A CONTROLLED TRIAL OF PRACTOLOL IN MILD HYPERTENSION

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- 1 Fifteen patients with diastolic blood pressures between 90 and 120 mmHg were admitted to a trial comparing placebo with practolol at doses up to 500 mg 12 hourly.
- 2 The trial was a double blind cross over study. Treatments were allocated at random and each treatment block lasted 12 weeks.
- 3 Ten patients completed the trial, and none of those who withdrew experienced serious unwanted effects.
- 4 Practolol caused significant falls in standing systolic and diastolic pressures and the supine diastolic pressure.

Introduction

A trial of the β adrenergic receptor blocking agent practolol was conducted to discover whether it is an effective hypotensive agent in man. Previous trials of practolol in hypertension are open to criticism because they were inadequately controlled (Esler & Nestel, 1973), or because the treatment periods used may have been too short for the hypotensive effect to develop fully (Leishman, Thirkettle, Allen & Dixon, 1970; Prichard, Boakes & Day, 1971).

Methods

Patients entering the trial had mild or moderate untreated essential hypertension with a systolic blood pressure at or over 150 mmHg and a diastolic pressure at or over 90 mmHg at the third outpatient visit. Patients with a diastolic blood pressure exceeding 120 mmHg or with severe hypertensive retinopathy with haemorrhages or papilloedema were excluded. Also excluded were patients who had had a stroke or a myocardial infarction within the preceding three months, or were in renal failure.

Patients were fully informed about the nature and purposes of the trial and were outpatients. Details of the trial design were approved by the Department Ethics Committee. Measurements of plasma urea, electrolytes, creatinine, glutamic oxalo-acetic transaminase and alkaline phosphatase concentrations, urinary 24 h creatinine clearance, protein and VMA excretion, and ECG and chest X-ray were performed at the beginning of the trial

and after each treatment block. An IVP was also performed before entry into the trial.

The trial was a double blind within-patient comparison between placebo and practolol in apparently identical tablets. Each patient was allocated to the first treatment at random for a period of 12 weeks, after which a crossover was made to the other preparation for a further 12 weeks. From the start of each 12 week treatment block doses were increased at each fortnightly clinic visit from 100 mg to 200 mg and 500 mg 12-hourly or until blood pressure control was satisfactory. At each visit symptoms were recorded. The patient lay quietly for 10 min, after which the supine blood pressure was measured with a zero-muddling sphygmomanometer. The patient then stood for 2 min and a second blood pressure was recorded. After a further 2 min supine the sequence was repeated.

The patient's co-operation was tested by a return tablet count and by measurement of urinary practolol (by the method of Fitzgerald & Scales, 1968) at each visit.

The trial controller, who knew the treatment code but who was not a trial physician, was instructed to end the trial if analysis showed any difference between the treatments with $\alpha = 0.05$, or no difference with $\beta = 0.1$. With β set at 0.1 there is a one in ten chance of accepting the incorrect conclusion that the drug has no effect. Values of β assume particular importance in trials of this nature where accepting a false null hypothesis has a pharmacological rather than a clinical significance. A within-patient comparison

of blood pressures measured at the final two visits of practolol and placebo periods was made using the Wilcoxon test. Values of β relating to the observed differences were calculated for the paired data using standard methods (Dixon & Massey, 1957) and assuming a power-efficiency ratio of 95% compared with the t -test (Siegel, 1956). Two-tailed tests were used throughout. Other design features which we take to be important include the use of a trial controller, reference to both α and β probabilities and a placebo-testing session when 'blind' observers failed to detect differences between the trial tablet preparations.

Results

Fifteen patients entered the trial. Five were withdrawn; of these three defaulted from tablet taking (two in the practolol group), one had recurrent migraine before and during treatment with practolol and one was admitted to hospital for revision of a colostomy. Six men and four women completed the trial; five took practolol first and five placebo. Clinical details are given in Table 1.

When compared with placebo, treatment with practolol was associated with significant but modest falls in diastolic blood pressure in the lying position (mean fall 7.2 mmHg) and in the standing position (mean fall 9.3 mmHg). Standing systolic blood pressure also fell (mean 14.0 mmHg) but the fall in systolic blood pressure measured supine (7.6 mmHg) was not statistically significant (Table 2 and Fig. 1). In three patients the supine diastolic pressure was slightly higher when taking practolol than when taking placebo and in two of these three patients the standing diastolic blood pressure was higher on practolol.

Three patients complained of constipation and one of depression during practolol treatment. One

Fig. 1 Mean blood pressures of the last two visits during placebo (●) and practolol (○) treatment blocks. (a) Standing; (b) supine.

patient on placebo developed depression and giddiness and another had an epistaxis; both had completed the practolol treatment period without symptoms.

No changes occurred during the trial in haemoglobin or total white cell count, renal function, SGOT, alkaline phosphatase or chest

Table 1 Description of patients on entry into the trial

Patient No.	Age (years)	Sex	Systolic supine	Blood pressure (mmHg)		
				Diastolic supine	Systolic standing	Diastolic standing
1	57	M	191	117	217	118
3	52	M	174	110	174	112
5	59	F	175	106	176	113
8	59	M	175	103	169	107
10	36	M	169	96	156	100
11	33	F	164	112	148	114
12	55	M	186	107	168	106
13	57	F	194	97	174	100
14	60	F	188	109	190	110
16	52	M	162	101	173	109

Table 2 Mean blood pressures during the final two weeks of the placebo (PL) and practolol (PR) treatment blocks

Patient No.	Blood pressure (mmHg)															
	Systolic supine				Diastolic supine				Systolic standing				Diastolic standing			
	PL	PR	Diff.	PL	PR	Diff.	PL	PR	Diff.	PL	PR	Diff.	PL	PR	Diff.	
1	211	192	19	124	100	24	189	178	11	113	96	17				
3	154	150	4	95	93	2	145	128	17	101	93	8				
5	176	154	22	101	87	14	163	155	8	102	93	9				
8	172	182	-10	101	105	-4	151	141	10	98	104	-6				
10	153	143	10	87	88	-1	154	136	18	99	87	12				
11	140	135	5	99	87	12	135	125	10	99	90	9				
12	174	179	-5	93	96	-3	152	158	-6	97	103	-6				
13	188	188	0	94	87	7	182	165	17	101	87	14				
14	166	148	18	96	89	7	150	131	19	98	85	13				
16	164	151	13	102	88	14	158	125	33	108	86	23				
Mean	169.8	162.2	7.6	99.2	92.0	7.2	157.9	144.2	14.0	101.7	92.4	9.3				
α			>0.5			0.05			0.01			0.01				
β			>0.9			0.5			0.1			0.3				

X-ray. Two patients developed minimal ischaemic changes in the ECG whilst taking practolol.

Urine practolol measurement confirmed the presence of practolol in the urine of all ten patients whose results were analysed.

Discussion

Evidence of the damaging effects of slight elevation of blood pressure accumulates (Dawber & Kannel, 1961; Kannel, Wolf, Verter & McNamara, 1970; Society of Actuaries, 1959) and some evidence of the benefits of treating it has been presented (Veterans Administration Studies 1970; 1972). It therefore becomes necessary to find drugs suitable for long-term treatment of the many asymptomatic patients with slight hypertension. The ideal drug would be safe, simple to take, effective and lack unwanted side effects.

Practolol has potential advantages over propranolol as a hypotensive agent. It is relatively cardioselective (Dunlop & Shanks, 1968), so reducing the risk of bronchospasm compared with propranolol (Macdonald & McNeill, 1968). It need be taken only twice daily (Barrett, 1971). Two previous trials of practolol have demonstrated a modest hypotensive action. One of these involved patients with very mild hypertension, and short treatment blocks of four weeks only were used (Prichard *et al.*, 1971). The other was not blind and the relatively marked falls in blood pressure recorded may have been related to observer bias (Esler & Nestel, 1973). Although our trial

attempted to avoid these problems, the initial severity of the hypertension and the falls in blood pressure in those who completed the trial were similar to those in Prichard's series (Prichard *et al.*, 1971). Detecting practolol metabolites in urine enabled us to record the patients' compliance with treatment.

The relatively high proportion of trial entrants who withdrew reflects the difficulties of treating patients for long periods for a disorder which causes no immediate symptoms. Small trials of this kind can only demonstrate the short-term clinical efficacy of practolol. Further work would be needed to discover for how long, and for how many patients, benefit might be sustained. While we have shown that practolol has a hypotensive effect, its therapeutic usefulness for that purpose is not established. If a fall in mean blood pressure of 10 mmHg is taken as the smallest change likely to be of value in the biological sense, only three of ten patients attained this in both lying and standing blood pressures. However, seven of the patients achieved both lying and standing diastolic pressures below 95 mmHg. Since those of our patients with the worst hypertension initially still had substantial hypertension after treatment, practolol at the doses given falls short of the ideal hypotensive agent.

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