Br. J. clin. Pharmac (1976), 3, 453-460

THE EFFECT OF PINDOLOL ON PLASMA RENIN ACTIVITY AND BLOOD PRESSURE IN HYPERTENSIVE PATIENTS

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1 The effect of pindolol administered to twenty-six patients with hypertension of unknown origin was compared with respect to blood pressure and plasma renin activity change after increase of the dose over a period of 6 weeks.

2 There was no clear correlation between the fall of plasma renin activity, which in some patients was very marked, and the fall in blood pressure. Some patients with a fall in plasma renin activity did not drop their pressure. Conversely, some with a fall of pressure did not drop their plasma renin activity.

3 The addition of hydrochlorothiazide to the pindolol finally caused further lowering of the blood pressure in all but one patient and the plasma renin activity rose in all but two patients. There was no clear correlation between change in plasma renin activity and the effect on blood pressure.

Introduction

The release of renin from the kidney is stimulated by β-adrenoceptor agonists such as isoprenaline (Winer, Chokshi & Walkenhorst, 1971), and conversely some β-adrenoceptor blocking drugs are very effective in preventing or reducing renin release not only by isoprenaline (Winer *et al.*, 1971; Ganong, 1972), but during the ordinary activities, such as change of posture, of normal subjects (Michelakis & McAllister, 1972). Since the initial statement that β-adrenoceptor blocking drugs like propranolol might be used with the expectation that they would reduce the blood pressure selectively in patients with high plasma renin activity and would be relatively ineffective in those with normal or low plasma renin activity (Bühler, Laragh, Baer, Vaughan & Brunner, 1972; Bühler, Laragh, Vaughan, Gavras, Brunner & Baer, 1973), many investigations have been undertaken to test this statement and the results have been conflicting. It has been claimed that some β-adrenoceptor blocking drugs will lower the blood pressure without affecting plasma renin activity, and conversely, that even when plasma renin activity is lowered, the blood pressure may be little affected (Hansson & Zweifler, 1974; Stokes, Weber & Thornell, 1974). One of the problems with this sort of study is that β-adrenoceptor blocking drugs are rather diverse in their activity and may have β-adrenoceptor stimulating effects, for example on the heart, so if the variable effects on the central nervous system are added to this (Frohlich, Tarazi, Dustan & Page, 1968; Julius, Pascual, Abbrecht & London, 1972; Tarazi & Dustan, 1972; Day & Roach, 1973; Dollery, Lewis, Myers & Reid, 1973), it is perhaps not surprising that there is variability in the relation of blood pressure and plasma renin activity in different studies. Propranolol will block renin release induced by either isoprenaline in the isolated perfused kidney (Vandongen, Peart & Boyd, 1973) or renal sympathetic nerve stimulation (Johns & Singer, 1974). It was thought worth while to examine the effects of pindolol, a non-selective β-adrenoceptor blocking drug, with some intrinsic sympathetic activity but producing a longer duration of β-adrenoceptor blockade than propranolol, in an unselected group of hypertensive patients, comparing the hypotensive effect with plasma renin activity after some weeks of treatment.

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Methods

Entry to the trial

The subjects were selected on the basis of a raised blood pressure for which no cause had been discovered on investigation. They were of either sex (seventeen female nine male), between the ages of 26 and 67 years. Of the twenty-six patients studied, nineteen were white European, the remainder being African, Indian or Chinese. The nature of the trial was explained to each patient and agreement to its form had been received from the Ethical Committee of the Hospital.

Form of the trial

The patients were not receiving any medication for high blood pressure at entry and at this time, as part of the investigation, blood was taken for plasma renin activity after 1 h of recumbency between 09.00 and 10.00 hours. Blood pressure was taken in the sitting and standing position, as was the pulse rate. No one was entered into the trial unless two consecutive sets of readings on different occasions indicated that treatment for high blood pressure would ordinarily be undertaken. At this stage treatment was commenced with pindolol placebo tablets, indistinguishable from the active compound and taken three times a day as with the active compound. The placebo treatment lasted between 2 and 4 weeks and then pindolol was substituted in an initial dose of 5 mg t.d.s., rising usually at two to four weekly intervals to 10 mg and 15 mg t.d.s. The plasma renin activity was then measured again under the same conditions when the final dose of pindolol at 15 mg t.d.s. had been given for at least 2 weeks.

Effect of thiazide

In fifteen of the subjects, hydrochlorothiazide in a dose of either 25 mg or 50 mg daily was added to the pindolol to see the effect on blood pressure and plasma renin activity after the combination had been administered for at least 2 weeks.

Measurement of blood pressure

This was measured by two observers in two different hospitals and the pressures were taken in the sitting and standing positions. The diastolic pressure was taken as the point of muffling. The pressure was measured with either an ordinary sphygmomanometer and the values noted without knowledge of previous readings or other data on the patient at each visit, or with a 'random zero' apparatus (Hawksley & Son, Ltd). The pulse rate was measured on arrival at the clinic in the sitting and standing position by a nurse before blood pressure was taken.

Results

Effects on blood pressure

A comparison was made between the blood pressure taken at the end of the placebo period and that taken at the end of the administration of pindolol. Out of the twenty-six patients, five had a fall in systolic pressure and diastolic pressure greater than 20%; ten had a fall in systolic pressure and diastolic pressure of 10-20%; three had a fall greater than 10% in systolic pressure and 5-10% in diastolic pressure; while in eight there was a fall in blood pressure of less than 5% or even a rise in pressure. In the group as a whole there was a 12.1 ± (s.d.) 8.75% fall in mean (diastolic + one-third of pulse pressure) sitting blood pressure and a 13.0 ± (s.d.) 8.63% fall in the mean standing blood pressure, the difference between the two positions not being statistically significant ($P > 0.5$).

Pulse rate

There was a highly significant fall in the average sitting pulse rate/min from 92 ± (s.d.) 20 to 77 ± (s.d.) 12 ($P < 0.005$) and in the average standing pulse rate from 94 ± (s.d.) 19 to 80 ± (s.d.) 12 ($P < 0.01$). The pulse rate fell in all but one subject in the sitting and in all but two subjects in the standing position.

Renin levels

The normal range of renin by the method used (Boyd, Adamson, Fitz & Peart, 1969) is 200-600 pg ml^{-1} 24 h^{-1} as AI and it can be seen that six of these subjects lay above this range and ten below it (Table 1). Twenty out of twenty-six subjects showed a fall in plasma renin level on pindolol, there being an average fall in renin from 350 ± (s.d.) 355 pg ml^{-1} 24 h^{-1} to 161 ± (s.d.) 209 pg ml^{-1} 24 h^{-1} ($P < 0.025$). A regression plot of the percentage change in mean sitting blood pressure on pindolol versus the percentage change in plasma renin activity (Figure 1) showed no statistically significant relationship between these values ($r = 0.11$, $P > 0.1$). Similarly there was no significant correlation between percentage change in mean standing blood pressure and the change in plasma renin activity. There was a greater fall in

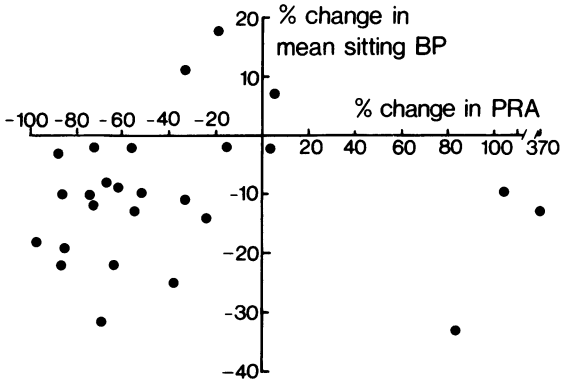

Figure 1 A regression plot of pindolol induced changes in mean sitting blood pressure and plasma renin activity (PRA), ($n = 26, r = 0.11, P > 0.1$).

the mean standing blood pressure 12.3 ± (s.d.) 14.8% for the high renin group than for the normal renin 7.89 ± (s.d.) 13.3% and the low renin group 6.0 ± (s.d.) 11.7%, but these differences were not statistically significant ($P > 0.3$). A regression plot of percentage change in mean standing blood pressure against pre-treatment plasma renin activity was just significant at the 10% level ($r = 0.32$).

Effects of pindolol plus a thiazide

In fifteen patients hydrochlorothiazide was added (25-50 mg/day) without potassium supplements and the effect on blood pressure and plasma renin activity measured between 2 and 4 weeks afterwards. There was a fall in the mean sitting blood pressure of 10.1 ± (s.d.) 8.6% and in the mean standing blood pressure of 14.7 ± (s.d.) 9.9% on hydrochlorothiazide, the difference in the fall in the two positions not being significant ($P > 0.2$), and there was no change in the sitting pulse rate, the pre-thiazide rate being 77.1 ± (s.d.) 11, and the post-thiazide rate 76 ± (s.d.) 16 (Table 2). There was a statistically significant rise in plasma renin activity from 128 ± (s.d.) 141 pg ml^{-1} $24\ h^{-1}$ to 409 ± (s.d.) 368 pg ml^{-1} $24\ h^{-1}$ ($P < 0.01$) but there was no correlation between the change in the mean blood pressure and the change in plasma renin activity in either the sitting ($r = 0.1$) or the standing positions ($r = 0.2$). Furthermore, there was no correlation between the fall in blood pressure in either position and the pre-thiazide plasma renin activity.

Side-effects

Only two patients had side-effects sufficient to stop the drug (patients 3 and 4, Table 1), both because of hallucinations which ceased immediately the drug was stopped.

Discussion

With long term administration of pindolol, plasma renin activity is reduced and in many instances to very low levels (Weber, Thornell & Stokes, 1974; Morgan, Roberts, Carney, Louis & Doyle, 1975; Werning & Vetter, 1975). Some of the patients in the present trial had repeat renin measurements made after the treatment had been maintained for some months with continued low levels. While there is known pharmacological variation in β-adrenoceptor blockers and probably in their ability to suppress renin activity (Bühler *et al.*, 1972; Michelakis & McAllister, 1972; Amery, Billiet & Fagard, 1974; Hansson & Zweifler, 1974), twenty out of the present twenty-six patients showed a fall and in six the level was to less than 20% of the starting value. In three the level was unchanged (patients 17, 18 and 21, Table 1). There is certainly no clear relationship between the starting level of plasma renin and the subsequent fall in blood pressure as the fall in blood pressure, though greater in the high renin group, was not significantly greater than in the normal and low renin groups. Also some patients with a higher than normal renin were resistant to the effect of pindolol on blood pressure and others in whom there was a marked reduction of plasma renin to less than 20% of the starting value, showed no fall in pressure.

The addition of hydrochlorothiazide to the regime showed that it was possible to lower the blood pressure in all but one of the patients and neither the pre-thiazide plasma renin activity nor the change in plasma renin activity predicted the hypotensive effect. It might have been argued that if the plasma renin activity rose, the blood pressure would not fall or might even rise. The results in the present study do not support such an argument but show that a fall in blood pressure was associated with a rise in plasma renin activity when a thiazide is added to pindolol. In other studies, Bravo, Tarazi & Dustan (1975) found that β-adrenoceptor blockade was much less effective in renin suppression when diuretic treatment was given previously. The results have been criticised (Davies & Slater, 1975; McAllister, 1975) due to doubts about effective plasma levels of propranolol but those initial results of Bravo *et al.*

Table 1 Data on the twenty-six patients treated

	Patient	Age (years)	Sex	Colour		Blood pressure from end of placebo to pindolol end (mmHg)		Pulse rate (beats/min) Start	Pulse rate (beats/min) End	Final dose (mg/day)	Renin ($pg\ ml^{-1}\ h^{-1}$) Start	Renin ($pg\ ml^{-1}\ h^{-1}$) End	Thiazide	Large falls of renin >20% of start
High renin	1	56	F	W	Sit	180/100	200/120	120	72	45	786	117	*	*
					St	180/110	180/120		80					
	2	42	M	W	Sit	190/130	146/110	120	72	45	771	25	*	*
					St	180/126	150/116							
	3	26	F	W	Sit	150/110	140/94		88	30	964	646		
					St	170/116	140/96		96					
	4	54	F	W	Sit	230/120	240/140	76	84	30	764	507		
					St	220/120	220/130							
	5	48	F	W	Sit	200/100	140/80	72	60	45	1247	777	*	
					St	190/114	140/80	72	64					
	6	38	M	W	Sit	155/110	120/85	110	96	15	1025	148		*
					St	160/120	120/85	118	98					
Normal renin	7	60	F	W	Sit	180/110	160/100	80	64	45	236	34	*	*
					St	190/110	180/110	80	64					
	8	41	F	W	Sit	180/130	186/120	140	92	45	544	72	*	*
					St	160/126	180/120							
	9	57	M	W	Sit	230/125	150/112	74	66	45	291	107		
					St	210/140	145/110	84	76					
	10	52	M	W	Sit	170/116	146/110	90	80	45	284	107		
					St	170/118	146/110	92	80					
	11	32	M	W	Sit	170/116	140/106	84	80	45	379	97	*	*
					St	170/120	130/104	78	80					
	12	49	M	W	Sit	174/100	170/110	84	64	45	308	324	*	
					St	170/110	180/110	84	64					
	13	28	M	W	Sit	150/110	140/96	72	72	45	229	474	*	
					St	160/116	140/104	80	72					

	14	53	M	W	Sit	190/120	125/85	88	80	30	227	69	
					St	170/100	120/100	96	84				
	15	67	F	W	Sit	180/105	180/90	104	92	45	270	89	*
					St	170/100	190/110	112	88				
	16	39	F	C	Sit	150/100	105/65	80	68	30	132	241	
					St	155/100	110/75	88	76				
Low renin	17	32	F	C	Sit	160/110	160/106	78	80	45	18.5	19.0	
					St	160/120	160/114		78				
	18	67	F	W	Sit	190/108	226/126	96	80	60	54	43	*
					St	190/106	230/126		84				
	19	61	F	W	Sit	190/100	190/110	72	64	45	126	55	*
					St	190/124	190/110	80	72				
	20	59	M	W	Sit	180/110	170/110	72	58	45	87	24	*
					St	160/110	170/124		64				
	21	49	F	C	Sit	200/100	180/105	112	96	45	39	33	
					St	200/115	175/110	140	108				
	22	49	F	C	Sit	180/120	170/100	83	72	45	97	27	
					St	160/125	135/100	100	74				
	23	23	F	C	Sit	185/115	155/105	96	84	45	47	21	*
					St	160/115	150/105	84	92				
	24	40	F	C	Sit	155/110	140/100	92	80	30	65	31	
					St	140/110	125/85	92	76				
	25	63	F	W	Sit	215/125	205/115	80	68	45	19.6	72	*
					St	220/130	205/115	80	76				
	26	44	F	C	Sit	240/130	170/130	130	96	45	83	20	*
					St	240/130	210/140	130	96				

Thiazide refers to those patients subsequently placed on this drug.
Large falls of renin refers to those finishing with a level less than 20% of the starting value.
High and low renin refers to an arbitrary cut-off point for the purpose of comparison.
Sit Sitting; St standing
C coloured; W white

Table 2 Data on patients treated with hydrochlorothiazide and pindolol

Patient	Age (years)	Sex	Colour		Blood pressure from end of pindolol to pindolol plus thiazide (mmHg)		Pulse rate (beats/min) Start	Pulse rate (beats/min) End	Dose (mg 24 h^{-1}) pindolol + thiazide	Renin (pg ml^{-1} 24 h) Pindolol	Renin (pg ml^{-1} 24 h) Thiazide
1	56	F	W	Sit	200/120	160/100	72	120	45 + 25	117	1333
				St	180/120	160/110	80	120			
2	42	M	W	Sit	140/90	140/105	80	72	45 + 25	108	352
				St	130/110	130/110	84	84			
5	48	F	W	Sit	200/96	140/80	76	70	40 + 25	365	554
				St	184/110	120/80	76	70			
7	60	F	W	Sit	160/100	140/90	72	60	45 + 25	34	70
				St	180/110	130/96	68	64			
8	41	F	W	Sit	180/120	180/100	88	88	45 + 50	72	958
				St	160/126	140/100	86	88			
11	32	M	W	Sit	140/106	130/90	80	64	30 + 25	97	471
				St	130/104	130/100	80	64			
12	49	M	W	Sit	170/110	140/90	64	68	30 + 25	324	710
				St	180/110	145/110	64	72			
13	28	M	W	Sit	140/96	128/96	72	72	45 + 25	474	388
				St	140/104	134/102	72	78			
15	67	F	W	Sit	180/90	150/100	92	88	45 + 50	89	270
				St	190/110	135/85	88	64			
18	67	F	W	Sit	200/104	180/104	88	70	45 + 50	43	201
				St	200/106	180/108	82	78			
19	61	F	W	Sit	180/98	146/90	66	68	45 + 25	55	60
				St	180/104	130/94	66	68			
20	59	M	W	Sit	170/110	140/80	58	60	45 + 25	24	32
				St	170/124	130/90	64	60			
23	23	F	C	Sit	155/105	145/95	84	96	45 + 50	21	170
				St	150/105	120/90	92	96			
25	63	F	W	Sit	205/115	185/105	68	64	45 + 50	72	72
				St	205/115	140/80	76	64			
26	44	F	C	Sit	170/130	180/120	96	88	45 + 50	20	493
				St	210/140	180/120	96	80			

Renin (pg ml^{-1} 24 h^{-1}) incubation at the end of pindolol treatment and pindolol + thiazide respectively.
Sit sitting; st standing
C coloured; W white

(1975) are very like the present ones with pindolol.

The most important general conclusion is that with normal or higher than normal plasma renin activity, the blood pressure can be lowered without any change in the plasma renin activity. Conversely, it is possible in some patients to markedly lower plasma renin activity without any change in blood pressure This is in accord with other studies, in particular Morgan *et al.* (1975). The original premise (Bühler *et al.*, 1972) that β-adrenoceptor blockers like propranolol are particularly effective in lowering the pressure in those with high plasma renin activity and ineffective in those with normal or lower than normal plasma renin activity obviously requires qualification, and especially in the knowledge that different β-adrenoceptor blockers are presumably having different effects on the circulation independent of their effect on suppression of plasma renin activity. The present results refer only to plasma renin activity measured after 1 h of recumbency. It is possible that a more important measurement would be the degree of suppression over 24 h during normal activities. It is known, for example, that propranolol will block renin release by renal nerve stimulation (Johns & Singer, 1974) which is probably related to blockade of the usual renin rise on upright posture (Michelakis & McAllister, 1972). These authors were the first to point out the dissociation between a fall in plasma renin activity and blood pressure with propranolol, and a very full study has recently shown that plasma renin activity is reduced by much smaller doses than is blood pressure (Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Bianchetti, Di Salle, Morselli & Chidsey, 1975). The general conclusion would be that β-adrenoceptor blockers may lower the blood pressure in a variety of ways and that this may well be independent of any lowering or failure to lower plasma renin activity.

Thanks are due to Mrs Jennifer Dulieu for the renin activity estimations, and to Sandoz Ltd for supplies of pindolol.

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(Received August 11, 1975)