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Comparison of the onset of the antihypertensive action of pindolol and propranolol. A 24 h haemodynamic study

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1 Haemodynamic changes during the onset of the antihypertensive action of pindolol, 10 mg twice daily, and propranolol, 80 mg three times daily, were studied for 24 h in two groups of 10 patients with uncomplicated essential hypertension.

2 Baseline haemodynamics were not different between the two groups.

3 Pindolol, with considerable intrinsic sympathomimetic activity (ISA) exerted its maximal antihypertensive efficacy within 3–4 h after dosing ($-15 \pm 3\%$, mean ± s.e. mean, $P < 0.001$). This effect was maintained for 24 h.

4 After propranolol, which is devoid of ISA, arterial pressure fell more gradually, but after 24 h the two drugs shared an equal antihypertensive effect.

5 Cardiac output rose after pindolol by $16 \pm 5\%$ ($P < 0.01$). It decreased transiently by $16 \pm 6\%$ ($P < 0.01$) 1–4 h after propranolol. At that time vascular resistance had risen by $18 \pm 5\%$ ($P < 0.001$).

6 The onset of the antihypertensive action of the two drugs was associated with reductions in vascular resistance. Since reflex vasoconstriction did not occur after pindolol, vascular resistance was always lower on this drug than on propranolol ($-29 \pm 4\%$, $P < 0.001$ *vs* $-15 \pm 5\%$, $P < 0.01$).

7 Cardiac filling pressures, pulmonary artery pressure and pulmonary vascular resistance did not change after pindolol but they rose after propranolol.

8 During the onset of the vasodilator and antihypertensive effects of the two β-adrenoceptor blockers heart rate, stroke volume and cardiac output rose, despite cardiac β-adrenoceptor blockade, suggesting a reduction of parasympathetic tone and an increase in venous return.

9 Thus, haemodynamic changes after administration of β-adrenoceptor blockers are much more complex, than would be expected from their ancillary properties and the effects of cardiac β-adrenoceptor blockade.

Keywords β-adrenoceptor blockers cardiac output vascular resistance hypertension pindolol propranolol

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Introduction

Increased vascular resistance is the hallmark of practically all forms of clinical hypertension. It seems logical therefore to treat this disease with drugs that are primarily active on the resistance vessels. A major challenge to this view has been the introduction of the β-adrenoceptor antagonists, of which propranolol was the first representative to be used on a large scale. Depression of cardiac output and an initial increase in vascular resistance, are prominent features of these drugs. However, after these initial changes, arterial pressure is ultimately lowered by the return of vascular resistance towards its pretreatment level (Tarazi & Dustan, 1972). Thus, in the long run, the antihypertensive effect of propranolol is associated with reduced cardiac output and unchanged or even increased vascular resistance (Man in 't Veld & Schalekamp, 1983a).

It has been reported that during long-term treatment with the non-selective β-adrenoceptor antagonist pindolol, cardiac output is not changed (Atterhög *et al.*, 1976). Consequently the long-term antihypertensive effect of pindolol should be characterized by reduced vascular resistance. Such a haemodynamic profile could be related to a relatively high degree of partial agonist activity (PAA). Pindolol's PAA on cardiac β-adrenoceptors is sufficient to maintain a normal cardiac output, at least acutely and under resting conditions (Svendsen *et al.*, 1979). Detailed studies, however, comparing the time course of the initial haemodynamic effects of pindolol and propranolol are lacking. In the present study we compared the haemodynamic responses to the first oral dose of pindolol for 24 h with the effects of the first oral dose of propranolol. Both pindolol and propranolol are non-selective β-adrenoceptor blockers, the former with strong PAA and the latter devoid of PAA.

Methods

Twenty male patients with mild to moderate essential hypertension participated in the study. They were selected for the study in the outpatient clinic, if they had sitting blood pressures over 160/95 mm Hg, when untreated, on at least three different occasions. Routine clinical and laboratory investigations did not reveal any cause of their hypertension. A history or clinical signs of coronary or valvular heart disease, congestive heart failure, cerebrovascular disease, renal disease or chronic obstructive lung disease were all negative. After the aim of the study and the procedures to be used had been explained, all patients gave their consent to participate in this study. The study protocol was approved by the local Hospital Ethics Review Committee.

Study design

The study was designed as a single-blind placebo-controlled trial. Antihypertensive and other medication, if any, was discontinued at least 3 weeks before the study. Placebo was then given for 2 weeks. At the end of this period the subjects were taken into the clinical pharmacology unit for 2 days. During their stay in the hospital for 2 days they had complete bedrest. After the first night in hospital either pindolol, 10 mg twice daily or propranolol, 80 mg three times daily was given for the first time and the acute effects on blood pressure and cardiac output were studied by invasive methods for 24 h after 2 h of baseline readings.

Measurements

Arterial pressure was measured intra-arterially for 24 h with the Oxford System (Bevan *et al.*, 1969). The brachial artery of the non-dominant arm was cannulated after local anaesthesia with a 2% lignocaine solution. A teflon catheter of 1.0 mm diameter (Plastimed, Saint-Leu-La Foret, France) was introduced by the Seldinger technique. The catheter was connected to a miniature transducer-perfusion device (Northwick Park Hospital, London, England) and the pressure signal was continuously recorded on magnetic tape (medilog Recorder II, Oxford Medical Instruments, Oxford, England). The analogue signal was digitized during replay of the tape at 60 times real time with a sampling frequency of 33 1/3 samples/s real time. The sensitivity of this procedure is 0.3–0.5 mm Hg. Traces were analysed beat by beat by using a Hewlett Packard 2113 E computer system. They were scrutinized for beat loss, damping and movement artefacts. These events accumulated to 1–2% of all data and were excluded from analysis. The mean values for systolic, diastolic and integrated mean arterial pressure and for heart rate were computed over hourly periods.

Cardiac output was measured by means of a 7F triple lumen flow directed Swan-Ganz thermodilution catheter (Edwards Laboratories). The catheter was inserted percutaneously in an antecubital vein by means of the Seldinger technique. Cardiac output was measured in triplicate by bolus injections of 10 ml of ice-cold dextrose

5% every hour, but not between 23.00 h and 07.00 h, because in a pilot study measurements appeared to wake up the patients. Systemic arterial pressure and pulmonary artery pressure were monitored using Gould Statham P23 ID transducers with zero reference at midaxillary level. The pressure signals were continously recorded on a Hewlett Packard 7754A recorder. Right atrial pressure and pulmonary capillary wedge pressure were measured immediately before and after the cardiac output determinations. Mean values of systemic and pulmonary artery pressure were obtained by electronic integration of the respective analogue signals. Heart rate was derived from the continuously monitored ECG. Cardiac output and pressures were always measured with the patient in a strictly horizontal position for at least 15 min. After baseline readings for 2 h, in ten patients the first oral dose of pindolol, 10 mg, was given and the second dose of 10 mg was given 12 h later. In the remaining patients the first oral dose of propranolol, 80 mg, was given. A second and a third dose of 80 mg was given respectively 6 and 12 h later. Values relevant to body size were converted to 1.73 m^2 body surface area. The following haemodynamic variables were derived:

$$SVR = \frac{MAP-RAP}{CO} \times 80 \text{ and}$$

$$PVR = \frac{MPAP-PCWP}{CO} \times 80$$

where MAP = mean systemic arterial pressure (mm Hg)
RAP = mean right atrial pressure (mm Hg)
MPAP = mean pulmonary artery pressure (mm Hg)
PCWP = mean pulmonary capillary wedge pressure (mm Hg)
CO = cardiac output (l min^{-1})
SVR = systemic vascular resistance (dyn s cm^{-5})
PVR = pulmonary vascular resistance (dyn s cm^{-5}).

Statistics

Data are presented as mean values ± s.e. mean. Student's two tailed *t*-test for unpaired or paired observations was used for comparison. *P*-values < 0.05 were considered to indicate a statistically significant difference.

Results

Baseline haemodynamic variables did not differ between the two groups (Table 1). The maximal fall in MAP on pindolol was already seen 3–4 h after dosing (Figure 1, −15 ± 3%, $P < 0.001$). This was caused by reduction of TPR, which amounted to 28 ± 4%, ($P < 0.001$) after 24 h. CO was increased by 16 ± 5% at that time ($P < 0.01$). Heart rate (HR) and stroke volume (SV = CO/HR) were increased by 15 ± 5% ($P < 0.05$) and 8 ± 6% ($P < 0.05$) respectively.

On propranolol the fall in MAP was somewhat delayed as compared with pindolol. The maximal antihypertensive effect was observed after 24 h (−15 ± 6%, $P < 0.001$). CO and HR initially fell by 16 ± 5% ($P < 0.01$) and 9 ± 3% ($P < 0.01$) respectively 2 h after dosing. MAP had not changed at that time, so that TPR was increased by 18 ± 5% ($P < 0.001$) above baseline values. The onset of the antihypertensive effect on propranolol was associated by return

Table 1 Patient characteristics before treatment

	Pindolol	*Propranolol*
Number of patients	10	10
Age (years)	45 ± 3	42 ± 4
Systolic arterial pressure (mm Hg)	161 ± 5	159 ± 4
Diastolic arterial pressure (mm Hg)	95 ± 3	97 ± 3
Mean arterial pressure (mm Hg)	118 ± 3	120 ± 3
Heart rate (beats min^{-1})	63 ± 2	63 ± 2
Cardiac output (l min^{-1} 1.73 m^{-2})	4.8 ± 0.2	4.7 ± 0.2
Stroke volume (ml 1.73 m^{-2})	75 ± 2	73 ± 3
Total peripheral resistance (dyn s cm^{-5} 1.73 m^{-2})	1950 ± 290	2100 ± 250
Right atrial pressure (mm Hg)	1.3 ± 0.4	1.5 ± 0.3
Mean pulmonary capillary wedge pressure (mm Hg)	4.1 ± 0.3	4.6 ± 0.3
Mean pulmonary artery pressure (mm Hg)	12 ± 1.0	12 ± 0.5
Pulmonary vascular resistance (dyn s cm^{-5} 1.73 m^{-2})	135 ± 14	139 ± 13

Values are mean ± s.e. mean. None of the differences between the two groups was statistically significant (Student's *t*-test for unpaired observations).

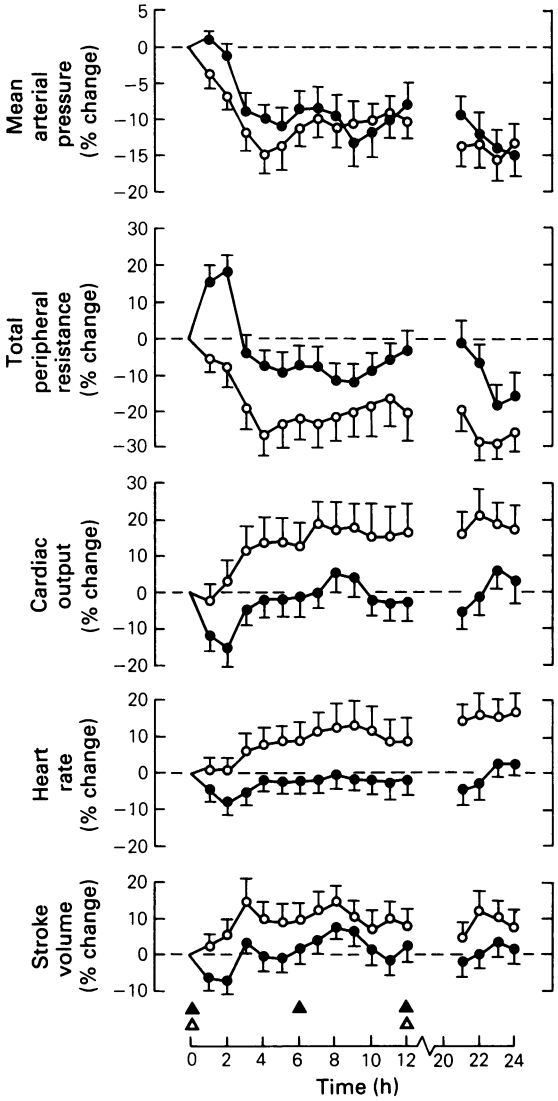

Figure 1 Haemodynamic changes after oral administration of pindolol, 10 mg (△, ○) or propranolol, 80 mg (▲, ●) in patients with uncomplicated essential hypertension.

of TPR towards pretreatment values. After 24 h it was lowered by 15 ± 7% ($P < 0.01$). During return of TPR towards baseline values, both HR, SV and CO also returned to baseline.

RAP, PCWP, MPAP and PVR did not change after pindolol, whereas these variables increased after propranolol.

Discussion

The present study confirms and extends an earlier observation, that the non-selective β-adrenoceptor antagonist pindolol lowers arterial pressure in the long run through vasodilatation (Atterhög *et al.*, 1976). Our study shows that the maximum of this vasodilator effect is already seen within 4 h after oral administration of 10 mg. Small but significant increments in HR, SV and CO were observed. Thus, the haemodynamic profile of pindolol is essentially different from the profile of β-adrenoceptor antagonists lacking PAA. After propranolol, the fall in HR and CO triggered a vasoconstrictor response, so that MAP remained unchanged for 2 h. However, as

observed with pindolol, the antihypertensive action of propranolol was associated with return of the TPR towards and later below pretreatment values. Since the initial rise in TPR was not seen on pindolol and the two β-adrenoceptor blockers shared an equal antihypertensive efficacy, TPR was always lower on pindolol at any level of MAP, as compared with propranolol.

Detailed haemodynamic studies at the time of onset of the antihypertensive effect of β-adrenoceptor antagonists are scarce. Recently two of these studies, one with the β_1-selective adrenoceptor antagonist atenolol (Simon *et al.*, 1981) and one with the non-selective antagonist timolol (Colfer *et al.*, 1984), have been reported. These two β-adrenoceptor blockers both lack PAA. After atenolol and timolol any reduction in arterial pressure was not observed within 3–4 h after dosing. The present study shows that after pindolol MAP was already reduced after 1 h, whereas the maximum antihypertensive effect was observed within 4 h. This time course confirms an early study with pindolol by Anavekar *et al.* (1975). The reason for the observed difference in the time of onset of the blood pressure reduction between β-adrenoceptor antagonists with different ancillary properties, could be that with drugs without PAA, the antihypertensive effect is initially offset by reflex vasoconstriction in response to the fall in cardiac output. Pindolol's PAA is apparently sufficient to compensate for the loss of basal sympathetic tone on the heart, so that cardiodepression and reflex vasoconstriction do not occur. It is therefore indeed appropriate to refer to pindolol's PAA on the heart as intrinsic sympathomimetic activity (ISA). This study also shows that pindolol, unlike propranolol, does not increase cardiac filling pressures and pulmonary artery pressure. This suggests that, in contrast to β-adrenoceptor antagonists devoid of PAA, pindolol does not exert a negative inotropic action.

The haemodynamic changes shortly after the onset of the antihypertensive action of the two β-adrenoceptor blockers deserve some further comments. The vasodilator effects of the drugs initiated the fall in MAP approximately 2 h after dosing. This event was associated with gradual rises in HR, SV and CO on both β-adrenoceptor blockers. This suggests, that these changes as observed after pindolol are, at least partly, independent of its relatively high degree of ISA. Indeed, it has been shown, that changes in heart rate in response to vasodilatation during β-adrenoceptor blockade are mediated by vagal withdrawal (Man in 't Veld *et al.*, 1980). The changes in afterload during the onset of the antihypertensive action of the β-adrenoceptor blockers will result in a rise in SV and consequently a rise in CO, despite blockade of cardiac β-adrenoceptors (Man in't Veld & Schalekamp, 1983a, 1984). Thus, the haemodynamic changes after administration of a β-adrenoceptor blocker, are much more complex, than would be expected from their ancillary properties or by blockade of cardiac β-adrenoceptors alone.

The vasodilator effect of β-adrenoceptor blockers cannot easily be explained by blockade of central, cardiac, juxtaglomerular or vascular β-adrenoceptors (Man in't Veld & Schalekamp, 1982, 1983b). Our data show, that under the basal conditions of our study protocol, even propranolol reduced blood pressure through vasodilatation, although peripheral resistance was at all times lower after pindolol. A remaining possibility to explain pindolol's and propranolol's antihypertensive action is that their vasodilator effect depends on blockade of peripheral presynaptic β-adrenoceptors. Reduced release of noradrenaline from sympathetic nerve endings and, consequently, attenuated α-adrenoceptor mediated vasoconstrictor tone could elegantly explain both their vasodilator as well as their antihypertensive action.

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