The anti-hypertensive efficacy of combined $\alpha$- and $\beta$-adrenoreceptor blockade with phentolamine–oxprenolol or with labetalol (AH 5158)

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Summary
1. The interaction of phentolamine with the $\beta$-receptor blocker oxprenolol was studied in a controlled trial.
2. The combination was generally well tolerated.
3. Oxprenolol alone produced modest but significant reductions in supine, standing and post-exercise blood pressures. Small reductions were seen only with sustained phentolamine administration.
4. The combined effect of the two drugs appeared to be additive only at the lower doses of oxprenolol.
5. Labetalol produced significantly greater reductions in supine and standing blood pressure than combined oxprenolol–phentolamine. At a daily dose of 400 mg, postural hypotension was not seen, though transient symptoms were frequent.

Key words: hypertension, labetalol, oxprenolol, phentolamine.

Introduction
Blockade of both $\alpha$- and $\beta$-adrenoreceptors by phenoxybenzamine and propranolol has been demonstrated to produce postural hypotension in man (Beilin & Juel-Jensen, 1972). However, combined therapy in which $\alpha$-adrenoreceptor blockade was produced by phentolamine has been reported to produce blood pressure reduction equally potent in the supine and standing positions in a group of six subjects (Majid, Meeran, Benaim, Sharma & Taylor, 1974). The suggestion that the combination of phentolamine with a $\beta$-adrenoreceptor blocker might provide an effective anti-hypertensive regimen has been examined. In addition, the anti-hypertensive efficacy of this combination has been compared with that of labetalol, a drug known to possess both intrinsic $\alpha$- and $\beta$-receptor-blocking properties.

Methods

Experiment 1
A within-patient, double-blind comparison was made of the anti-hypertensive property of phentolamine in a dose of 60 mg/day and of oxprenolol in a dose increasing from 160 to 480 mg/day, singly and in combination.

The subjects consisted of eighteen patients of either sex between 30 and 65 years, with supine diastolic pressures of 105–125 mmHg. Patients with evidence of secondary hypertension, a history of accelerated hypertension or of vascular complications, bronchial asthma, current therapy with tricyclic antidepressants or other psychotropic drugs, and pregnancy, were excluded.

The trial was divided into five phases, of which the first and fifth were placebo phases each of 4 weeks' duration. The three intervening phases were each of 12 weeks' duration. The third phase combined treatment with oxprenolol and phentolamine, the dose of oxprenolol being 80 mg (one tablet) twice daily for the first 4 weeks, 160 mg twice daily for the next 4 weeks and 240 mg twice daily for the final 4 weeks of the phase, whereas phentolamine was administered in a fixed dose of 20 mg (one tablet) three times a day. The second phase used only one active drug and the fourth phase the other, their dosage being the same as in the third phase. Appropriate dummy tablets for either active drug were used in these two phases, and the order in which patients received oxprenolol and phentolamine in the second and fourth phases was selected randomly.

Patients attended every 2 weeks. Blood pressures
were recorded supine after rest for 5 min, after standing for 1 min, and standing after 90 s of exercise, with a Hawksley random-zero sphygmomanometer. Exercise was graded for age, sex and weight by using Master’s (1935) tables. The pulse rate, body weight, peak expiratory flow rate and presence of any side effect and its severity grading were recorded at each visit. At the end of each phase the patient completed a symptom questionnaire (Bulpitt & Dollery, 1973). Determinations of haemoglobin, leucocyte count, plasma urea, electrolytes, creatinine clearance and blood lipids (after a 16 h fast), and multichannel analysis, ECG and chest X-ray, were carried out near the middle of each phase.

Results were analysed from thirteen patients who completed the study. Of this group seven were male: nine were white and four black. Ages ranged from 40 to 65 years, and body weights from 54 to 96 kg (120–212 lb). Five patients received phentolamine in the second phase, whereas eight received oxprenolol.

**Experiment 2**

Eleven patients who completed all phases of experiment 1 entered a further 12 weeks’ phase of treatment with labetalol. Dosage was begun at 200 mg twice daily, and progressively increased towards 1200 mg/day if hypertension was not fully controlled at the initial dose. Blood pressure and other determinations were continued as in experiment 1.

**Results**

**Experiment 1**

Phentolamine produced no important change in pulse rate in any position, and exercise-induced tachycardia was only slightly greater during phentolamine administration. By contrast, oxprenolol produced significant bradycardia and reduced exercise tachycardia ($P<0.01$), and phentolamine did not antagonize these effects.

Phentolamine caused a significant though slight reduction in systolic blood pressure during the second and third months of treatment ($P<0.05$). Oxprenolol produced more obvious and significant blood pressure reduction ($P<0.01$). The addition of phentolamine appeared beneficial only at low doses of oxprenolol, though post-exercise blood pressure reduction was enhanced at all doses of oxprenolol (Table 1). There was considerable between-subject variation in hypotensive response, but mean reductions with phentolamine and the maximal dose of oxprenolol were 24/15, 25/13 and 35/14 mmHg in supine, standing and post-exercise blood pressure readings respectively. No pronounced additive effect was seen, and there was no evidence that the hypotensive effect of any treatment regimen was predominantly postural.

Of eighteen patients admitted to the trial, five were withdrawn. One subject became depressed while taking oxprenolol or placebo. One patient dropped out for unknown reasons and another became pregnant. Only two patients suffered clearly drug-related symptoms, namely diarrhoea with phentolamine, and dyspnoea while taking oxprenolol. No other patient reported troublesome symptoms. Headaches and dry mouth were reported less frequently in the questionnaire completed while taking combined therapy than when on placebo.

**Experiment 2**

By comparison with the preceding placebo phase, daily doses of both 400 and 600 mg of labetalol produced insignificant reductions in pulse rate. Reductions in supine and standing systolic and diastolic blood pressure were significantly greater

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<th>Table 1. Systolic blood pressures with various trial procedures</th>
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than those recorded for the same patients while taking phentolamine in conjunction with the highest dose of oxprenolol. However, post-exercise blood pressure readings on labetalol were not significantly lower than those recorded on the drug combination. It was necessary to increase the dose of labetalol beyond 600 mg/day in five patients.

Six patients complained of new symptoms within 4 weeks of beginning treatment with labetalol. The most frequent symptoms were headache, nausea, lethargy and abdominal pain, but these symptoms usually dissipated with continued treatment.

No change in haematological or plasma biochemical determinations was observed during any treatment phase, nor was creatinine clearance or electrocardiographic evidence of ventricular hypertrophy consistently affected. Similarly, there was no evidence that peak expiratory flow rate was affected by any drug or combination.

Discussion

Drugs which reduce peripheral vascular resistance tend to produce reflex adrenergic over-activity, exemplified by tachycardia. Increased cardiac output may partially compensate for the hypotensive response, and palpitations, headaches or symptoms of myocardial ischaemia may occur. A further response is increased plasma renin activity. These reflex responses may be prevented, and the hypotensive effect potentiated, by the concurrent administration of a β-receptor-blocking drug (Gottlieb, Katz & Chidsey, 1972).

α-Receptor-blocking agents may also cause reflex adrenergic hyperactivity, and β-receptor-blocking drugs would therefore be expected to potentiate the hypotension. However, as sympathetic activity is necessarily greater in the standing position or during exercise, α-receptor-blocking agents would be expected to lower blood pressure maximally in those circumstances. The well-established α-receptor-blocking agent, phenoxybenzamine, has been shown to behave exactly in the above manner in man (Beilin & Juel-Jensen, 1972), producing moderate tachycardia and orthostatic hypotension, the latter being potentiated by propranolol.

Although the α-receptor-blocking properties of phentolamine are well established (Hecht, Crandall & Samuels, 1950; Heinzl, Mathes, Mechelke & Nusser, 1952), much of its effect upon the peripheral vascular resistance is best explained by a direct action on arteriolar smooth muscle (Taylor, Sutherland, McKenzie, Staunton & Donald, 1965).

It appears to be a much less potent vasodilator than diazoxide or hydralazine, which can substantially lower blood pressure when administered alone. However, blood pressure could be substantially reduced in six severely hypertensive patients when this dose of phentolamine was added to a regimen of up to 480 mg of oxprenolol daily for 6 months (Majid et al., 1974). Unfortunately, our results do not suggest that this combination can be successfully applied to less strictly selected hypertensive patients.

Labetalol has been shown to have both intrinsic α- and β-adrenoreceptor-blocking activity in man (Boakes, Knight & Prichard, 1971). At the lowest dose administered, it was more potent as an antihypertensive agent than 480 mg of oxprenolol/day, and it is probable that α-receptor-blockade contributes to its greater efficacy. At low doses postural hypotension was not experienced. It is possible that other symptoms could be avoided by instituting therapy at a lower daily dosage than 400 mg.

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References


