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Combined alpha- and beta-adrenoceptor blockade with labetalol in hypertension

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Summary

The antihypertensive effect of labetalol, a new alpha- and beta-adrenoceptor inhibiting agent, was studied in 20 patients in a double-blind crossover trial. A dose of 300 mg daily reduced blood pressure only moderately in the supine position, though in the sitting and standing positions the effect was more pronounced. A dose of 600 mg daily produced statistically significant and clinically relevant reductions in blood pressure in all positions studied. The effect on heart rate was small and of significance only in reducing the heart rate increment due to a change in posture. Side effects were mild: only one patient complained of postural dizziness with the higher dose. We conclude that labetalol is useful in the treatment of mild and moderately severe hypertension.

Introduction

Beta-adrenoceptor blocking drugs hold an established position in the treatment of hypertension,[1-6] and, though the exact mechanism(s) of blood pressure reduction under long-term treatment with these compounds is unknown, the haemodynamic changes have been well defined.[7-9] Initially cardiac output is reduced and peripheral resistance variably increased only to return gradually to the pretreatment level.[9 10] This initial increase in resistance has been attributed to the unmasked alpha-receptor activity in the resistance vessels. A parallel phenomenon in addition to vagal influences is the bronchoconstriction seen in asthmatics due to unopposed alpha-receptor activity in the bronchial wall.

The new salicylamide compound labetalol (5-[1-hydroxy-2-(1-methyl-3-phenylpropylamino) ethyl] salicylamide) has been shown in animals[11 12] and man[13] to have both alpha- and beta-adrenoceptor blocking properties. Thus theoretically it offers advantages over pure beta-adrenoceptor blocking drugs in the treatment of hypertension. We have studied the antihypertensive effect of labetalol at two different dose levels using placebo control and a double-blind design.

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Patients and methods

Eleven men and nine women aged 25-65 (mean 44) years were studied. All had diastolic blood pressures of over 100 mm Hg on repeated measuring. Intravenous pyelograms and serum potassium and urinary catecholamine determinations showed the hypertension to be essential in 17 patients. Chronic pyelonephritis was found in two patients, and one had congenital aplasia of the right kidney. Based on electrocardiograms and chest *x*-ray pictures the hypertension was graded as mild to moderate (WHO grades I and II). Nine patients were untreated; in 10 patients treatment was stopped one to two months before entry to the trial, and one continued with a diuretic throughout.

The study began with an assessment period of one month during which the blood pressure was measured weekly to ascertain the presence of chronic hypertension in the untreated patients and to determine the blood pressure without treatment in the patients previously treated. The patients were then allocated at random to treatment with either placebo or labetalol 100 mg thrice daily for four weeks followed by a crossover to the alternative compound for a further four weeks. The dose was then increased to 200 mg thrice daily and the procedure repeated. Thus each patient received eight weeks of treatment with each compound. Neither the doctors nor the patients were aware of the periods of active treatment.

Blood pressure was measured fortnightly in a standardised fashion using mercury sphygmomanometers with 13-cm cuffs. The point at which the Korotkoff sounds became muffled (phase IV) was taken as the diastolic pressure. Blood pressure and heart rate were measured after resting supine for five minutes, sitting for three minutes, and standing for two minutes. Haemoglobin and white cell count were determined at the end of each four-week period. Questions about side effects were asked at every visit.

Differences in values between the placebo and labetalol treatment periods were analysed by paired comparison and Student's *t* test. P values less than 0·05 were regarded as significant.

Results

With 300 mg labetalol daily only small changes were seen in blood pressure while supine (table) and the heart rate was not modified at all. Doubling the dose produced falls of 10 mm Hg and 5-9 mm Hg in the systolic and diastolic pressures respectively. Heart rate was also significantly reduced.

In the sitting position the blood pressure was already influenced by the starting dose of labetalol (table) with a further reduction after doubling the dose. The reduction in systolic pressure was about 20 mm Hg and that of the diastolic pressure 10-15 mm Hg. The heart rate was also significantly reduced.

In the standing position the blood pressure was greatly reduced by both dose levels of labetalol (table), amounting to over 20 mm Hg

Effects of placebo and labetalol on supine, sitting, and standing blood pressure (mm Hg) and heart rate (beats/min). Values are means ± SE of mean

	Systolic blood pressure		Diastolic blood pressure		Heart rate	
	Placebo	Labetalol	Placebo	Labetalol	Placebo	Labetalol
Supine						
Values in assessment period:	165 ± 3·4		107 ± 1·6		72 ± 2	
At 2 weeks	162 ± 3·5	154 ± 3·4*	106 ± 1·9	100 ± 1·9*	71 ± 3	69 ± 3
At 4 weeks	157 ± 4·4	152 ± 4·4	102 ± 2·2	99 ± 2·4	69 ± 3	66 ± 3
At 6 weeks	159 ± 3·8	149 ± 3·9*	106 ± 2·4	97 ± 2·7*	72 ± 3	62 ± 2*
At 8 weeks	159 ± 4·0	148 ± 4·1*	104 ± 2·4	97 ± 2·4*	69 ± 3	64 ± 2*
Sitting						
Values in assessment period:	161 ± 2·6		113 ± 1·5		76 ± 2	
At 2 weeks	157 ± 3·9	150 ± 3·7*	114 ± 2·2	105 ± 1·9*	74 ± 3	72 ± 3
At 4 weeks	159 ± 4·1	151 ± 3·4*	112 ± 1·8	107 ± 1·7*	75 ± 3	69 ± 3*
At 6 weeks	159 ± 4·0	142 ± 3·9*	114 ± 2·4	104 ± 2·8*	76 ± 3	66 ± 2*
At 8 weeks	158 ± 3·6	138 ± 3·4*	114 ± 2·5	98 ± 2·3*	72 ± 4	66 ± 2*
Standing						
Values in assessment period:	158 ± 2·7		116 ± 1·4		81 ± 2	
At 2 weeks	155 ± 4·6	144 ± 3·7*	115 ± 1·8	107 ± 2·2*	78 ± 3	74 ± 3*
At 4 weeks	156 ± 3·8	145 ± 3·6*	115 ± 1·8	109 ± 2·3*	81 ± 3	73 ± 3*
At 6 weeks	156 ± 4·7	135 ± 4·6*	113 ± 3·4	101 ± 2·9*	81 ± 4	70 ± 2*
At 8 weeks	152 ± 4·1	130 ± 4·1*	116 ± 2·8	99 ± 2·4*	78 ± 4	70 ± 3*

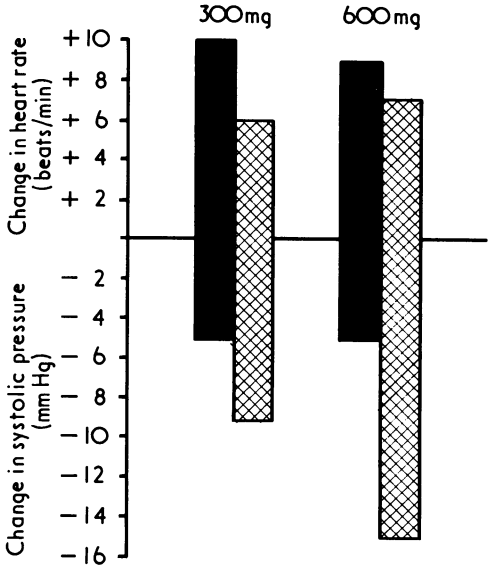
*Significantly different ($P < 0·05$) from placebo.
Daily dose of labetalol: 300 mg at 2 and 4 weeks, 600 mg at 6 and 8 weeks.

systolic and about 15 mm Hg diastolic with 600 mg daily. The heart rate was also significantly reduced.

Normotension (supine diastolic pressure <100 mm Hg) was restored in 11 patients (55%) with the 300-mg daily dosage, and in 15 patients (75%) with the 600-mg daily dosage. Placebo restored normotension in eight patients (40%). The systolic blood pressure achieved by two weeks of treatment with 300 mg labetalol daily was maintained without any further decline during the next two weeks (table). At the higher dose level, however, a trend towards further reduction was evident for both systolic and diastolic pressures (table). This did not, however, reach statistical significance.

Haemoglobin and white cell counts remained normal throughout.

Side effects—Side effects were surprisingly few. Thirteen patients were entirely asymptomatic throughout the trial. The commonest side effect was non-rotatory dizziness, in five patients. It occurred in four instances while on active treatment and in two while on placebo. Only one patient complained of dizziness in an upright posture while on 600 mg labetalol daily. Other minor complaints—dry mouth, hum in the ears, headache, itching, and constipation—occurred with equal frequency in the active treatment and placebo periods. One patient complained of a "funny feeling" in his scalp and another of "goose flesh" while on the active treatment.



Changes in heart rate and systolic blood pressure evoked by change in posture from supine to standing during treatment with placebo (black columns) and labetalol (hatched columns) at two daily dose levels.

Discussion

Labetalol is unique in having both alpha- and beta-adrenoceptor blocking properties. In hypertension this signifies dual targets, the heart and the resistance vessels. The anti-beta action is non-selective, so that the beta^2-receptors in both the vessel walls and bronchi are influenced.[11 12] Depending on the animal and organ systems studied, labetalol is five to 18 times less potent than propranolol as a beta-adrenoceptor blocking agent and two to seven times less potent than phentolamine in blocking alpha-receptors.[11] Small reductions in the supine heart rate in man after both intravenous[14] and oral administrations[13] of labetalol are in keeping with the modest beta-adrenoceptor blocking potency. In this study the reduction in heart rate was small in the supine position with 300 mg daily (table) but reached significant levels in the sitting and standing positions (table). Doubling the dose evoked a greater reduction in heart rate. The magnitude of the beta-blockade is best exemplified by relating the heart rate response to the change in pressure from supine to standing (fig). Labetalol enhanced the postural blood pressure drop and simultaneously attenuated the heart rate reaction. This type of blood pressure response differs from pure beta-blockade, which does not cause additional postural blood pressure reductions, and shows the alpha-blocking properties of labetalol.

At the lower dose level no decline in systolic pressure was observed with time, and although such a decline occurred at the higher dose level, it did not reach statistical significance. This may have been due to either the short observation periods or the modest beta-blocking property of the drug, since we have observed a steady decline in pressure over three months with treatment with beta-blocking compounds.[6 15]

Side effects were mild and in no way impeded daily activities. Only one patient on the higher dose complained of postural dizziness. Conceivably, however, an increase of the dose to over 600 mg daily would increase the incidence of postural side effects due to enhanced blood pressure drops in a standing position. Collier *et al*[14] reported tingling in the scalp in five out of seven patients given labetalol intravenously. The sensations in the skin reported by two of our patients may indicate pilo-erection, which is a sign of alpha-adrenoceptor stimulation. No pharmacological data exist, however, to support this assumption.

The final place of labetalol for hypertension must await the results of forthcoming comparative studies. Our data indicate that it is well suited for treating mild and moderate hypertension, in which we restored the blood pressure to normal in 75% of patients with a dose of 200 mg thrice daily. Evident advantages over pure beta-blocking substances include safer use in patients with initial bradycardia; in patients with atrioventricular conduction disturbances; and in asthmatics, who do not exhibit bronchoconstriction when on labetalol.[16]

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Four new anti-inflammatory drugs: responses and variations

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Summary

Ninety patients with rheumatoid arthritis completed a double-blind crossover trial comparing fenoprofen, ibuprofen, ketoprofen, and naproxen. Fenoprofen and naproxen were slightly more effective than the other two drugs but there were striking individual variations in response. Groups of patients could be identified who preferred each of the four drugs. The commonest side effects were those related to the upper gastrointestinal tract; these showed individual variation and seldom occurred with more than one or two of the drugs. Side effects were least common with ibuprofen and naproxen. Since naproxen combined greater effectiveness with a lower incidence of side effects it must be regarded as the first choice among these drugs. It may be necessary to try several drugs before finding the right one for a particular patient.

Introduction

If aspirin is no longer the first line of treatment of rheumatoid arthritis[1-3] its place must surely have been taken by one of the propionic acid derivatives. But which one? The four currently available compounds are claimed to have analgesic potency comparable to that of aspirin but with a much lower incidence of side effects. We have compared their effectiveness and tolerability.

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Methods

A total of 105 outpatients with definite or classic rheumatoid arthritis as defined by the ARA criteria were admitted to the study. They were treated for two weeks with each of four drugs—fenoprofen 2·4 g daily, ibuprofen 1·2 g daily, ketoprofen 150 mg daily, and naproxen 500 mg daily. The order of treatment was randomised and balanced in a latin-square design. Patients who withdrew from the study for reasons unrelated to treatment were replaced to ensure that at least three complete balanced blocks of 24 patients were included. The doses used were recommended by the manufacturers at the time of the study. To avoid patients recognising tablets that they might already have received each drug was supplied in a formulation different from the marketed form; fenoprofen was supplied in 300 mg white capsules, ibuprofen in 200 mg white tablets, ketoprofen in 25 mg white capsules, and naproxen in 125 mg yellow capsules. The bioavailability of the preparations was confirmed. Simple analgesics were allowed during the study, and 16 patients taking small doses of corticosteroids continued with these. No other antirheumatic treatment was allowed.

At the end of each fortnight measurements were made of pain using a visual analogue scale, the duration of morning stiffness, and proximal interphalangeal joint circumference. A preference was sought for each pair of treatments, and after the third and fourth treatment periods a rank order of preference was noted. The patient were asked at the end of each treatment period: "Has the treatment upset you in any way?" Any side effects elicited were recorded as slight, moderate, or severe. Returned tablets were counted. Measurements in a particular patient were carried out by the same observer at the same time of day. The observers were not aware of which treatment a patient was receiving.

Non-parametric statistical tests were applied to all measurements except joint size because the distribution of results was not normal. Friedman's two-way analysis of variance by ranks was used for measurements of pain, duration of morning stiffness, and preference. Wilcoxon's test was used for side-effect scores. Analysis of variance was applied to measurements of joint size.

Results

Ninety patients completed the trial. The mean pain scores (table I) were significantly lower in patients receiving fenoprofen and naproxen than in those receiving ibuprofen and ketoprofen ($\chi^2 = 12{\cdot}04$; $P < 0{\cdot}01$). Fenoprofen and naproxen were also significantly more effective in terms of both the duration of morning stiffness ($\chi^2 = 17{\cdot}7$; $P < 0{\cdot}001$) and preference ($\chi^2 = 10{\cdot}54$; $P < 0{\cdot}02$). There was no significant difference between the effects of the four drugs on