of autoantibodies detected. Further clinical and experimental studies are required to determine the precise mechanisms concerned in the pathogenesis of these two disorders.

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Requests for reprints to Dr. P. L. Golding, Division of Medicine, the London Hospital, Whitechapel, London E.1.

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Controlled Trial of Oxprenolol and Practolol in Hypertension

A. W. D. LEISHMAN,* D.M., F.R.C.P. ; J. L. THIRKETTLE,† M.B., M.R.C.P. ; B. R. ALLEN,‡ M.B., CH.B., M.R.C.P. R. A. DIXON,§ B.SC.

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Summary: In controlled trials of the beta-adrenergic blocking drugs oxprenolol and practolol in hypertension both drugs were well tolerated without side effects and caused statistically significant non-postural reduction of blood pressure. In less than half the patients on either drug the reduction of blood pressure was clinically adequate. No attempt was made to compare the two drugs.

Introduction

It is established that beta-adrenergic blocking drugs have blood-pressure-lowering action, but opinions on the value of propranolol, the most widely used drug of this character, in the management of hypertension have varied. Paterson and Dollery (1966), Humphreys and Delvin (1968), and Richardson *et al.* (1967) were unenthusiastic, but Prichard and Gillam (1969) and Zacharias and Cowen (1970) reported favourably. The hypotensive action of propranolol may be due to reduction of sympathetic cardiac drive and cardiac output, there being no alteration in peripheral vascular resistance (Frolich *et al.*, 1968). An advantage of this is that the drug causes neither postural nor exertional hypotension. In certain circumstances, however, propranolol may provoke heart failure and bronchospasm.

Both practolol (4-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide; Eraldin) and oxprenolol (1-(*o*-allyloxyphenoxy)-3-isopropylamino-2-propanol hydrochloride; Trasicor) are beta-adrenergic blocking drugs which are relatively cardioselective, showing much less activity than propranolol in blocking other beta-receptors. Practolol does not show the quinidine-like effect of propranolol, but its other cardiac effects are similar, slowing the heart rate and reducing cardiac output, most pronounced on exercise. In its action on the heart, however, practolol appears to have about 40% of the potency of propranolol (Barrett *et al.*, 1968). Oxprenolol appears to differ in one important respect from propranolol; for Wilson *et al.* (1968) showed that prolonged oral administration, though having varying effect on cardiac output, causes a noticeable increase in stroke volume, a property which might give it an advantage over propranolol.

This paper describes a small controlled trial of each of these drugs in the treatment of hypertensive patients.

Methods

Forty-eight patients were considered suitable for the trial, and after full explanation they agreed to take part; 24 were given oxprenolol and 24 received practolol. Allocation to either drug was by random selection. All had benign essential hypertension previously untreated. Patients with diastolic pressure exceeding 124 mm.Hg, blood urea higher than 50 mg./100 ml., heart failure, or chronic respiratory disease were not included. The blood urea, white blood count, aspartate aminotransferase, alanine aminotransferase, and airways resistance ($FEV_1/FVC \times 100$) were recorded at the start of the trial and immediately before the double-blind phase.

Initially, patients were admitted to the ward and kept under observation without treatment until the blood pressure reached a steady level. At this point a single test dose of the drug (10 mg. of oxprenolol or 50 mg. of practolol) was given to exclude any untoward effect. If this was tolerated the patients were started on the respective drugs, given three times daily.

Oxprenolol was supplied in 20-mg. tablets. The starting dose was 20 mg. three times daily, and this was increased on alternate days by 20 mg. (all three doses) until the diastolic blood pressure was controlled or the previously agreed maxi-

* Consultant Physician, Royal Infirmary, Sheffield.
† Senior Medical Registrar, Royal Infirmary, Sheffield. (Now Consultant Physician, Crawley Hospital, Crawley, Sussex.)
‡ Medical Registrar, Royal Infirmary, Sheffield.
§ Statistician, Department of Preventive Medicine, University of Sheffield.

mum of 140 mg. three times daily had been reached. Practolol was available in 50-mg. and 200-mg. tablets. Dosage began at 50 mg. three times daily and was similarly increased until the blood pressure was controlled or the maximum accepted dosage of 600 mg. three times daily had been reached. Blood pressure was taken in lying and standing positions, a London School of Hygiene and Tropical Medicine sphygmomanometer being used to reduce observer bias and digital preference (Rose *et al.*, 1964). Blood pressure control was considered satisfactory when the diastolic pressure (lying or standing) was below 100 mm.Hg.

After their discharge from the ward the patients' blood pressure was recorded at weekly intervals in the outpatient department, the dose being adjusted whenever necessary. The blood pressure was always measured by one observer and the treatment prescribed by another. When the blood pressure appeared to be adequately controlled or the daily dose of the drug was at the agreed maximum, patients entered a double-blind phase of the trial with a cross-over, during which for periods each of four weeks, they received, either active drug or placebo allocated at random. It was agreed that, at the discretion of the observer, patients could be withdrawn from the trial at any stage if their blood pressure was obviously uncontrolled and readings were unsuitably high.

Tablet counts were made at each outpatient attendance, and from these it seems likely that the dose prescribed was taken on average with at least 90% accuracy.

Results

Oxprenolol.—Nineteen patients completed the trial; five were withdrawn on account of inadequate control, the diastolic pressure of the excluded patients being persistently above 120 mm.Hg and none showing any lowering on maximum dose of the drug. The mean blood pressures recorded in each phase of the trial are shown in Table I, and the individual readings of diastolic pressure, lying and standing, during the double-blind phase of the trial are given in Table II. In the double-blind phase of the trial there was a statistically significant fall (using paired *t* test) in both systolic and diastolic blood pressures, but the fall was less significant in the case of lying diastolic pressure than in the other three results. Three patients (Cases 1, 10, and 19) showed controlled levels of blood pressure in both lying and standing positions on placebo, but in each case blood pressure was lower while on the active drug. The mean daily dose of oxprenolol was 320 mg., with a range of 60-420 mg., 11 patients requiring the maximum dose. No side effects were noted other than moderate slowing of the heart, the mean rate on the drug being 75/minute compared with 83/minute on placebo, a difference which is significant ($P<0.01$). There was no alteration in blood urea, blood count, enzyme levels, or airways resistance while taking the drug.

Practolol.—As with oxprenolol, 5 of the 24 patients starting the trial had to be eliminated because their blood pressure was uncontrolled despite maximal doses of practolol. The mean blood pressures of the remaining 19 patients are shown in Table I and the individual records of diastolic pressure during the double-blind stage in Table II. Statistical analysis of the results (using paired *t* test) shows that the drug has a significant blood-pressure-lowering effect. Four patients (Cases 2, 5, 8, and 11) maintained low diastolic readings on placebo but Cases 5, 8, and 11 had a further fall of blood pressure while on the active drug. Case 2 had very low blood pressures on the placebo. He was initially only mildly hypertensive and in retrospect should not have been included in the trial. Practolol, like oxprenolol, caused slowing of the heart, the mean rate on the drug being 76/minute compared with 84/minute on placebo ($P<0.001$). Side effects were minimal, only three patients complaining of constipation. The blood count, blood urea, enzyme level, and airways resistance did not change during treatment with practolol. The average daily dose of practolol was 1,097 mg., ranging from 150 to 1,800 mg., eight patients taking the maximum dose.

TABLE I.—*Mean Blood Pressures (mm.Hg) in Each Phase of the Trial*

	Before Admission	In Ward Before Drug	On Drug at Discharge	Before Double Blind	Double Blind		Significance*
					Placebo	Drugs	
			Oxprenolol				
Systolic standing ..	186	175	159	153	165	151	$P<0.001$
Systolic lying ..	194	182	166	159	173	160	$P<0.001$
Diastolic standing	115	110	99	101	106	99	$P<0.001$
Diastolic lying ..	114	108	95	99	102	99	$P<0.05$
			Practolol				
Systolic standing ..	194	182	158	160	175	161	$P<0.001$
Systolic lying ..	197	192	169	169	183	171	$P<0.01$
Diastolic standing	116	113	96	100	110	103	$P<0.05$
Diastolic lying ..	116	111	96	100	107	101	$P<0.05$

*Figures relate to 19 out of 24 patients.

TABLE II.—*Daily Dosage and Diastolic Blood Pressures (mm. Hg) Lying and Standing in 19 Cases Completing the Trial*

Case No.	Standing			Lying			Daily Dose Oxprenolol (mg.)
	Placebo	Drug	Change in B.P.	Placebo	Drug	Change in B.P.	
			Oxprenolol				
1 ..	90	88	− 2	85	82	− 3	120
2 ..	102	97	− 5	106	93	−13	420
3 ..	109	106	− 3	110	107	− 3	420
4 ..	102	100	− 2	103	102	− 1	420
5 ..	102	89	−13	100	92	− 8	60
6 ..	127	113	−14	126	126	0	420
7 ..	115	111	− 4	106	112	+ 6	360
8 ..	110	99	−11	100	102	+ 2	420
9 ..	110	91	−19	96	82	−14	120
10 ..	100	85	−15	98	86	−12	300
11 ..	101	99	− 2	103	96	− 7	360
12 ..	108	92	−16	95	92	− 3	240
13 ..	104	101	− 3	109	110	+ 1	420
14 ..	111	101	−10	105	97	− 8	420
15 ..	106	96	−10	101	103	+ 2	420
16 ..	108	111	+ 3	95	104	+ 9	420
17 ..	106	103	− 3	100	94	− 6	420
18 ..	114	110	− 4	106	105	− 1	420
19 ..	90	88	− 2	89	88	− 1	60
			Practolol				
1 ..	108	102	− 6	105	95	−10	450
2 ..	84	93	+ 9	76	86	+10	150
3 ..	111	95	−16	103	92	−11	1,800
4 ..	113	103	−10	105	103	− 2	1,200
5 ..	97	81	−16	92	84	− 8	150
6 ..	102	105	+ 3	99	113	+14	1,800
7 ..	109	101	− 8	102	95	− 7	1,800
8 ..	94	92	− 2	94	76	−18	300
9 ..	128	135	+ 7	122	131	+ 9	1,800
10 ..	113	118	+ 5	114	121	+ 7	1,800
11 ..	90	86	− 4	91	91	0	300
12 ..	116	106	−10	114	97	−17	1,800
13 ..	119	121	+ 2	120	115	− 5	1,200
14 ..	101	90	−11	100	98	− 2	600
15 ..	114	96	−18	111	96	−15	1,200
16 ..	115	104	−11	116	105	−11	1,800
17 ..	133	118	−15	125	113	−12	600
18 ..	107	95	−12	109	91	−18	300
19	126	113	−13	136	112	−24	1,800

Conclusions

Evidently both oxprenolol and practolol reduce blood pressure in both lying and standing positions, and statistical analysis confirms this. In the case of practolol this has been noted during trials of the drug in angina (Sandler and Clayton, 1970; George *et al.*, 1970). As with other antihypertensive drugs, the blood-pressure-lowering effect was inconsistent, but it was a little disappointing that less than half our cases on either drug achieved the relatively modest standard of blood pressure reduction regarded as effective.

Both drugs were well tolerated and there were no side effects, but within the range of dosage used they have not appeared to show great potential as antihypertensive agents, and subsequent to the trial all but two of the patients have been placed on alternative treatment.

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Preliminary Communications

Inhibition of Metastatic Spread by I.C.R.F. 159: Selective Deletion of a Malignant Characteristic

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Summary: Treatment with I.C.R.F. 159 completely inhibited metastasis formation in mice implanted with Lewis lung carcinoma at doses having little influence on the rate of growth of the primary implant. This inhibition was due to the effect of I.C.R.F. 159 on the development of blood vessels of the invading margins of the primary tumour. So far as is known, this is the first time a drug has induced a specific loss of the malignant characteristic of blood-borne tumour cell dissemination.

INTRODUCTION

Few attempts have been made to find new substances which prevent tumour cell dissemination (Handler, Sarris, and Wills, 1964; Donelli, Rosso, and Garattini, 1969; Rosso, Donelli, Franchi, and Garattini, 1969). This may largely be due to the difficulty of finding suitable experimental models, and most other workers have therefore bypassed the problem by injecting tumour cells intravenously. This expedient is not entirely satisfactory, since important early stages in the process of metastatic spread are thereby also bypassed.

We have used the Lewis lung carcinoma (3LL) in $C_{57}Bl$ mice as our test system because it has the important property, when implanted in the flank, of metastasizing spontaneously to the lungs (Ketcham, Wexler, and Minton, 1966; Wexler, Ryan, and Ketcham, 1969) and in our experience consistently, regularly, and predictably in all inoculated animals. Thus a precise experimental baseline is established of the organ invaded (the lungs) and of the time of invasion (nine days, microscopically). With this system a new cytostatic agent, (±)-1,2-bis(3,5-dioxopiperazin-1-yl) propane, I.C.R.F. 159 (Creighton, Hellmann, and Whitecross, 1969; Hellmann, Newton, Whitmore, Hanham, and Bond, 1969; Hellmann and Field, 1970; Sharpe, Field, and Hellmann, 1970), has controlled metastasis formation at doses having no overt influence on the growth of the primary tumour (Hellmann and Burrage, 1969). The mechanism of this inhibition has now been examined more closely, a preliminary account of the work being given elsewhere (Burrage, Hellmann, and Salsbury, 1970).

Essentially the experiments were designed to compare the microscopical changes in blood, lungs, and primary tumour after 3LL implantation in control and I.C.R.F. 159-treated animals to see if it was possible to discover morphological reasons for the inhibition of metastatic spread produced by I.C.R.F. 159. Cyclophosphamide was used for comparison.

MATERIALS AND METHODS

Effect on Primary Tumour Growth.—All mice used were $C_{57}Bl$ females of about 20 g. weight. All tumour inoculations were made subcutaneously in the flank. Methods of transplanting the tumour were those used routinely in the department of cancer chemotherapy of the I.C.R.F. (Hellmann, Marshall, and Stayt, 1967). Test mice received I.C.R.F. 159, 30 mg./kg., suspended in carboxymethyl cellulose solution intraperitoneally and the control mice received carboxymethyl cellulose alone intraperitoneally. Tumours were removed and examined macroscopically, and the test/control value was obtained by dividing the mean weight of test tumours by the mean weight of control tumours. The schedule of injections and the results are given in Table I.

TABLE I.—*Effect of I.C.R.F. 159 on Primary 3LL Tumour Growth*

Days After Implantation on which Injections Given	Days After Implantation on which Primary Tumour Removed	Mean Weight (g.) Test/Control (5 mice in each group)	Test/Control Value
1, 2, 3	4	0·056/0·075	0·73
1, 2, 3, 4	7	0·160/0·256	0·62
1, 2, 3, 4, 7, 8, 9	10	0·377/0·625	0·60
1, 2, 3, 4, 7, 8, 9, 10, 11	14	1·120/1·714	0·65
1, 2, 3, 4, 7, 8, 9, 10, 11, 14, 15	16	1·411/1·780	0·80
1, 2, 3, 4, 7, 8, 9, 10, 11, 14, 15, 16	19	1·780/2·343	0·76

Lungs and Blood in Mice Implanted with Tumour.—Tumour implantation and treatment were as described above, and are summarized in Table II. The lungs of these mice were removed, fixed, and individual lobes separated. After dehydration and embedding, a section (8μm.) was cut across the centre of each lobe. Pooled blood from the mice was collected into sodium edetate (Sequestrene) and averaged 4 ml. from each group of six. A nucleated cell concentrate was obtained by double centrifugation. Films were made of the whole of the nucleated cell layer, fixed in methyl alcohol, and stained with May-Grünwald-Giemsa.

TABLE II.—*Experimental Protocol to Show Effect of I.C.R.F. 159 on Pulmonary Metastases and Circulating 3LL Cells in Mice Implanted With 3LL Tumour. Six Mice in Each Group*

Mice Implanted with 3LL Tumour	
Days After Implantation on which I.C.R.F. 159 Given	Days After Implantation on which Lungs and Blood Removed
None	Each day from 1 to 14
Each day from 1 to 14	Each day from 1 to 14
None from 1 to 6. Each day from 7 to 14	Each day from 1 to 14*

*Blood only removed. 6 mice per group

Histological Examination.—Details of the experiment are given in Table III. Tumour implantation and treatment were