Acute Vasodilator Action of Pindolol in Humans

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SUMMARY The local hemodynamic effect of pindolol, a nonselective β-blocker with intrinsic sympathomimetic activity, was investigated in 17 healthy volunteers. Changes in forearm blood flow (FBF) in response to infusion of drugs into the brachial artery were measured by plethysmography. Pindolol increased FBF dose dependently to a maximal value of 62 ± 8% (mean ± SEM, p < 0.001) without inducing changes in heart rate or blood pressure. For a single dose of pindolol the maximal effect on FBF was seen after approximately 4 minutes of infusion, and this effect persisted for at least 12 minutes after the infusion. The pindolol-induced increase in FBF was reduced by concomitant infusion of propranolol (p < 0.001). Intra-arterial infusion of practolol did not influence FBF. No significant influence of pindolol was found on the vasoconstriction induced by the α1-adrenergic receptor agonist methoxamine, the α2-adrenergic receptor agonist BHT-933, or angiotensin II. Measurement of plasma pindolol concentrations in the venous effluent of the forearm suggested that vasodilatation occurred at drug levels within the therapeutic range. These results indicate that the β-blocker pindolol has vasodilatory properties owing to stimulation of vascular β2-adrenergic receptors and that this effect may be of therapeutic relevance. (Hypertension 7: 146-150, 1985)

KEY WORDS • pindolol • vasodilatation • β-adrenergic receptor • intrinsic sympathomimetic activity • β-adrenergic blocking agents • peripheral resistance

The β-adrenergic blocking agents are effective antihypertensive agents irrespective of whether they possess properties such as β1-adrenergic receptor selectivity, a membrane stabilizing effect, or partial agonist activity (intrinsic sympathomimetic activity, ISA).1 There is evidence, however, that the hemodynamic effects of β-blockers with ISA are different from those of other types, in that they lower blood pressure in hypertensive patients primarily by reducing an elevated systemic vascular resistance.2-4 The mechanism underlying this reduction in vascular resistance has not been fully elucidated. Recent experimental evidence has shown that pindolol, a nonselective β-blocker with strong ISA, has a direct vasodilator effect,5,4 and this effect could be relevant for its influence on systemic hemodynamics. The present investigations were designed to characterize the vascular effect of pindolol in humans by determining its influence on forearm blood flow (FBF) after intraarterial administration and to elucidate the underlying mechanism.

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Methods

Seventeen healthy volunteers, 11 men and 6 women, participated in this study. Their medical history, physical examination, and routine laboratory test results did not show evidence of cardiovascular or other disease. None of the subjects was receiving any medication at the time of the study or in the previous 2 weeks. Informed consent was obtained from all subjects, and the protocols of the study were approved by the Ethical Committee of the Leiden University Hospital.

The studies were performed in a quiet room at a constant temperature of 20 °C with the subjects in the supine position. On the day of the study all subjects refrained from drinking caffeine-containing beverages and smoking. After local anesthesia of the skin, the brachial artery of the nondominant side was cannulated for intra-arterial infusion of drugs and for blood pressure monitoring with a Statham P23Id pressure transducer (Gould Inc., Oxnard, CA). Six subjects also had a deep cubital vein cannulated for blood sampling. A one-lead electrocardiogram was registered continuously. The FBF was measured by venous occlusion plethysmography6 (EC-3 Plethysmograph, Hokanson Inc., Issaquah, WA). During measurements of FBF the hand was excluded from the circulation by a small cuff inflated to 40 mm Hg above the systolic blood pressure, and the arm was comfortably support-
ed above the level of the heart. Blood pressure, heart rate, and plethysmography tracings were recorded on a polygraph. With exception of the time-response curve for pindolol, FBF values presented are the mean of six consecutive recordings. All experiments started at least 30 minutes after the cannulation procedures. Plasma pindolol concentrations were determined by high-pressure liquid chromatography combined with fluorometry.

Two series of experiments were carried out. In the first, the direct vascular effect of pindolol and its dependency on β-adrenergic receptors was investigated in 11 subjects. Intra-arterial infusions of isoproterenol (0.02–1.2 ng/kg/min, n = 10), practolol (1–4 μg/kg/min, n = 5; or 4–60 μg/kg/min, n = 5), and pindolol (0.04–0.4 μg/kg/min, n = 6) were given in this order. Subsequently, the infusion of isoproterenol was repeated in the presence of a constant infusion of pindolol (0.16 μg/kg/min, n = 5), and the infusion of pindolol was repeated in the presence of a constant infusion of propranolol (1.0 μg/kg/min, n = 6). Finally, the highest dose of isoproterenol was repeated in the presence of propranolol (1.0 μg/kg/min, n = 3). The relationship between the pindolol-induced vasodilatation and blood levels of the drug, the time course of this effect, and the possible involvement of α-adrenergic receptor antagonism were investigated in a second set of experiments in six other subjects. Intra-arterial infusion of the selective α-adrenergic receptor agonist methoxamine (0.04–0.20 μg/kg/min), the selective α-adrenergic receptor agonist B-HT 933 (0.20–1.00 μg/kg/min), and angiotensin II (0.02–3.00 μg/kg/min) were given together with saline (0.4 ml/min) and repeated in the presence of a constant infusion of pindolol (0.16 μg/kg/min). Pindolol also was infused at doses of 0.01 to 0.80 μg/kg/minute, and at the end of each dose step, venous blood was sampled for determination of plasma pindolol concentration. Finally, pindolol, 2.40 μg/kg/minute, was infused for 6 minutes.

The constant dose infusions were begun 3 minutes before the cumulative dose infusions. Each dose was given for 3 minutes, and FBF was measured during the last 90 seconds of each dose step. During the pindolol infusions, when blood samples were taken, the dose steps lasted approximately 4 minutes. In none of the experiments did the infusate volume exceed 3.4 ml/minute. In between the various infusions, the wrist cuff was deflated and at least 15 minutes was allowed for FBF to stabilize. Blood pressure and heart rate were recorded immediately before and at the end of each infusion were used for analysis.

All solutions were freshly prepared on the day of the investigation. Isoproterenol sulfate (FNA [Formulium Nederlandse Apothekers] preparation), practolol (Eraldin), pindolol (Visken), propranolol (Inderal), B-HT 933-2HCl (azepexole), and methoxamine (Vasoxyl) were dissolved in saline. Angiotensin II amide (Hypertensin) was dissolved in saline with human serum albumin, 0.5 mg/ml.

Results are given as the mean value ± 1 SEM. The FBF data are presented as percentage change from baseline level. Analysis of variance was used to determine the significance of differences in or between dose-response curves and, where mentioned in the text, two-tailed Student's t test was used.

**Results**

Mean values and range for age, body weight, and basal values for blood pressure, heart rate, and FBF are given in Table 1. In the first study the intra-arterial infusion of pindolol, 0.04 to 0.40 μg/kg/minute, resulted in a dose-dependent increase in FBF with a maximum of 38 ± 5% above basal value (p < 0.001; Figure 1). This pindolol-induced increase in FBF was markedly reduced by the concomitant infusion of propranolol (p < 0.001; Figure 1). Intra-arterial infusion of practolol, 1 to 4 μg/kg/minute and 4 to 60 μg/kg/minute, did not influence FBF significantly (Figure 2). Isoproterenol, 0.02 to 1.20 ng/kg/minute, increased FBF dose dependently to a maximum of 265 ± 38% (p < 0.001; Figure 3); this effect was completely abolished by the simultaneous infusion of pindolol, 0.16 μg/kg/minute (p < 0.001; Figure 3). In three other
subjects it was shown that propranolol, 1.0 μg/kg/minute, also reduced the increase in FBF seen at the highest dose of isoproterenol by 98 ± 3%. A dose-dependent decrease in FBF was observed during the intra-arterial infusion of methoxamine, B-HT 933, and angiotensin II (p < 0.001 for each; Figures 4 and 5). The vasoconstrictor response to these drugs was not significantly affected by concomitant infusion of pindolol, 0.16 μg/kg/minute (Figures 4 and 5).

In the second series of experiments, intra-arterial infusion of pindolol, 0.01 to 0.80 μg/kg/minute (each dose infused for approximately 4 minutes), increased FBF to a maximum of 62 ± 8% (p < 0.001; Figure 1). Plasma pindolol concentrations in the venous effluent blood, sampled during these infusions in five subjects, varied from 1 to 304 ng/ml and the drug levels correlated directly with the effect on FBF (Figure 6). In one subject sampling did not succeed because of clotting in the venous cannula. The time-response curve of pindolol, 2.40 μg/kg/minute, infused intra-arterially for 6 minutes, shows a transient decrease, followed by a marked increase in FBF, the maximum being reached after approximately 4 minutes. After discontinuation of the pindolol infusion a marked effect on FBF persisted for at least 12 minutes (Figure 7).

None of the drugs used had any measurable effect on heart rate. Blood pressure was not influenced by infusion of the various drugs, except for angiotensin II, where mean arterial pressure increased 4.4 ± 1.0 mm Hg without pindolol and 8.0 ± 2.0 mm Hg with concomitant pindolol infusion (Student’s t test, p < 0.05 for each).

Discussion

Our experiments indicate that infusion of pindolol into the forearm arterial bed of healthy volunteers results in a dose-dependent increase in regional blood flow. As this result was observed in the absence of noticeable changes in heart rate or blood pressure, a
Local effect on vascular smooth muscle tone is the most likely explanation. These findings agree with the results of several studies in which the vasodilating properties of pindolol have been demonstrated (i.e., in the denervated hindlimb of anesthetized dogs,\textsuperscript{6,8} in isolated perfused mesenteric vessels of the dog,\textsuperscript{7} and in preparations of human arteries and veins\textsuperscript{5}). The degree of vasodilatation produced by pindolol in the present study was comparable to that observed in the denervated hindlimb of the dog after intravenous administration of corresponding doses of the drug.\textsuperscript{6} The greater vasodilatation of pindolol found in our second experiment is almost certainly due to the longer duration of each infusion step, as it was shown in the time-effect experiment that the maximal effect on blood flow was not achieved before 4 to 5 minutes.

The observation that intra-arterial infusion of the nonselective $\beta$-blocker propranolol does not influence resting muscle blood flow\textsuperscript{11,12} suggests that $\beta_2$-adrenergic receptor mediated vasodilatation is not important for basal vascular tone. It is conceivable that the vascular effect of pindolol is caused by its (partial) agonist activity at $\beta_2$-adrenergic receptor sites; this explanation is supported by two findings from the present study.

First, it was demonstrated that pindolol-induced vasodilatation was markedly diminished by simultaneous infusion of a $\beta$-blocking dose of propranolol. Second, it was shown that practolol did not influence FBF, despite the fact that it possesses ISA. This is presumably because the compound lacks affinity for the $\beta_2$-adrenergic receptor. The results of previous studies\textsuperscript{5,6,7,8} are also in accordance with a pivotal role for $\beta_2$-adrenergic receptors in mediating the vasodilator response to pindolol.

Intra-arterial infusion of propranolol did not completely prevent the pindolol-induced vasodilatation.
Although this finding could be related to the dose, experiments with isolated human and canine blood vessels suggest that a mechanism other than $\beta_2$-adrenergic receptor stimulation may contribute to the compound's vasodilator effect.

Involvement of $\alpha$-adrenergic blocking effects in the pharmaco logical actions of $\beta$-blockers, including pindolol, also have been suggested in the literature.\textsuperscript{15-16} Therefore, we investigated whether $\alpha$-adrenergic blockade contributed to the vasodilating effect of pindolol. Because two types of postsynaptic $\alpha$-adrenergic receptors ($\alpha_1$ and $\alpha_2$) have been identified in this vascular bed,\textsuperscript{17} highly selective agonists for these receptors were infused with and without pindolol. No evidence was found that either $\alpha_1$-adrenergic or $\alpha_2$-adrenergic blockade contributed to the vascular effect of pindolol. The finding that the angiotensin II effect also was not influenced by pindolol further argues against a nonspecific vascular effect.

Pindolol, 0.16 $\mu$g/kg/minute, abolished responses to isoproterenol; this dose of pindolol is well within the $\beta$-blocking range. During intra-arterial infusion of pindolol, 0.04 and 0.16 $\mu$g/kg/minute, the concentration of pindolol in the venous blood of the forearm was 11 to 98 ng/ml, which is the same range as that found during oral administration of the drug,\textsuperscript{18} and a significant ($p < 0.05$) vasodilatation was already present at a dosage of 0.04 $\mu$g/kg/minute. Provided that the arterial drug concentrations are not greatly different from the measured venous concentrations, these findings suggest that this effect of pindolol could be clinically relevant. Although one should be cautious in extrapolating the results of the present study on the forearm vascular bed of healthy volunteers to the situation in clinical practice, it is tempting to associate this direct vascular effect with the lowering of peripheral resistance below pretreatment levels during prolonged pindolol therapy in hypertensive patients.\textsuperscript{3, 4, 19}

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