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THE EFFECT ON BLOOD PRESSURE OF β-ADRENOCEPTOR BLOCKING DRUGS ADMINISTERED ONCE DAILY AND THEIR DURATION OF ACTION WHEN THERAPY IS CEASED

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1 The control of blood pressure achieved was similar whether pindolol or propranolol was given once or three times daily.

2 When the drugs were ceased the antihypertensive effect lasted for longer than 24 h. There was no rebound hypertension.

3 The full effect of the drug on blood pressure was seen within 24 h of its recommencement.

4 Changes in blood pressure, pulse rate, and plasma renin activity occurred but these were not considered to be causally related.

5 The response of plasma renin activity to posture was ablated when the patients were receiving β-adrenoceptor blocking drugs.

Introduction

One of the most important problems in the treatment of hypertension is the ability of the patient to comply with drug treatment programmes (Cohn, 1974). Many currently available drugs are administered at frequent intervals and frequency of administration is often based on the half-life of the drug. Few studies have investigated the effects of once daily dosage of drugs on blood pressure but if this were possible it would make compliance with a therapeutic regime more likely. Many patients at some stage of their treatment will omit their drugs for one or two days, and the importance of this has been emphasized by the rebound hypertension that may occur when clonidine is ceased (Hansson, 1973).

This study was planned to investigate whether once a day administration of propranolol or pindolol controlled the blood pressure as effectively as the same dosage of drug given in three divided dosages. In addition, the duration of the antihypertensive action when the drug was ceased and the rate at which hypertension was controlled when the drug was restarted were studied. During the later study the relationship between the change in blood pressure and the change in plasma renin activity were studied.

Methods

The patients studied were male, aged 44-63 years. Serum creatinine was less than 0.17 μmol/l in all patients and all patients had essential hypertension.

A group of eleven patients whose blood pressure had been satisfactorily controlled with a β-adrenoceptor blocking drug and a diuretic were selected. Prior to therapy the diastolic blood pressure of all patients had been greater than 105 mmHg and control below 100 mmHg had not been achieved by a diuretic alone. The diuretic and salt intakes were not altered throughout the study. All patients were receiving a β-adrenoceptor blocking drug three times per day at approximately 07.00, 13.00 and 19.00 h. While receiving a constant dose of their medication the blood pressure of eleven patients (lying 10 min, then standing 5 min) was recorded in duplicate on three occasions 1 month apart, between 09.00 and 10.00 h. The study described below was then performed and the patients were given the same dose of their β-adrenoceptor blocking drug once daily. The blood pressure was then recorded on three subsequent occasions 1 month apart. The mean blood pressures on once a day and three times a day therapy were compared using a paired

t-test. On the day immediately before changing the administration to once a day the patients' lying (10 min), standing (5 min) and exercise (75 steps) blood pressure and pulse rate were recorded hourly from 08.00 to 16.00 h. The patients were ambulant between blood pressure recordings. One week later, when on the same dose which was now taken once a day at 20.00 h, the same test was repeated. On each occasion plasma renin activity was measured on blood taken at 08.00, 12.00 and 16.00 h immediately after the lying blood pressure. The blood pressures of the patient throughout the day were compared. A mean of the daily blood pressure was obtained for each patient and the blood pressure when the group was on once a day therapy was compared with the blood pressure on three times a day, (paired *t*-test).

In twelve other patients a different study was performed. These patients were on a β-adrenoceptor blocking drug and a thiazide diuretic. On the first day of the study they continued their normal dose of β-adrenoceptor blocking drugs. They were seen as outpatients; they were put to rest at 07 h 30 min and the lying blood pressure and pulse recorded at 08.00, 09.00 and 10.00 h. Lying, standing and exercise blood pressure and pulse rates were measured at 11.00 and 12.00 h. At 11.00 h before standing, blood was taken for plasma renin activity: after the period of exercise a further sample of blood was taken for plasma renin estimation. β-adrenoceptor blocking drugs were then ceased but the same dose of thiazide diuretic was continued. On day 2, 3 and 8 the same procedure as above was carried out. The patients were then recommenced on three times a day administration of β-adrenoceptor blocking drugs in the same dose and regime as before. On day 9, 10, and 15 the tests were repeated.

The changes in a person's blood pressure, pulse and plasma renin were individually examined. The means of the lying blood pressure, pulse and plasma renin activity on each day were subtracted from the mean value on day 1 to find the change in these variables with cessation of their β-adrenoceptor blocking drug. The mean values obtained after reintroduction of the drug were subtracted from the mean values on day 8 to assess the changes when the drug was reintroduced. The significance of any changes were assessed using a paired *t*-test. Correlations between variables were calculated by the method of least squares.

Results

The mean blood pressure when the patients were on once a day therapy was not different from that when receiving β-adrenoceptor blocking drugs three times a day. This was true either measured at out-patients over a 3 month period (Table 1) or more frequently during the day (Table 2). This finding was also true for the standing and exercise blood pressures and pulse rates. One patient had a significantly higher lying, standing and exercise blood pressure when given pindolol once a day (patient 2). This was seen during the one day test and also during the long term observations (Table 1). During the one day test the mean blood pressure in the afternoon on once or three times a day therapy was not different from that in the morning with either pindolol or propranolol (Table 2). The results for propranolol and pindolol were similar except for the finding that pulse rates were lower in patients receiving propranolol. The plasma renin levels on the two dosage regimes were similar (Table 2).

In the second study when propranolol or pindolol were ceased the blood pressure 24 h later was slightly higher in both groups of patients (Figure 1). The mean blood pressure was higher in every patient. The pulse rate also showed a slight rise. Forty-eight hours after β-adrenoceptor blocking drugs had been ceased the pulse rate and blood pressure had risen markedly. There was little further change by day 8. In no patient did the blood pressure rise significantly above their pre-treatment level or their level when treated on a thiazide diuretic alone. In all patients the rise in blood pressure was equal to or less than the decrease that had occurred after the institution of β-adrenoceptor blocking drugs. When propranolol or pindolol were recommenced the blood pressure and pulse rate both fell within 24 h, and there was no further fall in the next week.

In general, the plasma renin activity of patients fell when β-adrenoceptor blocking drugs were administered and in addition, the response to posture and exercise was blunted or abolished (Table 3). This appeared to be more complete with propranolol than with pindolol. Patient 13 had no postural response on or off β-adrenoceptor blocking drugs and there was no change in plasma renin activity when pindolol was given. The blood pressure when not receiving pindolol was 154/102 and fell to 136/84 when pindolol was administered.

When the changes in plasma renin activity (PRA) and blood pressure were compared with either cessation or commencement of therapy, the linear regression was BP (diastolic) = 22.0 PRA−3.8 ($n = 62$, $r = 0.54$ $P<0.001$). A similar result held for changes in systolic BP. There was also a significant correlation between changes in pulse rate and changes in plasma renin activity, pulse rate = 28.1 PRA−4.4 ($n = 62$, $r = 0.53$ $P<0.001$), and between changes in pulse rate and

Table 1 Lying blood pressure (mean of six readings) at outpatients on different regimes of administration of β-adrenoceptor blocking drugs

Patient number	Drug (mg)	Pretreatment BP (mm Hg) S	D	BP on diuretic alone (mm Hg) S	D	β-adrenoceptor blocking drug three times a day BP (mm Hg) S	D	once a day BP (mm Hg) S	D
1	P 30	170	112	160	107	134	82	132	89
2	P 30	160	108	152	106	165	98	167	106*
3	P 25	185	121	161	115	146	102	138	97
4	P 45	152	106	147	101	135	87	131	85
5	P 15	160	105	145	100	134	78	125	81
Mean		165	110	153	105	143	89	139	91
s.e. mean		6	3	4	3	6	5	8	5
6	Pr 120	175	122	161	114	131	98	144	103
7	Pr 320	166	117	154	111	146	96	136	91
8	Pr 360	170	125	163	117	166	108	158	109
9	Pr 240	155	105	150	100	179	90	178	90
10	Pr 600	145	105	148	105	136	80	134	85
11	Pr 160	162	108	160	102	146	94	146	93
Mean		162	113	156	108	151	94	149	95
s.e. mean		5	4	3	3	9	4	8	4

* significantly higher than control on β-adrenoceptor blocker, $P<0.01$
P pindolol; Pr propranolol S systolic; D diastolic
All patients were on chlorothiazide (500 mg b.d.)

Table 2 Blood pressure, pulse rate and plasma renin activity during the one day test, (mean ± s.e. mean results)

		Propranolol (n = 6) three times a day	Propranolol (n = 6) once a day	Pindolol (n = 5) three times a day	Pindolol (n = 5) once a day
Lying BP (mm Hg) Morning	S	144 ± 3	141 ± 3	133 ± 3	135 ± 3
	D	90 ± 4	87 ± 2	86 ± 3	88 ± 4
	Pulse (beats/min)	66 ± 3	65 ± 3	78 ± 2	79 ± 1
Lying BP (mm Hg) Afternoon	S	146 ± 3	144 ± 3	132 ± 2	141 ± 4
	D	91 ± 3	91 ± 3	92 ± 4	93 ± 4
	Pulse (beats(min)	68 ± 2	64 ± 2	76 ± 2	77 ± 2
Standing BP (mm Hg)	S	138 ± 7	135 ± 7	131 ± 5	137 ± 5
	D	97 ± 5	95 ± 5	93 ± 2	96 ± 4
	Pulse (beats/min)	72 ± 2	71 ± 2	80 ± 1	78 ± 2
Exercise BP (mm Hg)	S	153 ± 10	144 ± 5	149 ± 9	144 ± 5
	D	100 ± 5	96 ± 5	97 ± 3	95 ± 4
	Pulse (beats(min)	81 ± 3	77 ± 3	91 ± 3	89 ± 3
Plasma renin activity (pmol angiotensin 1 ml^{-1} h^{-1})		0.34 ± 0.10	0.27 ± 0.11	0.22 ± 0.07	0.27 ± 0.06

No significant difference between variables on once and three times a day therapy when compared by paired *t*-test. The pulse rate of patients on propranolol was significantly lower $P<0.01$ than the pulse rate on pindolol. No significant difference between morning and afternoon blood pressure.

changes in blood pressure, BP = 0.64 pulse rate−0.75 ($n = 62$, $r = 0.84$ $P<0.0001$).

Discussion

In this study the control of blood pressure achieved with once a day therapy was similar to that achieved with the same dose of β-adrenoceptor blocking drugs given three times a day. The duration of effect lasted for 24 h and when the drug was ceased there was no rebound phenomenon. When the drug was reinstituted the blood pressure and pulse returned to the previous levels within 24 h. Certain of the patients in this study had side effects from their therapy. Two patients who had had nightmares associated with pindolol therapy found that these were avoided by taking their entire dose in the morning. One patient who became drowsy after propranolol found that this side effect was of no consequence when he took his dose before going to bed. This study demonstrates that propranolol and pindolol can be given on a once daily basis. We do not necessarily give all patients β-adrenoceptor blocking drugs on a once daily basis, but give the patient the option of taking them either once or twice a day. Male patients, in particular, find that this avoids the inconvenience of a midday dose which they frequently had forgotten in the past.

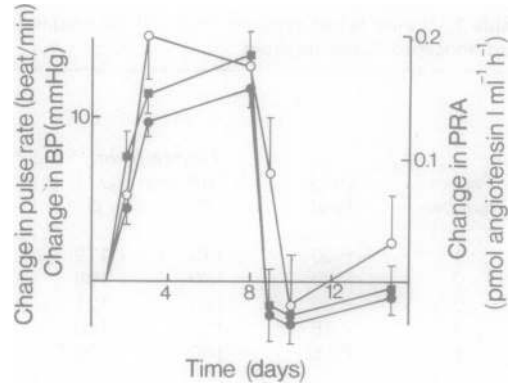

Figure 1 Effect of cessation and reinstitutuion of β-adrenoceptor blocking drugs on pulse rate (□), diastolic blood pressure (●) and plasma renin activity (○) (mean ± s.e. mean results, $n = 12$). The changes compared with the values obtained before cessation of drugs are plotted.

In this study we found that the major part of the antihypertensive response took place within 24 h. This is different from the report by Prichard

Table 3 Response of plasma renin activity to posture and exercise

Patient number	*Drug (mg)*	*Plasma renin activity (pmol angiotensin 1 ml⁻¹ h⁻¹)*			
		No β-adrenoceptor blocking drug		*On β-adrenoceptor blocking drug**	
		Resting	*Exercise*	*Resting*	*Exercise*
12	P 30	0.38	0.54	0.16	0.29
13	P 30	0.43	0.41**	0.44	0.38
14	P 20	0.17	0.21	0.12	0.19
15	P 25	0.16	0.27	0.16	0.10
16	P 25	0.31	0.36	0.22	0.24
17	P 30	0.07	0.13	0.08	0.12
Mean		0.25	0.32†	0.20	0.22
s.e. mean		0.06	0.06	0.05	0.04
18	Pr 320	0.12	0.21	0.09	0.09
19	Pr 120	1.18	1.74	0.84	0.71
20	Pr 160	0.84	1.31	0.62	0.54
21	Pr 120	0.48	0.62	0.41	0.35
22	Pr 160	0.15	0.25	0.07	0.10
23	Pr 160	0.08	0.14	0.05	0.05
Mean		0.48	0.72†	0.35‡	0.31
s.e. mean		0.20	0.30	0.12	0.10

* Taken as mean of values on day 1 and day 15. The response on both days for individual patients were similar.
** When exercised on day 4 off β-adrenoceptor blocking drug PRA also did not rise.
P pindolol; Pr propranolol
† $P<0.05$ compared with resting.
‡ $P<0.05$ compared with no β-adrenoceptor blocking drug.
Other changes are not significant.

& Gillam (1969), but may relate to the patient in this study being more responsive to smaller doses of propranolol. In a previous study we had shown that pindolol has a blood pressure lowering effect within 2 h of oral administration (Morgan, Roberts, Carney, Louis & Doyle, 1975).

In this study we again found that individual patients could have a marked fall in blood pressure with little change in plasma renin activity (Morgan, *et al.*, 1975). The converse a fall in plasma renin activity with no fall in blood pressure could not apply as such patients were excluded by our mode of selection of patients for this study. In this study we do show a correlation between change in blood pressure and change in plasma renin activity, but we also show a correlation between changes in pulse rate and changes in plasma renin activity and between changes in pulse rate and changes in blood pressure. This is a finding similar to that of Buhler, Laragh, Baer, Vaughan & Brunner, 1972, but we believe that these changes are not causally related but result from the fact that β-adrenoceptor blocking drugs have multiple specific actions of which change in pulse rate, change in blood pressure, and change in plasma renin activity are but three examples.

The β-adrenoceptor blocking drugs used inhibited the rise in plasma renin that occurs with posture. This appeared to be more complete with propranolol than with pindolol, but after both drugs the increase with posture and exercise was blunted.

The duration of the antihypertensive effect of β-adrenoceptor blocking drugs make them a suitable drug to use once daily. The absence of severe rebound hypertension and their rapid action when therapy is restarted means that the problems created by missing therapy for 24 or even 48 h are prevented.

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