Papers and Originals

Treatment of Hypertension with Propranolol

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Summary: When used in the treatment of hypertension propranolol is at least of similar potency to bethanidine, guanethidine, and methyldopa. Propranolol does not produce postural or exercise hypotension and it seems that it is often more acceptable to patients than conventional drugs. It usually produces the best control of the supine blood pressure.

A series of 109 hypertensive patients was treated with propranolol; in nine the drug was withdrawn. In 92 of the patients a supine or standing blood pressure of 100 mm. Hg or less was achieved. Eighty of the patients had previously been treated with other potent drugs, and close comparisons and prolonged follow-up in 17 patients showed that diastolic pressures of 100 mm. Hg or less were achieved in more patients after propranolol than with guanethidine, bethanidine, or methyldopa.

Sensitivity to propranolol varies widely, and dosage should be increased gradually. The hypotensive effect often takes six to eight weeks to reach its maximum. Propranolol reduces cardiac output but may also act by reducing the cardiac component of pressor stimuli; as a result the baroreceptors gradually regulate the blood pressure at a lower level. It is contraindicated in patients with obstructive airways disease or in uncompensated heart failure.

Introduction

Most potent drugs widely used in the treatment of hypertension suffer from the disadvantage that they interfere with the sympathetic control of blood vessels. The cardiovascular system is therefore unable to respond normally to situations requiring vasoconstriction to maintain blood pressure—for example, the erect posture. There are differences between the various sympathetic inhibiting drugs (Oates, Seligmann, Clark, Rousseau, and Lee, 1965; Prichard, Johnston, Hill and Rosenheim, 1968a), but all suffer from this disadvantage to some degree.

The use of beta-receptor-blocking drugs in the treatment of hypertension in a short-term study was reported with pronethalol (Prichard, 1964). The use of this drug was curtailed in view of its tumour-producing action in mice (Paget, 1963). Propranolol was also found to possess a hypotensive action (Prichard and Gillam, 1964, 1966). A feature of the hypotensive action of propranolol has been the relative absence of postural and exercise hypotension, in contrast to that seen with sympathetic blockade (Prichard, 1968b).

We have now enlarged our study of propranolol in hypertension to include 109 patients treated for periods of up to four years. Three of these patients have been reported in detail (Prichard, 1968a).

Method

Ninety-five patients were seen under standard clinic conditions. They were first asked standard questions by one physician, and blood pressures were taken by the second physician, who was unaware of changes in therapy.

Blood pressures and pulses were taken supine, after rest on a couch for one minute and then after three minutes. Throughout this paper the supine readings quoted are those at three minutes. The blood pressure and pulse were also taken one minute after standing, and then again standing after ascending and descending 18 stairs, except in four patients who were unable to climb stairs. Blood pressures in most instances were taken with the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland, and Crowley, 1964). This device is to ensure that the observer is unaware of the actual blood pressure at the time he auscultates. It also eliminates digit preference, and hence blood pressures are quoted to the nearest millimetre of mercury.

The remaining 14 patients were seen throughout by the same physician at a different clinic; blood pressures were taken as before, but no exercise blood pressures were taken.

Adjustment of Dose.—In most cases propranolol was started in the outpatient department, the dose of the previous drug (see under Patients) being gradually reduced as the dose of propranolol was increased.

Dosage was usually begun with 5 or 10 mg. q.d.s., and increments were made as required at each visit, most often fortnightly, usually about 25% per dose. It is exceedingly important to begin at a low dose, as sensitivity is very variable (see Table VII).

As the full hypotensive effect takes time to reach its maximum (see below), the blood pressure after final adjustment of the dose usually falls further. However, this does not lead to any untoward effects, as once normotensive levels are reached it usually seems to require a considerable increment for any significant further fall of blood pressure. This is in accord with experience, using large doses in normotensive anginal patients (Prichard and Gillam, 1968). In addition, the greater part of the hypotensive effect is seen within the first two weeks or so after dose adjustment. This progressive effect is less frequently apparent in patients with mild hypertension. The dose was increased until the diastolic blood pressures, supine and standing, were controlled in the range 80-100 mm. Hg, provided that this was not contraindicated by the patient's general condition. A bradycardia of 55 beats per minute after rest on the couch for three minutes was normally regarded as a side-effect. Only in some of the younger subjects was the dose occasionally increased with pulse rates at this level.

At lower dosage standard scored 10-mg. and 40-mg. tablets of propranolol were used. When higher doses were reached specially prepared 100-mg. tablets were used of similar overall size to the 40-mg. tablets. When a patient was already receiving a diuretic it was continued during the period of change from

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the previous drug to propranolol. Diuretics were continued or used for the first time with propranolol as indicated. In a few instances (see Table V) other hypotensive drugs were given with propranolol.

Patients

The hypotensive effect of beta-adrenergic-blocking agents was first noted in patients undergoing treatment for angina, and in the first instance patients who had relatively mild hypertension were treated, or those who suffered also from angina. Later the selection was extended to include severe hypertensives with side-effects on their previous therapy. A large postural drop in blood pressure in patients on sympathetic neurone-blocking drugs is now considered to be an indication for propranolol. It is important with a new drug, particularly one with an apparently different mode of action, to obtain some comparison with existing drugs at an early stage. Initially we were unwilling to regard propranolol as a drug of first choice, and therefore its use in patients already under treatment provided the required information. It is largely because of this that such a high proportion of this series of patients were previously being treated with existing potent drugs, bethanidine, guanethidine, or methyl dopa.

There were 105 patients (68 male, 37 female, average age 53 years) who were treated with propranolol for their hypertension. In four others propranolol was withdrawn at an early stage (see below). Seventy-eight of these had essential hypertension and in the remaining 27 the hypertension was thought to be of renal origin. The presenting fundal changes were grade IV in 18, III in 9, II in 48, I in 27, and in three the fundi were normal. The most recent E.C.G. showed evidence of left ventricular hypertrophy in 71 of the 105 patients, and in 57 the blood urea was over 40 mg./100 ml.

Close Comparison

Trials of new hypotensive drugs involve treating new patients or those already under treatment in the general outpatient clinic. Besides the administration of a new drug there is the benefit and aura of heightened physician interest in the patient's progress. This influence tends of itself to lower the blood pressure to a variable degree. In patients with mild hypertension prolonged observation with placebo may be justified, but this may be hazardous in the more severe hypertensive.

We have 17 patients now being treated with propranolol who have been under regular observation in the clinic for a prolonged period (two years or more). They had previously taken part in the within-patients comparison of bethanidine, guanethidine, and methyl dopa (Prichard *et al.*, 1968a). These patients, seen fortnightly, had been stabilized on each of these three drugs in turn (except one who could not tolerate guanethidine, and two who could not tolerate methyl dopa), and in each patient on each drug the average blood pressure from seven visits to the clinic has been taken over three months. After change to propranolol they were seen less frequently, on average monthly, but once again the average blood pressure of seven visits in each patient was taken. Throughout, patients were seen by the same physician (B. N. C. P.), who asked standard questions. In the previous study when the patients were on bethanidine, guanethidine, or methyl dopa, blood pressures were taken under the same conditions as described in the present study under Methods above by

A. W. J. (Prichard *et al.*, 1968a). Before the change to propranolol and subsequently, pressures were taken by P. M. S. G. Throughout, after blood pressures were taken, patients were again seen by B. N. C. P., who adjusted the dose of drug as indicated.

Results

Propranolol was given to 109 hypertensive patients; it was withdrawn at an early stage in four—one because of breathlessness on exertion, one who felt weak and tired, one who had nausea and heartburn, and one who experienced depression that subsided immediately on stopping the drug. In these patients it was not possible to gauge any response of the blood pressure. The blood pressures reported concern the remaining 105 patients. In five of these the drug was subsequently withdrawn. In the bethanidine group propranolol was stopped in two patients with chronic renal failure because of the onset of chronic heart failure; one seemed to benefit from drug withdrawal. The onset of persistent indigestion was the reason for stopping propranolol in one patient previously treated with methyl dopa. In a second patient in this group propranolol failed to lower the blood pressure. In the group who had had no previous treatment one patient experienced persistent tiredness and the drug

TABLE I.—Summary of Levels of B.P. Control (105 Patients)

	Table No.	Patients	Supine or Standing Diastolic B.P. (mm.Hg)				Supine and Standing, 100 or less
			120 or more	111–119	101–110	100 or less	
Bethanidine (B) } Propranolol	II	28 {	3 0	4 1	5 4	16 23	(4) (17)
Guanethidine (G) } Propranolol	III	11 {	0 0	1 0	2 0	8 11	(3) (8)
Methyl dopa (M) } Propranolol	IV	30 {	4 0	1 0	7 1	18 29	(11) (22)
B or G or M } Propranolol + B or G or M	V	11 {	2 2	1 1	4 1	4 7	(1) (6)
Reserpine or diuretics } Propranolol	VI	10 {	0 0	1 0	0 1	9 9	(6) (9)
No treatment } Propranolol	VI	15 {	2 0	4 0	7 2	2 13	(1) (11)
Totals:							
Pre-propranolol		105 {	11	12	25	57	(26)
On propranolol			2	2	9	92	(67)

FIG. 1.—Man aged 43 with essential hypertension. (Fundus grade IV, E.C.G. left ventricular hypertrophy, blood urea 39 mg./100 ml.) Record of supine and standing blood pressures over period of change from bethanidine to propranolol. FIG. 2.—Man aged 56 with essential hypertension. (Fundus grade II, E.C.G. left ventricular hypertrophy, blood urea 36 mg./100 ml.) Record of supine and erect after exercise (ascending and descending 18 stairs) blood pressures over period of change from guanethidine to propranolol.

was stopped. The levels of blood pressure control are given in Table I.

(1) Twenty-eight patients previously treated with bethanidine who were later controlled on propranolol are summarized in Table II. An example showing blood pressure control supine and the response to posture in the period of change from bethanidine to propranolol is given in Fig. 1. (2) The 11 patients previously treated with guanethidine and transferred completely to propranolol are summarized in Table III. Fig. 2 illustrates the supine and exercise blood pressures over the period of change from guanethidine to propranolol. (3) Thirty patients who previously had received methyldopa are summarized in Table IV. (4) Eleven patients had propranolol added to their therapy, bethanidine, guanethidine, or methyldopa being continued at a lower dosage; these cases are summarized in Table V. (5) Patients previously treated with thiazides alone, reserpine, or not previously treated are summarized in Table VI.

TABLE II.—Patients (20 Males, 8 Females, Average Age 52 Years) Transferred from Bethanidine to Propranolol. Summary of Results (Dose, Duration of Treatment, see Table IX)

	Supine			Standing			Exercise		
	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.
	S.	D.		S.	D.		S.	D.	
<i>Bethanidine</i>									
Mean ..	197	114	76	152	102	88	126	81	98
S.E. ..	4.5	2.4	2.2	4.3	2.7	2.7	6.3	3.9	4.0
(n) ..	(28)	(28)	(25)	(28)	(28)	(25)	(21)	(21)	(21)
<i>Propranolol</i>									
Mean ..	162	94	65	152	100	72	163	100	75
S.E. ..	5.3	1.8	2.4	5.0	2.1	2.8	5.4	3.3	2.4
(n) ..	(28)	(28)	(25)	(28)	(28)	(25)	(21)	(21)	(21)

S. = Systolic. D. = Diastolic.

Means calculated from last blood pressure on bethanidine and most recent blood pressure on propranolol.

Presenting fundi: IV 7, III 1, II 13, I 7. Most recent E.C.G., left ventricular hypertrophy in 23 patients. Blood urea over 40 mg/100 ml. in 16 patients.

TABLE III.—Patients (6 Males, 5 Females, Average Age 53 Years) Transferred from Guanethidine to Propranolol. Summary of Results

	Supine			Standing			Exercise		
	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.
	S.	D.		S.	D.		S.	D.	
<i>Guanethidine</i>									
Mean ..	195	109	67	161	98	74	128	72	71
S.E. ..	7.0	3.4	3.9	7.0	3.7	4.8	7.5	7.4	3.1
(n) ..	(11)	(11)	(9)	(11)	(11)	(9)	(5)	(5)	(5)
<i>Propranolol</i>									
Mean ..	156	95	64	145	94	72	133	87	78
S.E. ..	10.3	2.9	4.6	8.6	2.2	5.6	9.8	2.5	10.0
(n) ..	(11)	(11)	(9)	(11)	(11)	(9)	(5)	(5)	(5)

Means calculated from last blood pressure on guanethidine and most recent blood pressure on propranolol.

Presenting fundi: III 1, II 8, I 2. Most recent E.C.G., left ventricular hypertrophy in 7. Blood urea over 40 mg./100 ml. in 4.

TABLE IV.—Patients (20 Males, 10 Females, Average Age 51 Years) Transferred from Methyldopa to Propranolol. Summary of Results

	Supine			Standing			Exercise		
	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.
	S.	D.		S.	D.		S.	D.	
<i>Methyldopa</i>									
Mean ..	163	102	79	152	104	88	154	98	97
S.E. ..	5.4	2.9	2.5	5.2	2.8	2.6	7.9	3.8	2.9
(n) ..	(30)	(30)	(27)	(30)	(30)	(27)	(21)	(21)	(21)
<i>Propranolol</i>									
Mean ..	142	88	63	136	93	69	143	92	74
S.E. ..	4.4	1.6	1.9	3.2	2.0	2.2	4.1	2.1	2.3
(n) ..	(30)	(30)	(27)	(30)	(30)	(27)	(21)	(21)	(21)

Means calculated from last blood pressure on methyldopa and most recent blood pressure on propranolol.

Presenting fundi: IV 3, III 5, II 11, I 10, O 1. Most recent E.C.G., left ventricular hypertrophy in 18. Urea over 40 mg./100 ml. in 16.

TABLE V.—Patients (9 Males, 2 Females, Average Age 49 Years) on Bethanidine, Guanethidine, or Methyldopa with Propranolol Added. Summary of Results

	Supine			Standing			Exercise		
	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.
	S.	D.		S.	D.		S.	D.	
<i>On Previous Drug</i>									
Mean ..	224	131	73	161	106	83	131	87	90
S.E. ..	9.7	5.4	3.8	8.4	5.2	3.8	8.6	5.5	4.5
(n) ..	(11)	(11)	(11)	(11)	(11)	(11)	(8)	(8)	(7)
<i>With Propranolol Added</i>									
Mean ..	188	117	61	161	106	65	143	95	69
S.E. ..	9.1	4.4	3.8	10.4	4.7	2.5	7.5	4.9	11.5
(n) ..	(11)	(11)	(11)	(11)	(11)	(11)	(8)	(8)	(7)

Means calculated from last blood pressure on previous drug and last blood pressure on combination of previous drug and propranolol.

Presenting fundi: IV 8, III 1, I 2. E.C.G., left ventricular hypertrophy in 10. Urea over 40 mg./100 ml. in 8.

TABLE VI.—Patients Previously on Thiazide (2 Males, 1 Female, Average Age 56 Years), Reserpine (2 Males, 5 Females, Average Age 61 Years) or No Previous Treatment (8 Males, 7 Females, Average Age 54 Years). Summary of Results

	Supine			Standing		
	Blood Pressure (mm.Hg)		Pulse/min.	Blood Pressure (mm.Hg)		Pulse/min.
	S.	D.		S.	D.	
Thiazide	Mean .. 191	101	66	183	109	68
	S.E. .. 15.6	6.4	6.2	12.0	3.0	7.9
	(n) .. (3)	(3)	(2)	(3)	(3)	(2)
Propranolol	Mean .. 160	82	61	140	89	71
	S.E. .. 3.5	3.1	3.7	2.8	1.5	4.8
	(n) .. (3)	(3)	(3)	(3)	(3)	(3)
(Presenting fundi: III 1, II 2, E.C.G., left ventricular hypertrophy in 2. Urea over 40 mg./100 ml. in 1)						
Reserpine	Mean .. 160	86	76	158	90	81
	S.E. .. 7.7	4.0	4.9	6.6	3.8	4.8
	(n) .. (7)	(7)	(7)	(7)	(7)	(7)
Propranolol	Mean .. 155	84	68	141	87	70
	S.E. .. 6.7	3.5	6.4	8.7	4.9	5.4
	(n) .. (7)	(7)	(7)	(7)	(7)	(7)
(Presenting fundi: II 5, I 2. E.C.G., left ventricular hypertrophy in 2. Urea over 40 mg./100 ml. in 6)						
No previous treatment	Mean .. 187	112	88	177	114	95
	S.E. .. 4.4	1.9	2.9	5.3	3.9	2.8
	(n) .. (15)	(15)	(12)	(15)	(15)	(12)
Propranolol	Mean .. 152	91	73	142	93	81
	S.E. .. 5.9	2.7	3.5	6.3	3.2	3.8
	(n) .. (15)	(15)	(12)	(15)	(15)	(12)

(Presenting fundi: II 9, I 4, O 2. E.C.G., left ventricular hypertrophy in 9. Urea over 40 mg./100 ml. in 6)

Means calculated from last blood pressure on previous drug and last blood pressure on propranolol.

Dosage and Duration of Treatment.—These are summarized in Table VII, dosage of the previous drug being given for comparison. It will be noted that there is a wide variation in dosage for bethanidine, guanethidine, methyldopa, and propranolol. A low or a high dose on previous therapy does not necessarily mean that a similarly low or high dose was required on propranolol to control the blood pressure. The dose of propranolol required to control the blood pressure or to produce significant bradycardia therefore varies over a wide range, and it is necessary to adjust the dose individually. At the time of preparation of this report some patients had been receiving propranolol for over three and a half years for their hypertension.

Close Comparison

Blood pressures in the patients who received the four drugs—bethanidine, guanethidine, methyldopa, and propranolol—are given in Table VIII. There were 13 patients who were able to tolerate all four drugs and whose blood pressure was satisfactorily controlled; their blood pressures are plotted in Fig. 3. It can be seen that the standing diastolic pressures were similar on all four drugs.

TABLE VII.—Dosage and Duration of Treatment

	Previous Drug			Propranolol		
	Average Dose (mg./day)	Range	Diuretic	Average Dose (mg./day)	Range	Dose of Previous Drug
Bethanidine, n = 28 (S.E.)	170 (53.5)	20-1,200	17	364 (71.8)	15-1,600	—
Guanethidine, n = 11 (S.E.)	53 (11.1)	25-125	4	460 (128.6)	40-1,600	—
Methyldopa, n = 50 (S.E.)	1,917 (261.2)	250-5,500	13	291 (51.2)	40-1,400	—
Reserpine, n = 7 (S.E.)	1,000	—	3	279 (100.2)	40-1,000	—
Chlorothalidate, n = 3 (S.E.)	—	—	3	73 (29.1)	20-120	—
No previous treatment, n = 15 (S.E.)	—	—	—	171.7 (66.3)	10-640	—

Patients with propranolol added, previous drug continued

Bethanidine, n = 7 (S.E.)	385.7 (115.4)	100-900	5	1,540 (441.9)	500-4,000	—
Guanethidine, n = 2 (S.E.)	137.5	—	0	680 (520.0)	160-1,200	—
Methyldopa, n = 2 (S.E.)	1,875 (375.0)	1,500-2,250	1	140 (20.0)	1,500-2,000	—

* 3 patients on 0.3 mg., 1 patient 0.25 mg. reserpine; 1 patient 30 mg., 1 patient 45 mg. methoseridine; and 1 patient Rauwolfoid tabs. 2 daily.

† 1 patient on guanethidine 75 mg., 1 patient on bethanidine 25 mg.

‡ 1 patient also on methyldopa 1,750 mg and hydralazine 150 mg. 1 patient also on reserpine 0.3 mg.

TABLE VIII.—Blood Pressures on Propranolol Compared with Previous Pressures on Bethanidine, Guanethidine, and Methyldopa (with each drug, average of seven visits to outpatient clinic)

Case No.	Bethanidine (n = 17)				Guanethidine (n = 16)				Methyldopa (n = 15)				Propranolol (n = 17)			
	Blood Pressure (mm. Hg)		Dose (mg./day)	Diuretic	Blood Pressure (mm. Hg)		Dose (mg./day)	Diuretic	Blood Pressure (mm. Hg)		Dose (mg./day)	Diuretic	Blood Pressure (mm. Hg)		Dose (mg./day)	Diuretic
	Supine	Exercise			Supine	Exercise			Supine	Exercise			Supine	Exercise		
1	180/121	123/93	166	—	118/86	116/72	128	—	151/107	129/92	1,893	+	132/93	136/93	326	—
2	153/97	116/77	70	—	156/89	144/76	80	—	151/87	121/96	1,924	+	136/74	127/81	137	—
3	198/107	149/95	49	—	128/78	129/75	30	—	184/105	135/75	2,714	—	130/93	128/73	197	—
4	189/117	140/97	76	—	153/99	137/76	60	—	188/106	130/74	3,214	—	159/100	152/89	177	—
21	176/113	148/105	112	—	139/104	157/103	20	—	153/97	145/87	—	—	132/93	127/82	129	—
24	181/104	140/91	81	—	147/79	130/50	60	—	158/106	129/87	4,750	—	159/93	147/82	160	—
29	188/108	144/91	114	—	167/89	147/81	63	—	158/106	129/87	2,000	—	138/85	127/87	83	—
36	169/109	136/93	71	—	140/87	139/87	37	—	119/87	98/79	2,445	—	135/82	138/82	79	—
37	153/103	112/85	66	—	166/105	130/91	37	—	138/94	126/85	1,468	—	139/83	129/83	320	—
44	170/110	149/105	115	—	150/102	130/92	121	—	139/100	127/85	1,882	—	134/98	129/103	223	—
46	154/116	112/89	100	—	129/98	123/83	109	—	152/104	128/92	1,944	—	130/90	127/86	1120	—
47	179/119	127/99	134	—	121/81	121/81	109	—	153/102	126/102	5,145	—	127/86	127/86	1200	—
57	195/114	168/102	152	—	166/89	166/89	67	—	153/102	128/99	1,304	—	131/91	127/86	160	—
58	172/109	130/93	188	—	176/94	161/100	100	—	146/101	128/99	2,627	—	131/91	127/86	203	—
61	196/121	111/88	69	—	187/113	161/100	110	—	171/122	145/118	4,000	—	136/102	125/101	460	—
65	229/150	117/83	150	—	136/104	127/88	280	—	167/124	123/97	—	—	133/89	128/79	40	—
68	170/116	136/105	500	+	124/94	91/60	—	—	133/98	132/109	2,556	+	123/87	126/96	—	—
Average	180/114	134/94			141/92	132/81			154/103	127/94			143/90	135/94		
Age†	172/112	131/94			139/94	126/82			148/98	125/92			143/92	136/96		

* Figures taken from Prichard *et al.*, 1968a. † Average of the six patients not receiving diuretic on any of the four drugs.

Differences between propranolol and:	Values of P			
	Supine		Exercise	
	Systolic	Diastolic	Systolic	Diastolic
(a) Bethanidine (n = 17)	<0.001	<0.001	0.02 > P > 0.01	0.005 > P > 0.001
(b) Guanethidine (n = 16)	<0.001	<0.001	0.10 > P > 0.05	0.005 > P > 0.001
(c) Methyldopa (n = 15)	0.02 > P > 0.01	>0.001	0.10 > P > 0.05	0.20 > P > 0.10

Probabilities calculated from differences in logarithms of the patients who received both drugs of the pair being considered.

The absence of postural and exercise hypotension on propranolol is contrasted in Table IX. The figures show the percentage ratio of the average mean erect to the mean supine blood pressures from each individual patient, and the percentage ratio of the mean exercise to the mean supine blood pressure. A ratio below 100% therefore indicates a postural or exercise fall in blood pressure. In all instances there is a postural and exercise fall in blood pressure on bethanidine, guanethidine, and methyldopa that differs significantly from the response on propranolol ($P < 0.001$).

FIG. 3.—Average blood pressures, supine, standing, and erect after exercise (ascending and descending 18 stairs) on bethanidine, guanethidine, methyldopa, and propranolol for 13 patients whose blood pressure was satisfactorily controlled by all four drugs. For each drug the average of seven visits to outpatient department. (Bars indicate standard errors.)

The average blood pressures in the six patients who did not receive a diuretic on any of the four drugs is similar to the averages of the entire group (Table VIII). Similarly, the absence of a diuretic did not affect the differences in the response to posture and exercise (Table IX).

TABLE IX.—Comparison With Other Drugs. Effect of Posture and Exercise (Ratio % Mean Blood Pressure)

	All Patients			No Diuretic (on any Drug)		
	Ratio:	Erect Supine	Exercise Supine	Ratio:	Erect Supine	Exercise Supine
Propranolol ..	n = 17	100	101	n = 6	101	103
Bethanidine ..	n = 17	79	72	n = 6	81	75
Guanethidine ..	n = 16	83	75	n = 6	85	76
Methyldopa ..	n = 15	88	87	n = 6	90	90

$P < 0.001$ for the difference in values for propranolol *v.* bethanidine, guanethidine, and methyldopa for all patients, and for "no-diuretic" patients, for both erect/supine and exercise/supine. Probabilities calculated as in Table VIII.

Pulse Rates

The average pulse rates, calculated as for blood pressures from the mean of seven readings in each patient on each drug, are given in Table X. The pulse rates on bethanidine, guanethidine, and methyldopa in patients with similar standing blood pressures on each drug have been compared previously (Prichard *et al.*, 1968a).

TABLE X.—Average Pulse Rate/Min.

	Supine	Exercise
Bethanidine, n = 17 (S.E.)	74 (2.21)	89 (2.23)
Guanethidine, n = 16 (S.E.)	68 (1.66)	79 (2.60)
Methyldopa, n = 15 (S.E.)	77 (2.05)	93 (2.06)
Propranolol, n = 17 (S.E.)	66 (1.99)	73 (2.49)

Values of P for:

Propranolol *v.* bethanidine: supine $0.005 > P > 0.001$, standing $P < 0.001$.
 Propranolol *v.* guanethidine: supine $0.40 > P > 0.30$, standing $0.05 > P > 0.025$.
 Propranolol *v.* methyldopa: supine $P < 0.001$, standing $P < 0.001$.
 Probabilities calculated as in Table VIII.

Onset of Action (a) Initial Studies

At an early stage the impression was gained that the full hypotensive effect of propranolol took some weeks to reach its maximum. We briefly reported the blood pressures of a patient shown in Fig. 4 (Prichard and Gillam, 1966) who took part in a double-blind trial of propranolol in angina (Gillam and Prichard, 1965).

FIG. 4.—Man aged 46 with essential hypertension. (Fundi grade IV, E.C.G. left ventricular hypertrophy, blood urea 40 mg./100 ml.). Supine blood pressure and pulse in patient who took part in double-blind trial of propranolol in angina pectoris. FIG. 5.—Man aged 36 with essential hypertension. (Fundi grade I, E.C.G. no left ventricular hypertrophy, blood urea 31 mg./100 ml.) Supine blood pressure and pulse before, during, and after period of placebo administration.

(b) Subsequent Studies

Subsequently we performed experiments to confirm this gradual onset of action. Patients were seen repeatedly under standard conditions, and blood pressures were taken with the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose *et al.*, 1964). Readings were taken one and three minutes after patients had lain on the couch and one minute after standing.

(1) Fig. 5 illustrates the supine blood pressure and pulse from one such experiment over a period of 160 days. On propranolol 40 mg. q.d.s. the patient's last blood pressure was 120/89, and pulse 60. After change to placebo, over a period of 19 days his blood pressure gradually rose to 157/112. His last reading on placebo was 159/115, pulse 78. After 21 days back on active drug the blood pressure was 130/92, pulse 56; subsequently

there was apparently a further fall, and the final reading was 117/86, pulse 60. The pulse-rate changes in this patient were rather erratic, but there was no evidence of a progressive fall; three days after resuming active tablets the pulse was 60; 100 days later an identical rate was recorded.

(2) A similar response was seen in two other patients. After propranolol the blood pressure fell fairly rapidly over three weeks, with a possible further fall over another three weeks. We have reported one such case (Prichard, 1968b).

(3) In a mild hypertensive the last supine blood pressure on propranolol was 122/78, and pulse 60. After two days on placebo his blood pressure was 137/82; after five days on placebo it was 148/100. There was no further rise, and in fact five weeks later his supine pressure was 145/91. After two days back in propranolol it was 130/80. In another, milder, hypertensive this "square wave" response of blood pressure was also seen.

(c) Prolonged Follow-up

The greater part of the fall in blood pressure after final adjustment of the dose appears to occur within the first three weeks, and some further fall may occur over the next month.

The blood pressures in a group of patients who had been under prolonged observation in the clinic and were then changed to propranolol have been examined. The records of groups of patients on bethanidine, guanethidine, or methyldopa have also been analysed. The initial blood pressures (zero) are those recorded at the first visit to the outpatient department after stabilization of the dose of drug concerned; subsequent blood pressures are those taken one and three months later.

All patients were seen by the same physician at each visit, and blood pressures were taken with the London School of Hygiene and Tropical Medicine sphygmomanometer by the same observer physician for each patient, over the period of observation analysed. The records for bethanidine, guanethidine, and methyldopa were taken from the trial previously reported (Prichard *et al.*, 1968a). All patients included in this analysis were under repeated observation in the clinic at regular intervals for at least three months before final stabilization of the drug concerned, to minimize the hypotensive effect that often occurs initially from increased physician interest. Patients not meeting these two criteria were excluded.

The average blood pressure at time "zero" on propranolol was 147/95 mm. Hg supine (pulse 59) and 140/101 mm. Hg (pulse 66) standing, and at one month 139/87 mm. Hg (pulse 59) supine and 132/94 mm. Hg (pulse 67) standing. These changes in blood pressure were all significant. There was no further drop at three months—139/88 mm. Hg (pulse 59) supine and 132/95 mm. Hg (pulse 63) standing (figures for two months were very similar to those at three). The dose was stabilized on average 3.29 weeks before time zero, and change from previous therapy was completed 3.26 weeks before this. The dose of propranolol over this period was reduced, on average.

In patients on bethanidine, guanethidine, and methyldopa under similar conditions there was no significant change of supine or standing blood pressure in spite of an average increase in the dose of drug given.

Fig. 6 shows the supine systolic, diastolic, and mean (with standard error) blood pressures and the dose of drug expressed as a percentage of the dose at time zero, in the groups of patients on bethanidine, guanethidine, methyldopa, and propranolol.

Effect of Propranolol with other Hypotensive Drugs

Though a formal study has not been made, we have many instances where the hypotensive effect of propranolol appears additive to that of diuretics, bethanidine, guanethidine, or

methyldopa, as is also its effect on blockade of the sympathetic to the heart. Propranolol has also been used in combination with hydralazine and reserpine.

FIG. 6.—Supine blood pressure and pulse in patients on bethanidine, guanethidine, methyldopa, or propranolol who had been under regular observation for at least three months before stabilization of drug concerned. 0=visit after stabilization; 1 and 3=visits one and three months later. Differences in mean B.P. on propranolol at "0" and 1 month, $0.005 > P > 0.001$, systolic pressure $0.05 > P > 0.025$, diastolic pressure $0.005 > P > 0.001$ (probabilities calculated as in Table VIII). All other changes not significant. (Bars indicate standard errors of mean blood pressure.)

Side-effects, Subjective Feeling

Side-effects spontaneously mentioned by patients were: tiredness in four, dreams in one (present in three others, but abolished by taking last dose of propranolol at least four hours before bed), illusions on waking in one, looseness of the bowels in one, cold extremities in three, occasional dizziness in three, and morning weakness in one patient who had experienced similar symptoms on all previous therapy. In addition other patients mentioned slight nausea, abolished by taking tablets with food.

In order to obtain some evidence of the comparative subjective merit of propranolol compared with other drugs, a questionnaire was sent to those 31 patients who had been completely transferred from a sympathetic blocking drug within the last 18 months, excluding those who also had angina pectoris or severe renal insufficiency. The retrospective nature of this inquiry should be emphasized. There were 15 patients who had previously been on bethanidine, six on guanethidine, and 10 on methyldopa.

Question 1: Comparison with Previous Drug

Patients were asked if they felt better, the same, or worse than on the previous drug; 26 replied "better," 2 "worse," 3 "the same." Patients were asked to grade their replies, and of the 26 who felt better one replied "a little better," 12 "better," and 13 "much better." One of the two who felt worse replied "a little worse" and one did not grade his reply.

The patients were asked to record their reasons.

(a) *Patients feeling better, previously on bethanidine (11).*—Five cited the absence of dizziness (three mentioned particularly on exercise, and one of these on micturition as well) as the reason for feeling better; two the return of ejaculation, two "no tiredness," one "not depressed," and one merely "no side-effects."

(b) *Patients feeling better, previously on guanethidine (5).*—One mentioned the absence of diarrhoea, one felt less tired and able to think more clearly, another felt able to work better, and two did not state reasons.

(c) *Patients feeling better, previously on methyldopa (10).*—Four previously had loose bowels on methyldopa, not present on propranolol; three were no longer sleepy, one of these reporting

that he felt better mentally; another also felt less tired, but tiredness later returned. One merely felt better, and one patient had some probably intercurrent mouth ulcers, which subsided after change from methyldopa.

(d) Of those patients who felt worse one mentioned constipation; previously she had been taking guanethidine. Another reported "intestinal discomfort" and diarrhoea (previously bethanidine had been taken); however, this subsided without change of therapy.

Question 2: General Feeling

Patients were asked to record their general feeling according to categories, asked in the following order: well, 16; fair, 4; ill, none; very well, 11.

Question 3: Nocturia

Seventeen patients experienced nocturia on propranolol, 14 did not; on previous drugs 26 had nocturia, five did not.

Patients were asked to estimate the number of times they usually had nocturia each night; the maximum reported was four, "occasionally" was scored as a half. No individual patient had more nocturia on propranolol than on the previous drug. The average incidence of nocturia each night in the 31 patients on propranolol was 0.498, on the previous drugs 1.024, $P < 0.001$ (calculated from the differences of $\log n+1$ in view of the zero scores).

Question 4: Side-effects

Patients were asked three questions about actual side-effects. Had they noticed side-effects that they thought were definitely due to propranolol? (13 replied yes, 18 replied no); probably due to propranolol? (9 replied yes, 22 replied no); possibly due to propranolol? (5 replied yes, 26 replied no).

Of the total of 31 patients 11 had no side-effects at all, 7 had transient side-effects, and 13 experienced more-prolonged effects.

Two patients had difficulty in sleeping if they took the last dose of propranolol late at night; this was transient in one additional patient. One patient noticed tiredness, and in one this was present but transient. One had illusions on waking, and three had occasional dreams.

Two patients had persistent constipation; in another patient constipation occurred but later subsided. Three noticed looseness of the bowels; in one this symptom was transient. Three patients mentioned indigestion.

One patient noticed the cold persistently, and in one this symptom subsided. Dizziness and weakness of the leg occurred in one patient. Reduced libido was mentioned by two patients; a streaming nose and increased weight were each experienced by one patient.

Weights and Blood Ureas

Weights and blood ureas were compared in patients who received either diuretic on both propranolol and previous therapy or who had no diuretic with either drug. There were no significant differences in any group.

Discussion

Level of Blood Pressure Control

In most previous trials of potent hypotensive drugs control of the standing diastolic pressure to 100 mm. Hg was regarded as good control. As has been recently discussed (Prichard *et al.*, 1968a) about 40 to 60% of patients in various series treated with bethanidine, guanethidine, or methyldopa usually reach this level of control. In our series 92 of the 105 patients treated with propranolol achieved a blood pressure of this level (Table I)—that is, 84% of the original 109. The severity of the hypertension varies from series to series; this and other variations in methods reduce the value of comparison between different

reports. The present series (see under Patients) seems to be of at least average severity.

There have been reports of propranolol in hypertension suggesting it has no, or only a minor, effect (Paterson and Dollery, 1966; Richards, 1966; Waal, 1966; Richardson, Freund, Gear, Mauck, and Preston, 1968). However, these authors used it either for a shorter period or in a fixed or overall lower dosage.

Similarly, Humphreys and Delvin (1968), in a study of 18 Jamaican patients with hypertension, used propranolol alone for two or four months continuously up to a maximum of 360 mg. daily; they concluded that propranolol had no hypotensive effect. In this study, however, eight patients had supine and/or standing diastolic pressures below 110 mm. Hg on propranolol; in all instances pressure was higher on placebo. Hence these patients achieved some reduction of blood pressure with propranolol within the 360 mg. limit. The blood pressures of the other 10 patients were higher than this on both propranolol and placebo. These findings are in accord with our experience; for example, among the 28 patients previously treated with bethanidine (Table II) 9 required more than 360 mg. daily, and among the 19 patients receiving less than this 13 were also given a diuretic.

Recently in a longer study (average 32 weeks) in 19 patients it was found that propranolol was an effective hypotensive agent in those with mild and moderately severe hypertension (Frohlich, Tarazi, Dustan, and Page, 1968). Baczko, Dabrowska, and Wocial (1967) also showed a hypotensive effect in a series of 17 patients.

As we have deliberately treated many patients who were previously on other potent drugs we are able to make some comparisons. Of the 80 previously treated with bethanidine, guanethidine, or methyldopa, 46 achieved supine or standing diastolic blood pressures of 100 mm. Hg or less (Table I). On propranolol 70 did so (seven of these having the previous drug continued at a lower dosage). The average standing diastolic blood pressure tended to be lower on propranolol than on guanethidine (Table III) or methyldopa (Table IV). Further evidence that propranolol is a drug of similar potency to bethanidine, guanethidine, and methyldopa is given in Table VIII. In this group of patients, who received these three drugs in random order (Prichard *et al.*, 1968a) and then later propranolol, the average standing diastolic pressure on all four drugs was almost identical. In each patient on each drug the average of seven readings was taken; the patients were thoroughly familiar with the clinic routine (see above).

Control of Supine Blood Pressure

The excessive falls in blood pressure that result from physiological events which stress the sympathetic nervous system limit the dose of sympathetic blocking drug that can be used. At low rates of sympathetic activity—that is, the supine position—there is therefore usually insufficient blockade and blood pressure is less well controlled. There are differences between the drugs: thus for equal diastolic pressures in the standing position the supine pressure on methyldopa is lower than on guanethidine, and the supine pressure on guanethidine is slightly but significantly lower than on bethanidine, though, subjectively, patients preferred bethanidine (Prichard *et al.*, 1968a). When standing blood pressure is lowered by propranolol the supine blood pressure is also controlled to a similar degree (Tables II–VI). When standing pressures are similar the differences in supine pressures between propranolol and bethanidine, guanethidine, and methyldopa are highly significant (Tables VIII and IX).

Posture and Exercise; Environmental Temperature

When blood pressure is controlled with propranolol there is no postural drop in blood pressure or a drop on mild exercise

on ascending and descending 18 stairs (Tables II–VI, VIII, IX). This is illustrated in the examples given (Figs. 1 and 2). The difference in response to posture and exercise in patients who had been treated with bethanidine, guanethidine, or methyldopa and propranolol is illustrated by Table IX and Fig. 3. The difference between propranolol and each of the other drugs is highly significant. The response of the blood pressure to posture and erect exercise is largely the result of compensatory activity of the sympathetic to blood vessels, and propranolol does not inhibit this effect. The contribution of increased sympathetic activity to the heart is important in exercise, but at modest levels of exercise there is no fall of blood pressure in patients on propranolol (exercise sufficient to produce a fall in blood pressure on bethanidine, guanethidine, or methyldopa). Neither do high levels of exercise result in a further fall of blood pressure after prolonged oral administration of propranolol (Prichard, Shinebourne, Fleming, and Hamer, 1968b) or intravenous administration of propranolol (Shinebourne, Fleming, and Hamer, 1967) in hypertensive patients.

It has been shown that increasing the environmental temperature from 7° to 30° C. does not influence the response of blood pressure to posture and exercise in patients being treated with propranolol for their hypertension, in contrast to those being treated with bethanidine and guanethidine, where there is increased postural and exercise hypotension as temperature is increased (Prichard and Gillam, 1968). Raising the temperature from 7° to 30° C. in four patients on methyldopa did not increase the postural drop in blood pressure.

Valsalva's Manoeuvre and Intravenous Propranolol

The response to Valsalva's manoeuvre further illustrates that after propranolol vasoconstriction is unimpaired (Prichard and Gillam, 1966). While blood pressure is unchanged after intravenous propranolol the cardiac component of Valsalva's manoeuvre is reduced, and there is a reduction of the tachycardia of effort and a lower overshoot. After prolonged oral propranolol the vasoconstriction still occurs, in contrast to its absence on bethanidine (Prichard, 1968b). Others have found that intravenous administration of propranolol in hypertensives has no hypotensive action at rest (Ulrych, Frohlich, Dustan, and Page, 1968). Shinebourne *et al.* (1967) report no significant change in diastolic supine and standing blood pressures after intravenous propranolol, but a fall in systolic pressure.

Effect of Propranolol on Cardiac Output

Cardiac output is reduced by propranolol at rest and on exercise after intravenous administration in normals (Epstein, Robinson, Kahler, and Braunwald, 1965), ischaemic patients (Hamer and Sowton, 1965), and hypertensives (Shinebourne *et al.*, 1967). This has been confirmed in hypertensive patients at rest (Ulrych *et al.*, 1968). Cardiac output is also reduced at rest and on exercise in hypertensive patients after prolonged oral administration (Prichard *et al.*, 1968b) and also in patients at rest in the supine position (Frohlich *et al.*, 1968).

Use with Other Drugs

Propranolol may be used in combination with a variety of drugs. Table V summarizes the records from 11 patients who were receiving propranolol in addition to other drugs—bethanidine, guanethidine, methyldopa, reserpine, or hydralazine. We have examples with patients previously on bethanidine, guanethidine, or methyldopa where approximately half the dose of propranolol and the previous drug gave a lower blood pressure than either alone.

Propranolol is potentiated by diuretics. In the present series about equal numbers of patients received a diuretic with pro-

pranolol as with their previous treatment (Table VII). Though propranolol usually controls the blood pressure with or without a diuretic, it may also be used with a variety of other drugs.

Side-effects

Accurately to compare side-effects experienced with propranolol and with sympathetic blocking drugs it would be necessary to carry out a formal comparison. Patients often appear subjectively better on propranolol. This was supported by the results of the questionnaire sent to patients transferred from bethanidine, guanethidine, or methyldopa within the last 18 months. However, as this inquiry was retrospective these results must be regarded merely as suggestive, and patients usually prefer the most recently administered drug (Prichard *et al.*, 1968a).

Stephen (1966) has discussed many of the side-effects experienced from propranolol.

Cardiovascular and Respiratory Effects

Chronic heart failure was responsible for withdrawal of propranolol in two of the 105 patients treated, and heart failure was possibly the reason for intolerance in one of the four patients who received the drug for a very short time. We have previously reported on an ischaemic patient who was precipitated into acute heart failure (Gillam and Prichard, 1965) after two days on 10 mg. q.d.s. Though heart failure may be precipitated in patients whose cardiac compensation is critically dependent on the sympathetic drive to the heart, provided the possibility is recognized we do not consider it a problem in the use of propranolol in hypertension. If a patient has a history of left ventricular insufficiency (even without any signs of heart failure on either physical or chest x-ray examination) before administration of propranolol it is our practice first to give a diuretic and digitalis.

The risk of precipitating heart failure in an individual patient is relatively greater at *lower* dosage. When beginning therapy, increasing the dose from zero to 10 mg. q.d.s. is a greater percentage increase in dose than, say, the increment from 100 mg. q.d.s. to 120 mg. q.d.s., or from 400 to 450 mg. q.d.s. As small percentage increases can be readily made at high dosage the risk is less, the only sudden occurrence of cardiac decompensation in our experience in a total of some 200 patients (in hypertension, angina, arrhythmias, phaeochromocytoma) over nearly four years, with dosage up to 1,000 mg. q.d.s., has been at the commencing dosage of 10 mg. q.d.s. We have had one hypertensive patient who while on 150 mg. q.d.s. experienced a myocardial infarction, with no apparent untoward effect from his dose of propranolol. Uncontrolled heart failure is, however, a contraindication to propranolol. Asthma is another reason for avoiding propranolol, as it increases airways obstruction in these patients (McNeill, 1964). There were no cases of asthma in the present series.

Cold extremities, noticed usually in colder weather, are not uncommon. This finding is due to a reduction in peripheral blood flow (Gillam and Prichard, 1966), which in turn is probably dependent on a reduction in cardiac output.

Dizziness is exceptional in patients receiving propranolol, and not infrequently patients noticed improved exercise tolerance after change from a sympathetic blocking drug to propranolol, due to the loss of the marked exercise hypotension seen on the former drugs.

Central Nervous System Side-effects

In the original series of 109 patients there was one case of depression, which rapidly subsided when propranolol was

stopped. We have previously reported one anginal patient who became depressed on increasing the dose from 40 to 50 mg. q.d.s. and then improved when the dose was reduced to 40 mg. q.d.s. (Gillam and Prichard, 1965).

Tiredness was mentioned spontaneously in four patients continuing on the drug and was responsible for the drug being stopped in one patient. Tiredness is a limiting factor in dosage in a few patients, but this side-effect seems less frequent than with methyldopa. Several patients comment that they were less tired on changing from methyldopa.

Vivid dreams have been experienced by four patients—abolished in three, and reduced in the other—by taking the fourth dose not more than four hours before going to bed. Occasional difficulty in getting off to sleep may be similarly alleviated. In one patient it was necessary to prescribe the drug three times a day (80, 80, and 40 mg.) with the last dose at 6.30 p.m. (see Pritchard, 1968a).

Gastrointestinal Side-effects

In one patient severe indigestion was the reason for stopping the drug. Another patient, an elderly woman, could not tolerate the drug because of nausea, and another because of heartburn. Direct questioning found three other patients with indigestion. Other patients have mentioned slight nausea, abolished by taking the tablets with food. Looseness of the bowels or constipation may occasionally occur.

Weight

One patient mentioned increase in weight due to propranolol. There is no significant difference in the weight of patients treated with bethanidine, guanethidine, or methyldopa compared with their weight when treated with propranolol.

Possible Mechanism of Action

There seems little doubt that in the moderate and severe hypertensive treated with oral propranolol, though there is immediate full cardiac slowing, the full hypotensive effect is often delayed up to one to two months (Figs. 4 to 6). There is no delay in the reduction of the cardiac component of Valsalva's manoeuvre. Propranolol immediately reduces cardiac output, and the possibility that long-term administration may result in a progressive fall in cardiac output is being investigated (Prichard *et al.*, 1968b). There is no progressive fall in heart rate, so a progressive fall in cardiac output seems unlikely, more especially as it seems that the reduction in cardiac output following prolonged oral propranolol can be explained largely, though not entirely, in terms of the reduced pulse rate (Shinebourne, 1968).

It is possible that the hypotensive effect of propranolol is not due to its beta-receptor-blocking action. However, other beta-blocking drugs have a hypotensive effect—pronethalol (Prichard, 1964)—and preliminary observations suggest that Inpea (*N*-isopropyl-*p*-nitrophenylethanolamine), though easily prone to produce side-effects, can also lower the blood pressure (Prichard, 1968b). Inpea is of interest because, in contrast to propranolol and pronethalol, it does not produce any local anaesthetic effects (Teotino, Polo Friz, Steis, and Della Bella, 1963; Somani and Lum, 1965).

In our previous reports we tentatively proposed that the hypotensive action of propranolol is a result of its blockade of the cardiac sympathetic (Prichard and Gillam, 1964; Prichard, 1966). The blocking of the cardiac sympathetic reduces the cardiac component, and therefore the magnitude of transient rises in blood pressure in response to various stimuli—as seen, for example, with Valsalva's manoeuvre. To explain the delayed onset of full hypotensive action it was suggested that

the baroreceptors are gradually conditioned by the reduced pressor responses to regulate the blood pressure at a lower level, so that mean blood pressure falls. The baroreceptors are thus conditioned by the reduction in the peak of pressor responses to produce vasomotor inhibitory impulses at a lower level of blood pressure. A parallel situation probably exists when a hypertensive patient is put to bed. Bed rest results in a reduction in sensory stimuli (and baroreceptors regulate the blood pressure at a lower mean level), and over several days blood pressure falls by an amount varying with the individual patient. When blood pressure is controlled by propranolol, while the baroreceptors regulate the blood pressure at a lower mean level, there is a virtually normal response to cardiovascular reflexes, demanding acute alterations in vascular tone.

Dosage and Use

There is a wide variability in the sensitivity of patients to propranolol, and this necessitates individual adjustment of the dose. The dose range used in this series ranged from 5 mg. b.d. to 1,000 mg. q.d.s. (Table VII). Provided they are carefully adjusted the high-doses appear to be safe (see under Methods).

Conclusions

Propranolol is a hypotensive drug of a potency that appears to be comparable to that of bethanidine, guanethidine, and methyldopa. Propranolol usually results in good control of the supine blood pressure, and it does not prevent the vascular response to important physiological stresses such as posture, exercise, and increased environmental temperature. It differs in mode of action from other established potent hypotensive drugs. Postural and exercise hypotension is not a feature of propranolol therapy. Though no formal comparison has been made it seems possible that it may produce fewer side-effects than other potent drugs.

It is considered to be a valuable drug in the treatment of hypertension. It is also particularly useful in patients who have a postural drop in blood pressure on other therapy without good control of the supine pressure.

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Acetazolamide and Sodium Bicarbonate in Treatment of Salicylate Poisoning in Adults

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Summary: Ten adults suffering from salicylate overdosage were treated successfully with a combination of sodium bicarbonate and acetazolamide to exploit the increase in salicylate clearance which is known to occur in very alkaline urine. The advantages of the method include the absence of important complications and the small volume of fluid required.

Introduction

More than 20 years ago the renal clearance of free salicylate was shown to increase approximately fivefold when the pH of the urine was raised from 7 to 8 (Smith *et al.*, 1946). Alkaline diuresis has since become an established method of treating salicylate overdosage, but its exponents—for example, Dukes *et al.*, 1963; Beveridge *et al.*, 1964; Matthew and Lawson, 1967—have laid more emphasis on achieving a high urine flow than on a very high urine pH. If this emphasis were reversed some of the hazards of a very rapid throughput of fluid might be avoided.

MacPherson *et al.* (1955) suggested the use of a combination of acetazolamide (Diamox) and sodium bicarbonate to maintain a urine of nearly maximal alkalinity. Either substance alone will have this effect, but with acetazolamide it wears off as the plasma bicarbonate and pH fall (Counihan *et al.*, 1954); with bicarbonate it is sustained, though at the expense of some elevation of plasma bicarbonate and pH (Pitts *et al.*, 1949). The combination should produce a sustained effect with little change in blood pH. However, where there is an initial metabolic acidosis, which makes some elevation of plasma bicarbonate and pH desirable, the effect of acetazolamide in delaying this elevation is likely to be slight (Schwartz *et al.*, 1959). Though treatment with acetazolamide and bicarbonate has had varying success in children (Schwartz *et al.*, 1959; Feuerstein *et al.*, 1960), we feel that the results in a small series of adult patients are sufficiently favourable and consistent to warrant this report.

Material and Methods

Studies were made of 10 patients admitted to the Royal Portsmouth Hospital with moderate or severe salicylate intoxication. Details of the cases are included in Table I. Cases A and B are listed separately because of minor deviations from the treatment regimen (see Results). Treatment was begun if

the serum salicylate level was above 50 mg./100 ml. or if obvious clinical signs of salicylate intoxication were present.

On admission one venous blood sample was taken for salicylate estimation, and a second sample one hour later provided that treatment had not been started. A small-volume gastric lavage was performed. The patient was then catheterized, and closed bladder drainage set up. An intravenous infusion was started and 250 mg. of acetazolamide given intravenously.

Intravenous Infusion.—In the first hour, 1 litre of 1.4% sodium bicarbonate. In the second hour, 1 litre of 1.4% sodium bicarbonate plus 20 mEq KCl. Then if the patient is still clinically dehydrated, 1 litre of 0.9% sodium chloride plus 20 mEq KCl hourly until the patient is rehydrated. If the patient is not clinically dehydrated (or when dehydration has been corrected by 0.9% sodium chloride), 1 litre of 1.4% sodium bicarbonate plus 40 mEq KCl two-hourly for four hours.

If treatment is still required (serum salicylate >40 mg./100 ml.) a further 250 mg. of acetazolamide is given intravenously and the following solutions are infused in rotation every two hours: (1) 1 litre of 0.9% sodium chloride plus 40 mEq KCl, and (2) 1 litre of 1.4% sodium bicarbonate plus 40 mEq KCl.

The infusion should be stopped and this method of treatment abandoned if a positive fluid balance of two litres develops after the correction of dehydration.

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The following investigations were carried out.

Clinical.—Frequent physical examinations were made, particular attention being given to the state of hydration and to cardiovascular, respiratory, and neurological disturbances.

Blood Samples.—Venous samples were taken on admission and after each litre of intravenous fluid, and the following serum constituents were measured: creatinine, sodium, total CO₂, chloride, potassium, calcium, magnesium, and salicylate. Capillary blood pH measurements (Docrat and Kenny, 1965) were made initially, after two hours, and at the end of treatment.

Urine Samples.—Urine collections were made serially, each ending when a litre of fluid had been given intravenously—that is, after one to two hours. Urine pH and volume were measured and an aliquot was refrigerated for creatinine, sodium, chloride, potassium, and salicylate estimation.

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