Br. J. clin. Pharmac. (1984), **18**, 90–93

Chronic effects of metoprolol and methyldopa on calf blood flow in intermittent claudication

M. LEPÄNTALO
The IV Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland

In a placebo-controlled double-blind study 14 hypertensive patients with intermittent claudication were treated with metoprolol (100–200 mg daily) and methyldopa (500–1000 mg daily) for 3 weeks and their effects on heart rate, blood pressure as well as on resting and hyperaemic calf blood flow and vascular resistance were compared.

In their antihypertensive effect metoprolol and methyldopa did not differ significantly. In 23 diseased limbs the calf blood flow and vascular resistance remained unchanged at rest during the trial. The active drugs reduced hyperaemic flow ($P < 0.05$). The peak flow was reduced by 20% ($P > 0.01$) with metoprolol and by 15% with methyldopa below the initial level and by 17% and by 12% below the level recorded on placebo, respectively. Neither of the drugs influenced vascular resistance during reactive hyperaemia.

Thus, in patients with intermittent claudication antihypertensives should be used with care.

Keywords calf blood flow intermittent claudication β-adrenoceptor blocking drugs methyldopa adverse effects

Introduction

β-adrenoceptor blocking drugs may cause exacerbation of intermittent claudication (Conway, 1975; Rodger *et al.*, 1976). There is evidence to suggest that this problem is related to decreased muscle perfusion due to diminished blood pressure caused by reduction in cardiac output (Trap-Jensen *et al.*, 1975; Lepäntalo & Tötterman, 1983) rather than to blockade of β_2-adrenoceptors in peripheral vasculature (Kendall, 1981). Regardless the presence of β_1-selectivity or intrinsic sympathomimetic activity, all β-adrenoceptor blockers seemed to decrease the mean exercise muscle blood flow in patients with intermittent claudication (Smith & Warren, 1982).

The aim of this study was to establish whether the flow reduction is characteristic of β-adrenoceptor blockers only or of other antihypertensives as well. The drugs used were metoprolol, a β_1-selective blocker without intrinsic sympathomimetic activity, a drug affecting mainly cardiac output, and methyldopa, a central antihypertensive agent which also reduces peripheral vascular resistance. Their effects were compared in hypertensive patients with intermittent claudication.

Methods

Seventeen patients with intermittent claudication and mild essential hypertension were initially recruited for the study. Fourteen (aged 41–73 years, male/female ratio 9/5) were able to follow the drug regimen throughout the trial and completed it. Their medical histories showed no evidence of coronary heart disease, heart failure, stroke or advanced limb ischaemia. The arterial origin of the intermittent claudication was verified by pathological ankle/arm systolic blood pressure ratio. The diseased lower limbs with pressure ratios 0.20–0.80 totalled 23.

The study was double-blind consisting of four 3-week periods: one run-in period with placebo, and three treatment periods with either metoprolol (100–200 mg daily), methyldopa (500–1000 mg daily) or placebo in random order.

After a 30 min rest, supine blood pressure, heart rate and calf blood flow were measured. Blood pressure was measured using a mercury sphygmomanometer. Heart rate was obtained from ECG tracings. Calf blood flow was measured with venous occlusion plethysmography using a mercury-in-rubber strain gauge first described by Whitney (1953). Mean blood pressure was approximated to diastolic pressure plus one third of the pulse pressure. Vascular resistance was calculated by dividing mean blood pressure (mm Hg) by blood flow (ml min^{-1} l^{-1} of tissue) and expressed in arbitrary units. After a 5 min ischaemia, hyperaemic calf blood flow was measured repeatedly to record the initial and peak flows. The initial blood pressure was measured and the respective vascular resistance calculated.

The study was approved by the Ethical Committee of the IV Department of Surgery, Helsinki University Central Hospital. The patients gave their informed consent.

The effects of the different treatments on the haemodynamic parameters were investigated by two-way analysis of variance followed, when appropriate, by the Scheffè test.

Results

Metoprolol tended to reduce heart rate (Table 1). However, according to analysis of variance heart rate levels did not differ significantly ($F = 2.05$; $P = 0.12$). Lowered blood pressure (Table 1) by the active drugs was verified on each occasion ($F = 5.28 - 11.7$; $P = 0.004 - <0.001$). The diastolic blood pressure reduction by metoprolol and methyldopa was confirmed also by the Scheffè test. Methyldopa lowered the systolic blood pressure, the reduction being insignificant only during reactive hyperaemia, as compared with the placebo. No significant differences were observed between the active drugs, although methyldopa exhibited a slightly better antihypertensive effect than metoprolol.

The resting blood flow (Figure 1) was not affected by the active drugs ($F = 1.77$; $P = 0.16$). The initial flow was reduced by the active drugs ($F = 4.39$; $P = 0.008$), although no statistically significant pairwise differences could be observed. The peak flow was also reduced by the active drugs ($F = 4.47$; $P = 0.007$). Metoprolol reduced the peak flow below the levels measured after the run-in period ($P < 0.05$). The vascular resistance (Table 1) was unaltered at rest ($F = 1.38$; $P = 0.26$) as well as at the beginning of reactive hyperaemia ($F = 0.68$; $P = 0.58$).

Discussion

The relevance of the results from acute studies in healthy subjects on the effect of β-adrenoceptor blockers on peripheral circulation to the situation in a clinical setting is questionable. The chronic haemodynamic response to β-adrenoceptor blockade differs markedly from the acute response (Tarazi & Dustan, 1972). Furthermore, patients with cold extremities and inter-

Table 1 The effect of 3-week antihypertensive treatment with metoprolol (100–200 mg daily), methyldopa (500–1000 mg daily) and placebo on mean heart rate, blood pressure and vascular resistance (s.d. in brackets).

	Run-in	*Placebo*	*Metoprolol*	*Methyldopa*
Rest				
Heart rate (beats/min)	68 (13)	71 (14)	64 (15)	68 (11)
Systolic BP (mm Hg)	190 (18)	187 (21)	179 (23)	167 (20)
Diastolic BP (mm Hg)	99 (7)	98 (10)	89 (9)	88 (10)
Vascular resistance (arbitrary units)	3.6 (0.9)	3.8 (1.1)	3.9 (1.3)	3.4 (1.0)
Reactive hyperaemia				
Systolic BP (mm Hg)	201 (22)	195 (32)	187 (27)	179 (26)
Diastolic BP (mm Hg)	103 (9)	103 (11)	95 (12)	94 (10)
Vascular resistance (arbitrary units)	1.5 (0.6)	1.5 (1.0)	1.7 (0.9)	1.5 (0.5)

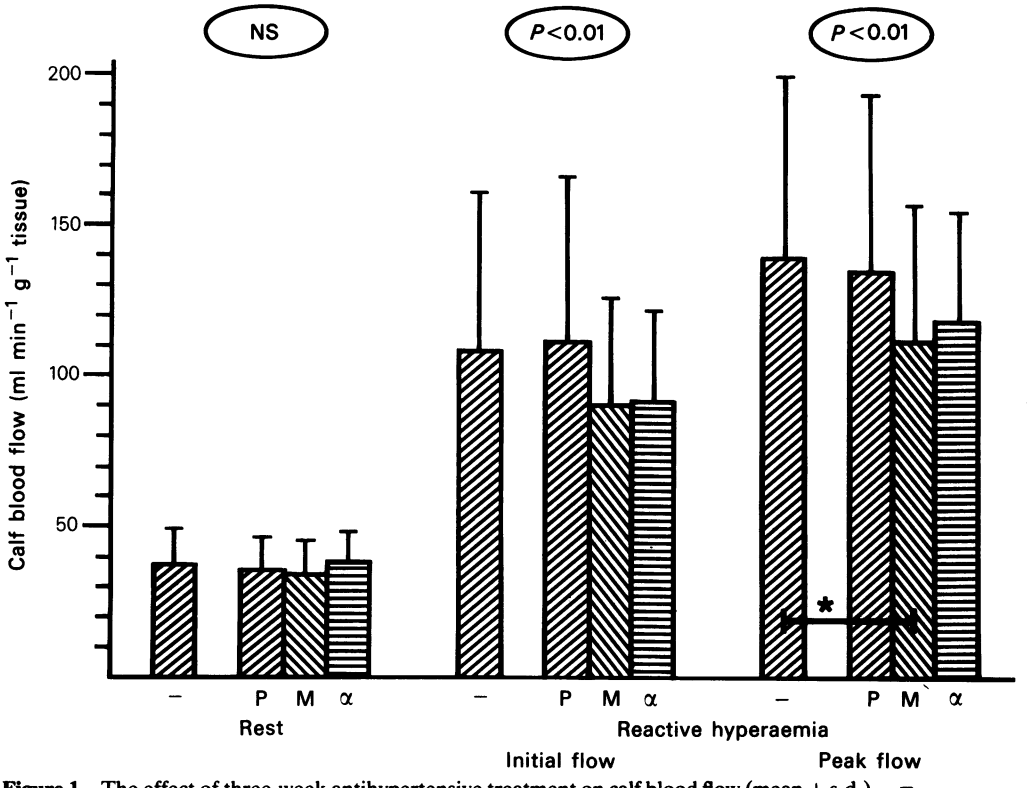

Figure 1 The effect of three-week antihypertensive treatment on calf blood flow (mean + s.d.). – = run-in, P = placebo, M = metoprolol, α = methyldopa. Encircled symbols indicate significances between the groups according to analysis of variance. * $P < 0.05$ according to the subsequent Scheffè test.

mittent claudication during β-adrenoceptor blockade often suffer from generalized arteriosclerosis. Peripheral perfusion depends probably more on cardiac output and the extent and severity of peripheral major arterial disease than on β-adrenoceptor mediated changes in vascular tone (Kendall, 1981). As shown by Young *et al.* (1976), the influence of peripheral arterial disease is accentuated by increasing flow rates, as during reactive hyperaemia in the present study. Therefore, it cannot be concluded from the resting haemodynamics of the lower limb whether the effects of antihypertensive treatment on peripheral circulation in patients with intermittent claudication are detrimental.

The marked vasodilatation in skeletal muscles during exercise, simulated in the present study by reactive hyperaemia, is mainly mediated by local autoregulation (Clausen, 1976). In patients with arteriosclerotic changes, this autoregulation capacity is partly used to compensate for the reduced perfusion pressure distal to the arteriosclerotic lesion. At maximum vasodilatation, autoregulation is not able to compensate for any decrease in the systemic blood pressure. In the present study, the active drugs decreased the calf blood flow during reactive hyperaemia. The vascular resistance was unaltered reflecting unchanged vascular tone. Thus, the flow reduction could be attributed to blood pressure reduction as such, as suggested by Thulesius (1979), regardless of the haemodynamic mechanism by which the blood pressure was reduced. However, the somewhat greater hypotensive effect of methyldopa on the hyperaemic calf blood flow might have slightly biased the results. The potential positive effect of methyldopa on vascular resistance (Morin *et al.*, 1964; Onesti *et al.*, 1964) was masked during reactive hyperaemia. Contrary to metoprolol (Eliasson *et al.*, 1982), methyldopa has been observed to elicit an inhibitory effect on peripheral vasospasm (Varadi & Lawrence, 1969). Thus, it may be preferred by patients with cold feet.

As suggested by Sivertsson (1978) antihypertensive treatment should be used with care in patients with intermittent claudication to avoid further reduction of the calf blood flow already impaired by peripheral arterial disease. Metoprolol did not differ in this respect from methyldopa.

This study was supported by a grant from the Sigrid Juselius Foundation.

References

Clausen, J. P. (1976). Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease. *Prog. cardiovasc. Dis.*, **28**, 459–495.

Conway, J. (1975). Beta adrenergic blockade in hypertension. In *Modern trends in cardiology -3*, ed. Oliver, M. F., pp. 376–403. London and Boston: Butterworths.

Eliasson, K., Lins, L. E. & Sundqvist, K. (1982). Peripheral vasospasm during β-receptor blockade—a comparison between metoprolol and pindolol. *Acta med. Scand.*, suppl. 665, 109–112.

Kendall, M. J. (1981). Are selective beta-adrenoceptor blocking drugs an advantage? *J. Roy. Coll. Physicians Lond.*, **15**, 33–40.

Lepäntalo, M. & Tötterman, K. J. (1983). Effect of long-term beta-adrenergic blockade on calf blood flow in hypertensive patients. *Clin. Physiol.*, **3**, 35–42.

Morin, Y., Turmel, L. & Fortier, J. (1964). Methyldopa: clinical studies in arterial hypertension. *Am. J. med. Sci.*, **248**, 633–639.

Onesti, G., Brest, A. N., Novack, P., Kasparian, H. & Moyer, J. H. (1964). Pharmacodynamic effects of alpha-methyldopa in hypertensive subjects. *Am. Heart J.*, **67**, 32–38.

Rodger, J. C., Sheldon, C. D., Lerski, R. A. & Livingstone, W. R. (1976). Intermittent claudication complicating beta-blockade. *Br. med. J.*, **1**, 1125.

Sivertsson, R. (1978). Effect of blood pressure reduction on tissue perfusion. *Acta med. Scand.*, suppl. 628, 13–16.

Smith, R. S. & Warren, D. J. (1982). Effect of β-blocking drugs on peripheral blood flow in intermittent claudication. *J. cardiovasc. Pharmac.*, **4**, 2–4.

Tarazi, R. C. & Dustan, H. P. (1972). Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. *Am. J. Cardiol.*, **29**, 633–640.

Thulesius, O. (1979). Beta-adrenergic blockade and vasospasm. *Acta med. Scand.*, suppl. 625, 41–44.

Trap-Jensen, J., Clausen, J. P., Noer, I., Mogensen, A., Christensen, N. J., Krogsgaard, A. R. & Larsen, O. A. (1975). Regional hemodynamic changes during exercise in essential hypertension before and after beta-receptor blockade. *Scand. J. clin. lab. Invest.*, **35** (suppl. 143), 60.

Varadi, D. P. & Lawrence, A. M. (1969). Suppression of Raynaud's phenomenon by methyldopa. *Arch. intern. Med.*, **124**, 13–18.

Whitney, R. J. (1953). The measurement of volume changes in human limbs. *J. Physiol.*, **121**, 1–27.

Young, D. F., Cholvin, N. R., Kirkeeide, R. L. & Roth, A. C. (1977). Hemodynamics after arterial stenoses at elevated flow rates. *Circulation Res.*, **41**, 99–107.

(Received November 10, 1983, accepted March 10, 1984)