A LONGITUDINAL STUDY OF THE MECHANISMS OF ACTION OF DEBRISOQUINE AND PROPRANOLOL

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- 1 The mode of action of hypotensive drugs is not necessarily the same early and late in a course of treatment.
- 2 It was aimed to study this possible difference of effects for the drugs debrisoquine and propranolol, using a clinical trial design and measuring as many cardiovascular functions as possible by non-invasive methods in out-patients.
- 3 Several well known effects of these drugs were noted; in addition it was found that in some subjects there was a small but progressive salt retention during propranolol treatment, that the displacements of the slopes in baroreceptor function tests were different for the two drugs tested, and that venous distensibility was reduced at first with propranolol but soon increased again.
- 4 It is useful to combine longitudinal measures of body functions with a clinical trial when studying mechanisms of drug action.

Introduction

Much is known about the short-term effects of hypotensive drugs, and of their long-term effects on blood pressures in hypertensive subjects. It is uncertain, however, whether their mechanism of hypotensive action remains constant during long-term use. It has been shown that the mechanism of sustained hypertension changes with time in the clipped rat (Ledingham & Cohen, 1964; Langston, Guyton, Douglas & Dorsett, 1963; Guyton, Coleman, Fourcade & Navar, 1968) and in man (Pickering, 1968) as does the mechanism of sustained oedema in the nephrotic syndrome (Vere, 1971). It is therefore reasonable to ask similar questions about sustained reductions in blood pressure induced by drugs in human hypertension.

Methods

Patients

Patients with mild to moderate hypertension were selected for two reasons. The development of satisfactory long-term treatments for this group is a relevant issue which will not be discussed further here. Also, ethical problems are minimized if all patients who have complicated hypertension, or are at risk from complications, are excluded from a long-term

study. All patients gave their free consent to the study after a full explanation of it had been given to them. Their clinical details are given in Table 1.

Laboratory methods

Blood pressure was measured by cuff, zero muddled, sphygmomanometer. Readings were taken supine and erect in the clinic, beginning from the third successive visit (Dunne, 1969), and supine or passively tilted to 80° on a motor driven table in the laboratory.

Heart rate was counted from the e.c.g. for three samples of ten beats drawn at random from 50 R-R intervals in each position.

For the Valsalva overshoot tachycardia the subjects blew into an aneroid manometer to 40 mmHg and maintained the effort to the point of tolerance. The number of R-R intervals in the first 5 s after breaking were counted.

Forearm blood flow was measured by Whitney, (1953, 1954 & 1963) mercury in rubber strain gauges. Only changes in flow were of interest, not flow in absolute terms (Sigdell, 1969). The Whitney method was modified (Aminu, 1972) and a balanced bridge circuit used. The silicone rubber (Symel sleeving QS00705, 0.7 mm bore, 0.5 mm wall) was smaller than that originally used by Whitney (1953). A 6 cm arterial pressure cuff was used to exclude the hand.

Table 1 Clinical details of trial subjects

Subject	Sex	Age (years)	Race	Initial blood pressure (mm Hg)		Pyelo-gram	Urea (mg/100 ml)	Investigations		Other
				Supine	Erect			CCr (ml/min)	ECG	
F.J.(—)	F	46	West Indian	195 111	182 115	Pyelo-nephritis	45	N	N	—
M.A.(—)	F	49	West Indian	182 103	182 98	N	N	N	N	—
C.T.(D)	F	51	Caucasian	195 113	174 114	Calcified right kidney	N	N	N	—
M.S. Urine: E. Coll										
L.H.(D)	M	34	Caucasian	154 97	159 98	N	N	N	N	—
M.P.(P)	M	42	Jewish	178 105	192 104	N	N	N	N	—
W.W.(D)	M	46	Caucasian	171 111	169 112	N	46	182	LVH	—
A.M.(P)	F	57	Caucasian	158 99	142 100	N	N	N	ST-T changes Ischaemic	—
H.C.(D)	M	55	Caucasian	167 104	153 111	N	36-N	N	—	—
D.W.(D)	F	57	Caucasian	230 125	230 125	N	N	N	LVH	—
H.A.(—)	M	59	Caucasian	173 95	191 105	N	60	N	Infero-lateral ischaemia , LVH	—
J.F.(P)	F	28	Caucasian	172 100	147 109	N	N	N		Chest X-ray: large heart N
C.C.(P)	M	24	Caucasian	163 96	152 107	N	N	N	N	
B.H.(P)	M	33	Caucasian	136 95	144 101	N	N	N	LVH	—

N = normal; LVH = left ventricular hypertrophy
 D = debrisoquine first; P = propranolol first
 CCr = Creatinine clearance

Figure 1 Diagram of condenser, soldered from brass shim with insulated veins, to be cemented to skin over a vein on the back of the hand.

Venous occlusion was maintained at 40–50 mmHg for 10–15 s at chart speeds of 120 mm/s. The mean of six or seven slopes was taken.

Forearm vascular resistance was calculated by the method of Epstein, Stampfer & Beiser (1968).

To measure superficial venous distensibility a small condenser (Figure 1) was cemented to the skin over the vein and changes in its capacity measured by a capacitance bridge. Connections were by co-axial cable. Calibrations were checked before and after each test using paper strips and a micrometer gauge. Room temperatures were kept above 32°C (Webb-Peploe & Shepherd, 1968). The vein was distended by an occlusion cuff (40–50 mmHg) above it, inflated for 1 minute. Longer occlusion times did not affect the values obtained (Nachev, Collier & Robinson, 1971). The distension curve was also obtained by stepwise increases in cuff pressure (5 mmHg) from 0 to 50 mmHg. These curves were linearized by taking the logarithm of the cuff pressure.

Baroreflex responses were measured by a modification of the method of Smyth, Sleight & Pickering (1969) by Aminu (1972). Phenylephrine (50–100 mg depending on body weight) was given in syrup by mouth, and cuff blood pressures and e.c.g. pulse rates measured over the next 60 minutes. Phentolamine injection was available. The R-R interval was regressed upon systolic blood pressure up to the peak response.

Urine sodium was measured over 48 h collections made from Friday to Sunday evenings. Patients were asked to keep as closely as possible to their usual sodium intake. A trained dietician took a dietary history, and based advice upon the patients' common intake. Sodium was measured by internal standard flame photometry.

Statistical methods were standard paired or unpaired *t*-tests and regression and correlation techniques (baroreflex slopes). Regressions were of the second kind, of R-R interval upon change in systolic pressure. Quenouille's test 14 (Quenouille, 1959) was used for the analysis of groups of baroreflex responses, since those data were not normally

Figure 2 Trial design and timetable. ■ Laboratory session; □ weekend 48 h urine collection for 24 h urinary sodium excretion; □ test of baroreflex sensitivity.

distributed and required a distribution-free test. The α probability was in general accepted as significant at 0.05 or less. When numerous significance tests were made the 'significance of significances' was found from nomograms (Sakoda, Cohen & Beall, 1954). The conclusions stated in the paper were made on the basis of these tests; only standard errors are shown in the tables.

The clinical trial design

The trial was a double-blind, within subject crossover study (Figure 2). The entry criterion was sustained hypertension above 160/90 (standing) after the second clinic visit. Prior treatment with β -adrenoceptor blocking drugs was an exclusion as were complications of hypertension including heart failure or cardiac dilation. Patients with endocrine hypertension

and bronchial asthma were also excluded. Each patient received hypotensive drugs in three blocks. The first block was always commercial debrisoquine, the dose being varied until hypertension was controlled. The second and third blocks were randomly allocated to be either debrisoquine or propranolol in matched capsules. The capsules contained either 10 mg debrisoquine or 20 mg propranolol.

These were prepared by Roche Laboratories Limited in collaboration with Imperial Chemical Industries Limited, with careful checks made to demonstrate disintegration times comparable to the equivalent commercial drugs. In either case doses were taken thrice daily, the dose being varied till the clinician judged the hypertension to be controlled. Each block lasted at least 8 weeks, and not more than

Table 2 Clinical outcome of trial

<i>Subject</i>	<i>Debrisoquine treatment. Mean daily dose (mg), and clinical control</i>	<i>Complications</i>	<i>Propranolol treatment. Mean daily dose (mg), and clinical control</i>	<i>Complications</i>	<i>Remarks</i>
F.J. (-)	150 Poor	—	—	—	Withdrawn defaulter
M.A. (-)	60 Fair	—	—	—	Withdrawn, developed heart failure
C.T. (D)	30 Poor at first, good later	Viral infection	120 Good	—	—
L.H. (D)	30 Good	—	240 Good	—	—
M.P. (P)	60 Good	Generalized muscle aches. ESR 67 EMG-N probable viral infection	240 Good	Dyspnoea-Rhonchi Crepitations. Enlarged heart. Block II: 6 weeks only	Continued on debrisoquine
W.W. (D)	90 Good	Failure of ejaculation	240 Good	Severe impotence	After trial, acute constipation. Rt. hemiparesis
A.M. (P)	30/60 Good	Nil	240 Good	Nil	Continued on propranolol
H.C. (D)	30 Good	Polyuria, nocturia, Blood urea: 57 mg/100 ml dietary protein reduced, symptoms ceased. Dizziness	240 Good	Nil	Continued on propranolol
D.W. (D)	150 Fair	Headaches, Acute myocardial infarction	120 Good	Angina at end of trial	Continued on propranolol
H.A. (-)	60 Good	Nil	—	—	Withdrawn from study
J.F. (P)	30 Good	Nil	240 Good	Gain in weight of 3.8 kg Increase in heart size	Continued on debrisoquine
C.C. (P)	30 Good	Nil	240 Good	Nil	Continued on debrisoquine
B.H. (P)	30 Good	Nil	240 Good	One attack of hemiplegic migraine	Continued on debrisoquine

D = debrisoquine first; P = propranolol first
EMG = electromyogram.
N = Normal

Figure 3 Blood pressure measurements (a) after commercial debrisoquine, (b) trial debrisoquine and (c) propranolol. Each point is the average of the group of trial patients. ● supine, ■ standing (clinic blood pressure), or on passive tilt 80° (laboratory values). A clinic, systolic measurements; B clinic, diastolic measurements; C laboratory systolic measurements; D laboratory diastolic measurements; P preliminary, E early, L late, W washout periods of trial, described in the text.

12 weeks. Wash-out periods were used between blocks. During each wash-out matched placebo was substituted for active treatment, and the patients seen weekly until the blood pressure rose to pre-treatment levels, or by 10 mmHg, whichever was less. The next treatment block was then begun. Ten of the thirteen patients who presented were included in the trial, and nine completed it. Withdrawal criteria included the development of asthma or heart failure, detected incooperation, or any kind of drug intolerance. The patients were not permitted any other drugs, or if they proved necessary they were withdrawn from the trial. The reasons for withdrawal are shown in Table 2, among the clinical outcomes of all the cases.

Results

These are given in Table 3 and Figure 3. All treatments were effective hypotensive agents, and in the clinic blood pressure responses were almost indistinguishable but for the slightly smaller postural fall with propranolol. Laboratory blood pressures show a much greater postural effect from debrisoquine, reflecting the use of passive tilt.

The hypotensive effect is in each case sustained into the late treatment period, but with debrisoquine it was maximal in every case in the early phase of the laboratory measurements; by contrast propranolol effects seemed to grow more slowly up to the end of the treatment period.

Those tests which reflect sympathetic blockade (heart rate, tilt tachycardia, Valsalva overshoot), were all changed throughout the observations for both drugs, returning sharply in the succeeding wash-out period to pretreatment values. It seems that not only was hypotension sustained, but there was evidence of remanent adrenergic neurone blockade for debrisoquine, and β -adrenoceptor blockade for propranolol, throughout.

Propranolol, but not debrisoquine, appeared to be associated with a fall in salt excretion and rise in weight. The effect did not attain significance in the grouped results reported here. Their interpretation is also complicated by the fact that whereas all subjects who took propranolol had previously received only debrisoquine in one or other formulation, those who took 'trial' debrisoquine had received either ordinary debrisoquine or propranolol in the previous treatment block. Separation of these two subgroups produced no significant differences for the numbers were too small and the variance too great. This was because three propranolol treated subjects retained sodium markedly while the rest showed little or no effect.

In the whole groups there was a fall in forearm blood flow and a rise in forearm vascular resistance with propranolol. By contrast an initial fall in venous distensibility was shorter lived.

None of these effects is seen with debrisoquine. An apparent diuresis among the debrisoquine subjects was found to be confined to those subjects who had previously received propranolol. It probably represents sodium retention during former therapy and did not occur when debrisoquine was taken first.

The baroreceptor reflex test results are summarized in Table 4. To follow these it is necessary to consult Figure 4 which shows a characteristic set of results in one subject. It appears that propranolol reset the baroreceptor response slope towards the left, i.e., lowered the blood pressure and slowed the pulse without altering the responsiveness of the baroreceptor reflex very much, whilst debrisoquine both did this and markedly reduced the slope. It was not possible to make sequential estimates of this function during each treatment block, hence it is not known how these changes developed in time. They reverted to normal within 14 days after drugs were withdrawn.

Discussion

These experiments give some support to the idea that certain aspects of the action of hypotensive drugs

Table 3 Mean measurements made in relation to three courses of treatment. The figures in brackets are s.e. mean. Before and after measurements were made within 2 weeks of the start and end respectively of each treatment. Early and late measurements were made at the times shown in Figure 2. It should be noted that, whereas all subjects who took propranolol had previously taken only debrisoquine, those who took trial debrisoquine might have received either 'commercial' debrisoquine or 'trial' propranolol in their preceding treatment block

Variable	After 8–12 weeks' commercial debrisoquine	Trial debrisoquine				Propranolol			
		Before	Early	Late	After	Before	Early	Late	After
Heart rate (beats/min)	—	69.8 (2.8)	61.0 (2.4)	58.0 (1.8)	72.6 (2.3)	70.7 (2.6)	58.0 (2.0)	54.7 (1.9)	69.9 (3.3)
	80° tilt	87.2 (4.6)	73.7 (3.1)	74.3 (3.0)	94.0 (3.3)	85.6 (3.7)	67.5 (2.7)	63.4 (2.5)	86.7 (3.9)
Valsalva tachycardia (beats/5 s)	7.2 (0.4)	7.3 (0.6)	6.6 (0.4)	6.3 (0.4)	8.2 (0.4)	7.5 (0.4)	6.0 (0.3)	5.5 (1.0)	7.3 (1.0)
Forearm flow (ml 100 ml ⁻¹ min ⁻¹)	Supine	4.5 (0.68)	3.0 (0.46)	3.2 (0.42)	4.0 (0.79)	4.3 (0.8)	3.0 (0.4)	2.5 (0.3)	4.1 (0.7)
	80° tilt	2.8 (0.38)	1.9 (0.4)	2.0 (0.46)	2.3 (0.32)	2.8 (0.5)	2.0 (0.37)	1.4 (0.28)	2.8 (0.8)
Forearm vascular resistance (arbitrary units)	Supine	28.7 (—)	40.3 (6.4)	38.7 (4.0)	39.1 (—)	36.9 (—)	37.0 (5.6)	44.1 (5.3)	29.3 (—)
	80° tilt	52.0 (4.6)	69.7 (8.9)	36.7 (9.6)	58.2 (10.4)	50.1 (5.4)	68.3 (8.3)	111.1 (8.3)	43.8 (3.6)
Venous distensibility (arbitrary units)	Peak	7.0 (0.79)	7.9 (0.89)	6.5 (0.85)	7.4 (0.66)	6.6 (0.63)	4.3 (0.67)	6.4 (1.07)	7.1 (0.83)
	Slope	11.3 (1.96)	14.5 (1.55)	11.5 (1.5)	10.7 (1.2)	11.5 (2.0)	7.9 (1.4)	10.7 (1.7)	11.1 (2.2)
Bodyweight difference from starting figures (kg)	0.05 (0.64)	1.72 (1.18)	0.68 (0.50)	1.23 (0.64)	1.32 (0.41)	0.86 (0.27)	1.59 (0.23)	2.36 (0.41)	2.63 (0.36)
24 h urine sodium (m mol)	178.5 (19)	124.2 (12.4)	134.4 (20.4)	139.1 (16.7)	157.9 (22.4)	176.6 (20.1)	154.5 (14.0)	143.2 (14.8)	124.2 (9.5)

Figure 4 Regression slopes of electrocardiographic R-R against systolic blood pressure, in patient HT. ● common means. (a) preliminary results; (b) after 4 days' propranolol; (c) after 8 weeks' debrisoquine; (d) 4 days after debrisoquine withdrawal; (e) 11 days after debrisoquine withdrawal.

change with time during a long course of treatment, though their hypotensive efficacy may well be sustained.

Some of the findings are what might be expected from the known pharmacological effects of the drugs. These include the bradycardia, some of the effects on baroreceptor reflex function, the attenuated Valsalva response, and the small changes in e.c.g. The initial fall in forearm flow seen with propranolol was also no

surprise; a non-selective β -adrenoceptor blocking drug would be expected to reduce forearm muscle flow, and might also reduce skin flow either by an overall fall in flow through the limb, leading to local adjustments in arterial calibre, or by a central nervous mechanism.

Less expected were the demonstrations of salt and water retention in some subjects during propranolol treatment, with a late increase in venous distensibility, perhaps to accommodate some of the fluid so retained. The variance within the results for sodium excretion and weight gain was large, and no general conclusions can be drawn from them: Goldberg & Raftery (1974) reported weight increase in subjects whose blood pressure was lowered by oxprenolol, a finding which was differently interpreted in the review which preceded their paper (Scottish Medical Journal, 1974). Noradrenaline and adrenaline are local vasoconstrictors in man (Collier, Nachev & Robinson, 1972), and the constrictor effect of adrenaline is potentiated by prior β -adrenoceptor blockade.

Patients who take β -adrenoceptor blocking drugs occasionally develop left ventricular failure. In some of these it is possible to demonstrate progressive salt retention during treatment, though these patients usually can be shown to have had either partial heart block or a recently dilated ventricle, even if overt failure was not present at the start of treatment, (Dunne & Vere, 1973). Neither heart block nor prior ventricular decompensation was present in any of our patients in this study, so these features cannot explain their salt retention when taking propranolol.

The effects on baroreceptor function were not entirely expected from the work of Pickering, Gribbin, Strange, Peterson, Cunningham & Sleight (1972) and Sleight,

Table 4 Slopes, intercepts and correlation coefficients for the relationship between R-R interval and systolic blood pressure in six subjects during, and at least 7 days remote from, treatment with either debrisoquine or propranolol

	Debrisoquine			Propranolol		
	Slope	Intercept	Correlation coefficient	Slope	Intercept	Correlation coefficient
At the end of 6 weeks' treatment	1.26	0.65	0.37	2.82	0.63	0.33
	1.53	0.57	0.27	3.58	0.52	0.60
	1.78	1.11	0.73	5.99	0.36	0.88
	1.27	1.02	0.41	5.68	0.35	0.81
	2.47	0.47	0.38	5.66	0.37	0.90
	2.69	0.44	0.31	5.42	0.36	0.83
Mean	1.83	0.71	—	4.86	0.43	—
> 7 days off treatment	15.07	—0.55	0.95	3.93	0.32	0.59
	10.75	—0.58	0.94	3.44	0.38	0.47
	13.07	—0.64	0.92	6.86	—0.14	0.70
	6.83	—0.06	0.64	6.50	—0.14	0.71
	7.18	—0.60	0.87	10.32	—0.52	0.95
	4.98	—0.20	0.77	9.47	—0.39	0.92
Mean	9.65	—0.44	—	6.75	—0.08	—

Gribbin & Pickering (1971) who found that propranolol increased the slope of the relationship between pulse interval and blood pressure in resting subjects. This they took to be evidence that the reflex operates largely through a parasympathetic mechanism at rest. We found that in some subjects the slope increased, but not in most, at the end of 6 weeks' propranolol treatment. Sleight *et al.* (1971) used more direct measures than ours, and used a single parenteral dose of propranolol. More surprising, perhaps, is our finding of marked attenuation of baroreceptor responses by debrisoquine, a drug which we would not expect to

influence a largely parasympathetic mechanism. Debrisoquine potentiates the hypertensive effect of pheynyleprine (Allum, Aminu, Bloomfield, Davies, Scales & Vere, 1974), and so might be expected to attenuate a baroreceptor response if sympathetic nerves were in its efferent pathway.

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