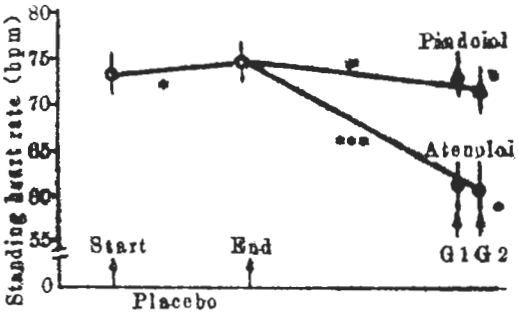

Fig 2. Standing heart rate on placebo and the two β-blockers at rest. $^{*}P>0.05$, $^{***}P<0.01$.

Circulatory and ECG changes during exercise test

1 Systolic BP Both atenolol and pindolol attenuated the usual increase in systolic BP during all 3 phases of exercise compared to the placebo. Atenolol produced a greater reduction than pindolol, however, the differences were not statistically significant.

2 HR Both atenolol and pindolol reduced the increase in HR during exercise when compared with the placebo. The effect on HR was greater in the patients treated with atenolol than with pindolol (Fig 3).

3 HR × systolic BP product The double product was maintained at a significantly lower level at the end of exercise by both β-blocking drugs compared with the placebo. Within the 2 treatment periods, atenolol produced a significantly lower double product value than pindolol for the same level of exercise (Fig 4).

4 Effects of treatment on exercise tolerance The β-blocker therapy with both drugs increased the exercise tolerance in both treatment periods. Atenolol allowed a longer time of exercise (+76 and +100 s) and a greater maximal tolerated workload

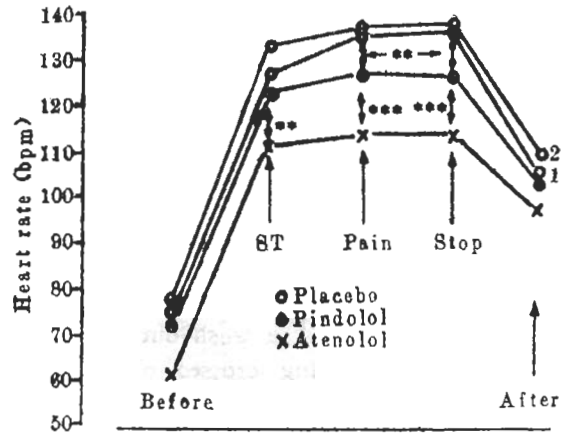

Fig 3. Changes in heart rate during exercise. ST = appearance time of ST depression, Pain = appearance time of anginal pain, Stop = stopping time of exercise. $^{**}P<0.05$, $^{***}P<0.01$.

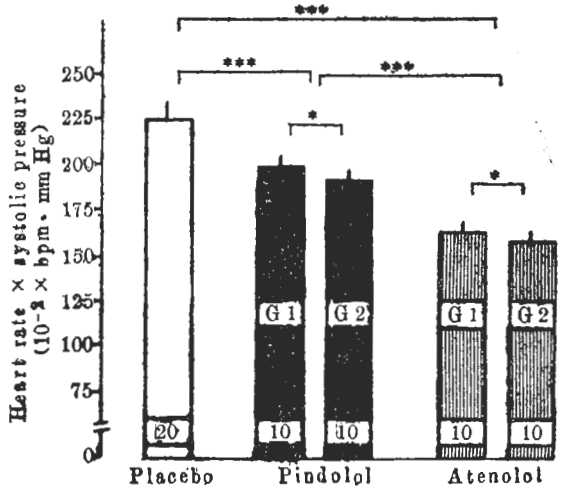

Fig 4. Heart rate × systolic pressure product. □ = number of patients. $^{*}P>0.05$, $^{***}P<0.01$.

(+168 and +132 W, $P<0.05$) than did pindolol (Fig 5).

5 Side effects No side effect serious enough to warrant discontinuation of the medication was observed, and no changes in laboratory parameters were seen at the end of the trial.

Discussion

Several studies with atenolol and pindolol have confirmed the efficacy of these drugs for the treatment of stable angina pectoris[4-8]. However, it is not yet clear

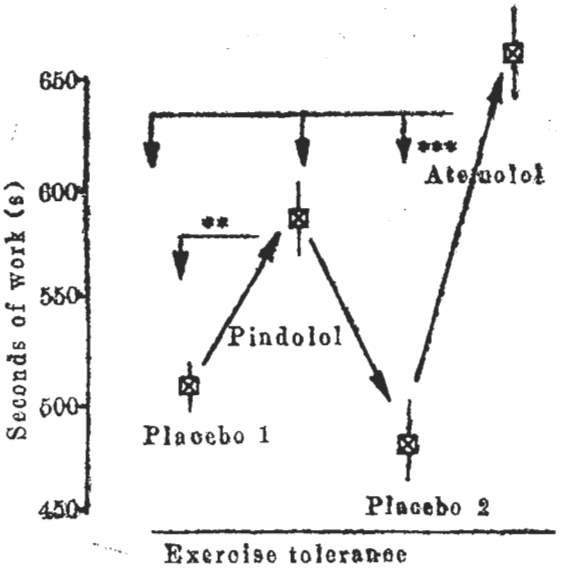

Fig 5. Exercise tolerance on placebo and the two β-blockers. $^{**}P<0.05$, $^{***}P<0.01$.

whether ISA or cardioselectivity can offer advantages in treatment of angina pectoris. β-Blockers with ISA, such as pindolol, may offer protection against worsening airway obstruction, thereby resulting in a higher resting HR than that induced by agents which do not possess this activity. The β-blockade is evident during exercise or when the resting HR is high. It has been suggested that ISA decreases the anti-anginal activity of β-blockers[4,9-10].

It seems that cardioselectivity dose not influence the effects of a β-blocker on HR and BP during exercise. Atenolol as a cardioselective β-blocker without ISA has a longer half-life and therapeutic activity, allowing a single daily dose[5,8]. It results in a strong decrease in the resting HR[8,11,12].

The widely accepted explanation of the antianginal effect and the increased exercise tolerance produced by β-blockers in patients with effort angina is a reduction in HR. Some investigators have observed that the reduction in HR during exercise seen in patients taking β-blockers without ISA was greater than in those taking β-blockers with ISA[9,13].

Both β-blockers increased the exercise tolerance, however, the total duration of exercise and the maximal tolerated workload were greater with atenolol than with pindolol. Patients taking pindolol reached their threshold of angina sooner.

At the doses used, both atenolol and pindolol were well tolerated and no side effects were observed.

The special properties of β-blockers, such as cardioselectivity and ISA, may have some clinical importance in the treatment of patients with stable effort angina pectoris.

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阿替洛尔和吲哚洛尔对定期发作心绞痛病人的作用

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提要 选20例慢性心绞痛病人(病史至少半年、每周发作5次以上)，用双盲法、随机交叉试验，比较阿替洛尔100 mg qd po和吲哚洛尔5 mg tid po的抗心绞痛作用。在服用安慰剂后，2药分别服2 wk，记录心绞痛发作次数和硝酸甘油(NTG)的消耗量。在自行车运动试验期间，测量BP，HR，以及两者的乘积和运动的耐受性。与安慰剂对照组相比，2药均能减少心绞痛发作次数和NTG的消耗量，但阿替洛尔比吲哚洛尔更有效。在运动期间，这2个β阻滞剂均能导致BP和HR的轻微上升。在相同负荷下服用阿替洛尔HR偏低，阿替洛尔与吲哚洛尔相比，能使病人的总运动时间更长、最大耐受负荷更大。这两药所具有的β阻滞剂的特性，如心脏选择性或内源性拟交感活性(ISA)，可能在治疗心绞痛中有重要的临床意义。

关键词 阿替洛尔；吲哚洛尔；心绞痛；运动试验；临床试验；血压；心率；心电描记术；拟交感神经药