Comparison of medroxalol and labetalol, drugs with combined α - and β -adrenoceptor antagonist properties

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- 1 Medroxalol, a new drug which has been reported to possess both α - and β -adrenoceptor antagonist properties, was compared with labetalol in single dose studies in normotensive males.
- 2 Oral doses of 400 mg of each drug significantly reduced blood pressure, both supine and erect, without significant changes in heart rate.
- 3 The chronotropic and diastolic depressor responses to isoprenaline were significantly antagonised by both drugs, for at least 6-8 h after drug administration. Medroxalol was associated with significantly greater β -adrenoceptor antagonism than labetalol.
- 4 There was no significant antagonism by either drug of the pressor response to nor-adrenaline. However, in a sub-group of subjects the responses to the selective α_1 -adrenoceptor agonist, phenylephrine, were consistent with modest α_1 -adrenoceptor antagonism. This was significant only for labetalol.
- 5 The ratios of β_1 - to α_1 -adrenoceptor antagonism as calculated from the relative shifts of the isoprenaline and phenylephrine dose-response curves, were 3 to 1 for labetalol and about 7 to 1 for medroxalol.

Keywords medroxalol labetalol α -adrenoceptor antagonism
 β -adrenoceptor antagonism

Introduction

β -adrenoceptor antagonist drugs are widely used in the management of essential hypertension, either as monotherapy or in combination with a vasodilator or α -adrenoceptor antagonist as an integral part of a 'stepped' approach to antihypertensive therapy. β -adrenoceptor blockers are not free of side effects, however, and in some patients with angina or peripheral vascular disease the effects on the peripheral vasculature of β -adrenoceptor antagonism and unopposed α -adrenoceptor activity are potentially harmful.

Labetalol, introduced about 10 years ago, was the first drug to possess both α - and β -adrenoceptor antagonist properties in a single molecule. It has been shown to be an effective antihypertensive drug which may have advantages over standard β -adrenoceptor blockers (Farmer *et al.*, 1972; Rosei *et al.*, 1975; Joeke & Thomson, 1976; Richards *et al.*, 1976; Brittain & Levy,

1976) particularly in those patients also suffering from angina or peripheral vascular disease (Frishman *et al.*, 1981).

Medroxalol, Merrell Pharmaceuticals Ltd, Hounslow, Middlesex, U.K. (Figure 1) is a new drug which also possesses antagonist properties at both α - and β -adrenoceptors in animal studies (Dage *et al.*, 1981). It has been shown to be effective in the treatment of experimental hypertension where α -adrenoceptor antagonism appears to be a major factor in its antihypertensive effect (Vlachakis *et al.*, 1980). However, although the β -adrenoceptor antagonism of medroxalol and labetalol is comparable it has been noted *in vitro* that medroxalol has less than one third of the potency of labetalol as an α -adrenoceptor antagonist (Dage *et al.*, 1981). It is suggested, however, that this difference in α -adrenoceptor antagonism is less marked *in vivo*

Figure 1 Structures of a) medroxalol and b) labetalol.

(Dage *et al.*, 1981). This study in normotensive subjects was designed to compare the pharmacodynamic profiles of medroxalol and labetalol, including an assessment of the relative α - and β -adrenoceptor antagonist activities, and to permit an analysis of the drug concentration-effect relationships. The detailed pharmacokinetic analysis is described separately (Elliott *et al.*, 1984).

Methods

In a double-blind, crossover study, nine normotensive male volunteers, age range 21–38 years, gave informed consent to participate in a comparative evaluation of medroxalol, labetalol and placebo. The study was approved by the local Research and Ethical Committee and conducted in the Clinical Pharmacology Research Unit to which subjects reported on each study morning, at weekly intervals.

All nine subjects received three treatments consisting of 400 mg medroxalol, 400 mg labetalol or matching placebo capsules by mouth, with the treatment order randomised according to a Latin square design. Additionally, four of the subjects were randomly selected to receive medroxalol and labetalol in random order by a 2 min intravenous injection in a dose of 1 mg/kg (approximate volume 15 ml) on 2 days at least 1 week apart.

The following measurements were made during each study day at intervals for up to 24 h:

- (i) Blood pressure, supine and for up to 5 min

standing by Roche Arteriosonde 1225 semi-automatic sphygmomanometer.

- (ii) Heart rate, supine and erect, from a standard ECG recording of precordial leads.
- (iii) Plasma drug concentrations (detailed separately).
- (iv) Plasma noradrenaline was measured radioenzymatically by the method of Da Prada & Zurcher (1976). Venous blood samples were taken from an indwelling intravenous cannula at 0 and 90 min.
- (v) β -adrenoceptor responsiveness was assessed by blood pressure and heart rate responses to an incremental intravenous infusion of isoprenaline (maximum possible dose range 0.02–1.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$) at two time periods—between 2–4 and 6–8 h after dosing. The increase in heart rate and the decrease in diastolic blood pressure were analysed by derived log dose-response curves and used as indices of β -adrenoceptor responsiveness (β_1 and β_2 respectively).
- (vi) α -adrenoceptor responsiveness was also assessed between 2–4 and 6–8 h, by the increase in blood pressure induced by an incremental intravenous infusion of noradrenaline (maximum possible dose range 0.02–1.0 $\mu\text{g kg}^{-1} \text{min}^{-1}$). In a sub group of three subjects an assessment of post-junctional α_1 -adrenoceptor responsiveness was made on additional study days using an incremental intravenous infusion of phenylephrine (dose range 0.5–10.0 $\mu\text{g kg}^{-1} \text{min}^{-1}$).

The infusion studies were commenced at

approximately 2.25, 3.25, 6.25, and 7.25 h, i.e. following a period of 10 min recumbency after the hourly standing blood pressure recording. The order of the infusions was randomly assigned for each individual on day 1 but thereafter was kept constant throughout the whole study for that individual. Infusions were administered via a Braun pump (Perfusor ED II) at not less than four incremental dose levels until a target response was achieved. Each dose level was maintained for 5 min, with minute-by-minute recordings of blood pressure and heart rate, and upper limits were set for the permissible increases in blood pressure and heart rate—45 and 30 mm Hg for systolic and diastolic pressures respectively and 50 beats/min for heart rate. With 4–6 dose levels, each infusion lasted for about 30 min in total.

Results are expressed throughout as mean $\pm$ s.d. Statistical evaluation was by analysis of variance for the repeated measurements throughout the study days and by Student's paired *t*-tests as appropriate. The responses to the agonist infusions were analysed by fitting all data points to a quadratic function as described by Sumner *et al.* (1982).

Results

Supine blood pressure and heart rate (Figures 2 and 3)

After 400 mg oral medroxalol both systolic and diastolic blood pressure were significantly re-

duced ($P < 0.05$) between 2 and 6 h. At 4 h the average blood pressure was 109/71 $\pm$ 6/7 mm Hg after medroxalol, compared to 119/77 $\pm$ 6/8 after placebo. The corresponding pressure after labetalol was 110/68 $\pm$ 9/7 mm Hg. There was no significant difference between medroxalol and labetalol. Following 1 mg/kg intravenous medroxalol (mean dose 70 mg) the onset of the hypotensive effect was observed within 30 min but the overall fall in blood pressure was similar to that following oral administration. At 4 h after intravenous medroxalol the average blood pressure was 108/70 $\pm$ 6/5, compared to 116/74 $\pm$ 7/10 after placebo and compared to 115/66 $\pm$ 4/5 mm Hg after labetalol. Again there was no significant difference between medroxalol and labetalol. There were no significant differences between medroxalol and labetalol in the overall supine blood pressure responses following the oral or intravenous administration of either drug. There were no significant changes in supine heart rate in association with the reductions in blood pressure by either drug, by either route of administration, compared to placebo.

Standing blood pressure and heart rate (Figures 4 and 5)

On standing, with both medroxalol and labetalol, there were significant falls in both systolic and diastolic blood pressure, maximal at 2 h after oral administration when the average blood pressure was 89/64 $\pm$ 14/11 after medroxalol, compared to 108/76 $\pm$ 7/9 after placebo ($P < 0.05$), and compared to 88/63 $\pm$ 17/12 mm Hg after labetalol.

Figure 2 Average supine blood pressures and heart rates following the oral administration of 400 mg medroxalol (■), 400 mg labetalol (□) and placebo (Δ).

Figure 3 Average supine blood pressure and heart rates following the intravenous administration of placebo (Δ), medroxoalol ($\blacksquare$) and labetalol ($\square$) (1 mg/kg).

With intravenous medroxoalol the hypotensive effect occurred earlier and was maximal between 30 min and 3 h. At 2 h following intravenous medroxoalol the average blood pressure was $99/68 \pm 7/5$ mm Hg, compared to $108/73 \pm 6/11$ mm Hg following placebo ($P < 0.05$) and compared to $102/72 \pm 6/8$ mm Hg following labetalol. Again there was no overall difference between

medroxoalol and labetalol although the early fall with i.v. medroxoalol appeared to be greater.

With oral medroxoalol there was no significant alteration in heart rate but following intravenous medroxoalol there was a modest, transient increase in heart rate in the first hour. This was most apparent within the first 30 min with a mean of 91 ± 5 beats/min following medroxoalol com-

Figure 4 Average standing (5 min) blood pressure and heart rates following the oral administration of 400 mg medroxoalol ($\blacksquare$), 400 mg labetalol ($\square$) and placebo (Δ) 400 mg.

Figure 5 Average standing (5 min) blood pressure following the intravenous administration of placebo (Δ), medroxalol ($\blacksquare$) and labetalol ($\square$) (1 mg/kg).

pared to 80 ± 12 beats/min on placebo. Throughout the full period of study, however, there were no significant differences between medroxalol, labetalol and placebo.

There were no significant side effects reported or observed on any of the study days.

Plasma noradrenaline

There were no significant alterations in plasma noradrenaline at 90 min after medroxalol, or labetalol, corresponding to the time of maximal reduction in blood pressure. The mean plasma noradrenaline concentrations following medroxalol were 4.4 ± 2.5 (supine) and 9.2 ± 7.5 (erect) compared to 3.4 ± 2.2 and 13.2 ± 8 nmol/l after labetalol, and 3.9 ± 2.2 and 7.9 ± 3.0 nmol/l after placebo.

Responses to isoprenaline

The chronotropic responses to isoprenaline are summarised in Figure 5 with significant rightward shifts of the mean dose-response curves after each of the drugs, both in the morning and the afternoon ($P < 0.01$). The mean dose of isoprenaline to produce an increase in heart rate of 20 beats/min (CD_{20}) was 13-fold greater after medroxalol and 7-fold greater after labetalol than placebo, for the early period, and by respectively 8-fold and 5-fold for the late period. The mean values for CD_{20} and the dose ratios are shown in Table 1. Similar results were obtained for the diastolic depressor responses, compared

in terms of the dose of isoprenaline required to lower diastolic pressure by 10 mm Hg. For the 'early' period there was a 15-fold shift with medroxalol and a 5-fold shift for labetalol. The corresponding shifts for the 'late' period were respectively 11-fold and 6-fold. There was a significant difference between medroxalol and labetalol in the extent of β -adrenoceptor blockade ($P < 0.01$) as assessed by both the increase in heart rate (β_1) and the reduction in diastolic pressure (β_2).

Responses to noradrenaline and phenylephrine

For noradrenaline the mean dose to produce an increase in mean arterial pressure of 20 mm Hg (PD_{20}) following either medroxalol or labetalol was not significantly different from placebo (Table 2). However for phenylephrine, in the sub-group of three subjects, a significant degree of α_1 -adrenoceptor antagonism was found with labetalol, particularly in the morning, when there was a greater than two-fold shift in the log dose-response curve (Figure 7). After medroxalol there were slight increases in the PD_{20} but the changes were not significant in the small number of subjects studied (Table 2).

Discussion

In these single dose studies both medroxalol and labetalol caused significant reductions in blood

Table 1 Comparison of the isoprenaline-induced mean chronotropic and diastolic depressor doses and dose ratios

<i>Chronotropic dose-responses</i>					
CD ₂₀ = the dose of isoprenaline ($\mu\text{g kg}^{-1} \text{min}^{-1}$) required to increase the heart rate by 20 beats/min					
	<i>Medroxalol</i>		<i>Labetalol</i>		<i>Placebo</i>
	CD ₂₀	Dose ratio	CD ₂₀	Dose ratio	CD ₂₀
<i>Early</i> (2–4 h)	0.39 $\pm$ 0.11	13 $\pm$ 6.4	0.19 $\pm$ 0.07	7 $\pm$ 4	0.033 $\pm$ 0.012
<i>Late</i> (6–8 h)	0.21 $\pm$ 0.07	8 $\pm$ 2	0.13 $\pm$ 0.04	5 $\pm$ 1.2	0.027 $\pm$ 0.010
<i>Diastolic depressor dose-responses</i>					
DD ₁₀ = the dose of isoprenaline ($\mu\text{g kg}^{-1} \text{min}^{-1}$) required to reduce diastolic blood pressure by 10 mm Hg					
	DD ₁₀	Dose ratio	DD ₁₀	Dose ratio	DD ₁₀
<i>Early</i> (2–4 h)	0.31 $\pm$ 0.3	15 $\pm$ 12	0.05 $\pm$ 0.02	5 $\pm$ 4	0.02 $\pm$ 0.007
<i>Late</i> (6–8 h)	0.19 $\pm$ 0.1	11 $\pm$ 7	0.09 $\pm$ 0.07	6 $\pm$ 5	0.019 $\pm$ 0.009

pressure, particularly in the standing position. With medroxalol the mean maximal fall in standing blood pressure was 19/12 compared to 7/6 mm Hg in the supine position. Conventional β -adrenoceptor blocker therapy is not typically associated with an orthostatic hypotensive effect (McKenna *et al.*, 1966) and this finding therefore reflects an additional pharmacological property which is presumed to be α -adrenoceptor antagonism. α_1 -adrenoceptor antagonists such as prazosin (Elliott *et al.*, 1981) or doxazosin (Vincent *et al.*, 1983) have such an orthostatic effect in normotensive subjects particularly if combined with a β -adrenoceptor blocker (Elliott *et al.*, 1981). However, while it was possible by isoprenaline infusion to demonstrated substantial β_1 - and β_2 -adrenoceptor antagonism by both labetalol and medroxalol, similar evidence of α -adrenoceptor antagonism was less obvious. Only

with the α_1 -adrenoceptor selective agonist phenylephrine was there any alteration in the pressor responsiveness and this was statistically significant only with labetalol. Other studies with labetalol, particularly after intravenous administration, have shown that the pressor responsiveness to noradrenaline is also shifted (Richards & Prichard, 1978). The lack of a significant shift in this study is most likely to be related to drug dose and concentration insofar as the other studies were undertaken within the first hour or so after intravenous dosing with labetalol. Alternatively, however, it may be related to differences between oral and intravenous dosing with respect to the relative amounts of the labetalol isomers (or their rates of metabolism) which have been shown to have varying α -adrenoceptor antagonist potencies (Sybertz *et al.*, 1981) and direct vasodilator activity (Baum *et al.*, 1981).

Table 2 Comparison of the pressor responsiveness to noradrenaline and phenylephrine

PD ₂₀ = the dose of agonist in $\mu\text{g kg}^{-1} \text{min}^{-1}$ required to raise mean arterial pressure by 20 mm Hg					
<i>Noradrenaline (n = 9)</i>					
	<i>Medroxalol</i>		<i>Labetalol</i>		<i>Placebo</i>
	PD ₂₀	Dose ratio	PD ₂₀	Dose ratio	PD ₂₀
<i>Early</i>	0.29 $\pm$ 0.13	1.6 $\pm$ 1.0	0.27 $\pm$ 0.12	1.0 $\pm$ 0.8	0.25 $\pm$ 0.15
<i>Late</i>	0.17 $\pm$ 0.09	1.1 $\pm$ 1.2	0.25 $\pm$ 0.12	1.4 $\pm$ 0.8	0.24 $\pm$ 0.17
<i>Phenylephrine (n = 3)</i>					
<i>Early</i>	3.1 $\pm$ 1.0	1.6 $\pm$ 0.3	4.3 $\pm$ 1.7*	2.5 $\pm$ 1.3	2.0 $\pm$ 0.8
<i>Late</i>	2.4 $\pm$ 0.3	1.4 $\pm$ 0.5	3.1 $\pm$ 1.0	1.7 $\pm$ 0.6	1.9 $\pm$ 0.7

Figure 6 Mean log dose-response curves for the chronotropic responses to isoprenaline following placebo (○), 400 mg oral medroxalol (●) and 400 mg oral labetalol (◆).

Figure 7 Mean log dose-response curves for the pressor responses to phenylephrine following placebo (○), 400 mg medroxalol (●) and 400 mg labetalol (◆).

Thus, while both drugs are non-selective β -adrenoceptor blockers the evidence from this study indicates that labetalol, relative to medroxalol, has greater α_1 -adrenoceptor antagonist activity. In this study the ratio of β_1 to α_1 antagonism for labetalol at 2–4 h was $2.6 (\pm 1.3)$ to 1 which is closely in agreement with a previously reported ratio of 3 to 1 (Richards *et al.*, 1976). Although a significant degree of α_1 -adrenoceptor antagonism was not obtained for medroxalol in this study the corresponding calculation of β_1 to α_1 antagonism gives a ratio of $7.2 (\pm 2.1)$ to 1. In studies with higher doses of medroxalol (800 and 1200 mg orally) it has been possible to demonstrate significant α_1 antagonism and the β_1 to α_1 ratios in human volunteers have been reported as 24 to 1 and 39 to 1 (Jaillon *et al.*, 1982). These differences may be related to the doses selected. The magnitude of the fall in blood pressure tended to be greater with 400 mg oral medroxalol, despite the lesser α_1 -adrenoceptor blocking effect, compared to 400 mg oral labetalol. This may be related to medroxalol's greater β -adrenoceptor blocking activity, as adduced from the extent of the shifts in the isoprenaline dose-response relationships, which in turn may partly reflect differences in the pharmacokinetics of the two drugs. Medroxalol does not undergo extensive 'first pass' metabolism and it has a significantly longer elimination half-life than labetalol (16 h compared to 5.5 h). Therefore for the same oral dose of 400 mg a relatively larger amount of medroxalol will reach the systemic circulation (Elliott *et al.*, 1984). Alternatively, medroxalol may have other cardiovascular actions contributing to the fall in blood pressure such as partial β_2 -adrenoceptor agonism (Dage *et al.*, 1983) or indirect vasodilator activity.

In conclusion, medroxalol has a blood pressure lowering effect associated with non-selective β -adrenoceptor blockade and modest α_1 -adrenoceptor antagonism. With oral dosing it has comparable antihypertensive activity and a slightly greater β -adrenoceptor blocking effect than labetalol. However, in comparison to labetalol the additional 'vasodilator' property of medroxalol can less conclusively be attributed to α_1 -adrenoceptor antagonism: for comparable degrees of β -adrenoceptor blockade (at 2–4 h) the α -adrenoceptor blocking activity of medroxalol is less than half that of labetalol. On the basis of its half-life of 15.6 h following oral dosing, and the significant β -adrenoceptor blockade at 6–8 h, it is possible that medroxalol may be useful as once daily therapy in the management of hypertension.

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(Received October 11, 1983,
accepted February 3, 1984)