BLOOD PRESSURE, HEART RATE, CATECHOLAMINES AND PLASMA RENIN ACTIVITY FOLLOWING INSTITUTION AND WITHDRAWAL OF GUANFACINE TREATMENT IN MODERATE HYPERTENSION

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1 Five patients with essential hypertension of WHO grade II–III were treated with guanfacine 0.5–2 mg three times daily. They were hospitalized for 6–8 d during the institution and the withdrawal of medication for the determination of blood pressure, heart rate, plasma and urinary catecholamines, and plasma renin activity (PRA) in the supine and the upright position.

2 During the institution of medication, blood pressure became normal in four patients given 3 mg daily. Heart rate was moderately reduced. One patient needed 6 mg daily for normalization of blood pressure but, due to sedation, the dosage had to be reduced to 4 mg daily after 48 hours. After 3 weeks guanfacine was withdrawn completely in this patient because of an acute attack of mental confusion.

3 Guanfacine caused a marked reduction in plasma noradrenaline, PRA and urinary noradrenaline excretion. Plasma adrenaline was somewhat reduced.

4 When guanfacine was withdrawn abruptly following 4–8 weeks of medication, blood pressure, heart rate, plasma catecholamines and PRA gradually returned to pretreatment levels within 4 days. Urinary noradrenaline excretion was slightly higher, though not significantly, on day 4 after withdrawal of guanfacine than before treatment.

5 This short study in a small number of patients supports the view that guanfacine is effective in reducing blood pressure and to some extent heart rate in hypertensive patients. The blood pressure lowering effect was closely related to a decrease of noradrenaline in plasma and urine, indicating inhibition of sympathetic activity. Guanfacine also lowered PRA. Following the abrupt cessation of treatment after 4 weeks there were no rebound phenomena with respect to blood pressure, heart rate, plasma catecholamines or PRA.

Introduction

EARLY clinical studies showed that clonidine, in doses which lowered blood pressure in hypertensive patients, also reduced catecholamine excretion and lowered PRA (Hökfelt, Dymling & Hedeland, 1968; Hökfelt, Hedeland & Dymling, 1969). Following cessation of clonidine treatment, blood pressure, catecholamines and PRA gradually returned to pretreatment levels in some patients, whereas others showed clinical and laboratory findings denoting rebound (Hökfelt *et al.*, 1968; 1969; Hökfelt, Hedeland & Dymling, 1970; Hansson, Hunyor, Julius & Hoobler, 1973; Geyskes, Boer & Dorhout Mees, 1979).

In experimental studies, guanfacine has been found to have many clonidine-like pharmacological properties, although there are some differences (Scholtysik, Lauener, Eichenberger, Bürki, Salzmann, Müller-Schweinitzer & Waite, 1975). We

have studied the effect of treatment with guanfacine and its cessation on blood pressure, heart rate, catecholamines in the blood and urine, and on PRA, in the supine and the upright position, in a limited number of patients.

Methods

The investigation was carried out in four men and one woman with essential hypertension, WHO grade II–III, aged 28–55 (mean = 48) years. All patients had been previously treated with antihypertensive drugs. Three of them were being treated with clonidine. With the exception of clonidine, all antihypertensive medications were withdrawn no later than 4 weeks before the start of the study. Clonidine was gradually withdrawn at a later stage

Figure 1 Blood pressure and heart rate (mean $\pm$ s.d.) in the supine position during onset ($n=5$) and withdrawal ($n=4$) of guanfacine treatment. Open columns, control; stippled columns, guanfacine 0.5 mg three times daily; hatched columns, guanfacine 0.5–1.0 mg three times daily.

and completely withheld for at least 4d before the trial proper began. During the studies no medication other than guanfacine was given.

Patients were hospitalized for 6–10 d during the institution of guanfacine treatment and then again at the time of its withdrawal after 4–8 weeks. The first 2d of hospitalization were used for the collection of basal data (day 1 and 2) before commencing guanfacine treatment. A similar procedure was applied before withdrawal of treatment.

During hospitalization, blood pressure and heart rate were measured three times daily in the supine and the upright position (at 1300, 1600 and 1900h). Blood samples were drawn from an antecubital vein for the determination of catecholamines and PRA daily at 0800h, the patients being in the supine position following an overnight rest and fasting; and at noon after a 30-min walk. Urine was collected daily during the whole period of hospitalization for the determination of catecholamines.

Treatment with guanfacine was started with a dosage of 0.5 mg three times daily for 2d and then increased to 1 mg three times daily. Four patients responded adequately to this dosage, which was then maintained. In one patient the dosage was increased to 2 mg three times daily on day 5 of treatment. During the whole study, the tablets were taken at 0600h, 1400h and 2200 hours. Four of the patients were discharged from hospital taking 3 mg and one

patient taking 4 mg daily given in divided doses. The patients were then followed weekly in the outpatient clinic. Further alteration of the guanfacine dosage was needed only in one patient, in whom 1 mg three times daily resulted in too low a blood pressure. Accordingly, the dosage was reduced to 0.5 mg three times daily. All patients were maintained on an unchanged dosage for at least the 4 weeks preceding rehospitalization. During the second period of hospitalization, guanfacine was abruptly withdrawn on day 2.

Blood pressure was recorded using a mercury manometer. Plasma catecholamines were determined using a double-isotope derivative technique (Engelman & Portnoy, 1970) in four patients and a single isotope technique (Poyler & Johnson, 1977) in one. Radioimmunoassay (Haber, Koerner, Page, Kliman & Purnode, 1969) was used for the estimation of PRA, and a fluorometric procedure (von Euler & Lishajko, 1961) for the determination of urinary catecholamines.

The data presented in the text are given as means $\pm$ s.d. Arithmetic means and standard deviations were calculated using a conventional formula. The statistical significance of differences was assessed using Student's *t* test for the mean of two samples. A difference was considered significant when *P* was smaller than 0.05.

Informed consent was obtained from all the patients investigated. The studies were approved by the Ethical Committee of the Medical Faculty of Lund University.

Results

All five patients were studied during the introduction of guanfacine treatment, whereas only four patients were included during withdrawal. On a dosage of guanfacine 1 mg three times daily, four patients showed normalization of blood pressure (Table 1 and Figure 1) and a moderate slowing of the heart rate both in the supine (Figure 1) and the upright (Tables 1 and 2) position. These effects on blood pressure and heart rate were still present when the patients were rehospitalized after medication for 4–8 weeks. Following abrupt withdrawal of guanfacine, blood pressure and heart rate gradually increased and reached pretreatment values on day 4. For the group as a whole, neither blood pressure (Table 1 and Figure 1) nor heart rate (Table 2 and Figure 1) significantly exceeded the pretreatment values during the 4 d of observation after cessation of guanfacine treatment. The same was also true for each patient individually.

In one patient, guanfacine 1 mg three times daily did not normalize blood pressure, and on day 5 of

treatment the dosage was increased to 6 mg daily. Blood pressure then became normal but the patient was so sedated that the dosage had to be reduced to 4 mg daily. Furthermore, 3 weeks after leaving the hospital, the patient became mentally confused and was admitted to hospital as an emergency. Guanfacine medication was withdrawn and other antihypertensive medication instituted. The mental confusion disappeared within 1 week. This patient was then excluded from further studies in this trial.

Medication with guanfacine resulted in reduced levels of noradrenaline in plasma and urine (Table 3 and Figure 2). When guanfacine was stopped, plasma noradrenaline returned to pretreatment levels, whereas urinary noradrenaline gradually increased,

and on day 4 of withdrawal was slightly but non-significantly higher than before treatment (Figure 2). The changes in plasma noradrenaline during institution and withdrawal of guanfacine treatment showed the same pattern in the supine and the upright position. Furthermore, the ratio of supine to upright plasma noradrenaline concentration was essentially the same during as before treatment with guanfacine. The plasma adrenaline concentration was somewhat reduced both in the supine ($P < 0.01$) and the erect ($P < 0.01$) position during medication, and then returned to pretreatment levels following withdrawal of guanfacine (Table 3 and Figure 2). PRA fell markedly, though not significantly, during medication, and then returned gradually to

Table 1 Mean systolic and diastolic blood pressures (three determinations daily) in the upright position during introduction and withdrawal of guanfacine.

Subject	Onset						
	Day	1	2	3	4	5	6
H.B.		161/116	161/109	146/112	144/105	129/93	128/91
S.S.		142/121	146/118	141/117	134/106	120/98	101/81
S.E.		149/101	144/106	134/106	124/98	122/94	118/91
M.N.		163/123	155/122	153/117	153/107	145/108	132/98
S.G.		180/132	182/132	176/131	165/123	160/119	150/112
Mean $\pm$ s.d.		159.0/118.6 $\pm 14.6/\pm 11.4$	157.6/117.1 ± 15.3	150/116.6 $\pm 16.1/\pm 9.2$	144/107.8 $\pm 16.0/\pm 9.2$	135.2/102.4 $\pm 17.0/\pm 11.0$	125.8/94.6* $\pm 18.1/\pm 11.5$
	Withdrawal						
	Day	1	2	3	4	5	
H.B.		133/98	138/102	162/113	167/115	160/115	
S.S.		117/92	130/100	142/109	147/113	154/116	
S.E.		116/100	128/89	135/97	134/108	143/107	
M.N.		138/100	140/100	147/113	151/117	143/112	
		126.0/97.5	134.0/97.8	146.5/108.0	149.8*/113.3	150.0*/112.5	
Mean $\pm$ s.d.		$\pm 11.2/\pm 3.4$	$\pm 5.9/\pm 5.9$	$\pm 11.5/\pm 7.6$	$\pm 13.6/\pm 3.9$	$\pm 8.5/\pm 4.0$	

For detailed information about medication, see text. * $P < 0.05$.

Table 2 Mean heart rate (three determinations daily) measured in the upright position during institution and withdrawal of guanfacine

Subject	Onset						Withdrawal				
	Day	1	2	3	4	5	6	1	2	3	4
H.B.		89	96	81	83	80	83	75	82	98	101
S.S.		106	104	91	96	98	81	93	111	104	92
S.E.		85	91	82	75	75	75	74	81	89	102
M.N.		88	98	91	93	85	74	67	77	89	94
S.G.		113	122	110	110	98	98				
Mean $\pm$ s.d.		96.2 ± 12.5	102.2 ± 12.0	91 ± 11.6	91.4 ± 13.3	85* ± 8.6	85.2* ± 11.3	77.3 ± 11.1	87.8 ± 15.7	95.0 ± 7.4	97.3* ± 5.0
											108.3** ± 8.2

For detailed information about medication, see text. * $P < 0.05$; ** $P < 0.01$.

Figure 2 Plasma concentrations of noradrenaline and adrenaline (mean $\pm$ s.d.) in the supine position and urinary noradrenaline excretion/24h during onset ($n=5$) and withdrawal ($n=4$) of guanfacine treatment. Columns as in Figure 1.

pretreatment levels following cessation of treatment (Table 4 and Figure 3).

Side-effects were systematically asked for, according to a check-list designed by Sandoz Ltd, Basel. During the first days of treatment with guanfacine all patients felt tired, and three out of five experienced dryness of the mouth. These side-effects disappeared completely within 7d in four patients, whereas one patient continued to complain about dryness of the mouth during the whole period of treatment. On day 4 after withdrawal of guanfacine, one patient complained of headache, restlessness and sweating, and for this reason was again given his previous antihypertensive treatment (clonidine). One patient complained of slight dizziness 3d following withdrawal of guanfacine, but was free of symptoms on the following day.

Discussion

Our studies confirm that guanfacine is effective in lowering high blood pressure in man (Jäätelä, 1976). In four of our five patients with moderate hypertension, blood pressure became normal during medication with 1 mg three times a day. As also reported by Jäätelä (1976), guanfacine caused a minor decrease in heart rate.

Following cessation of treatment with guanfacine for at least 4 weeks, there were no marked withdrawal phenomena, either clinically or with respect to laboratory findings. Thus, there was no overshoot of blood pressure, heart rate, plasma catecholamines or

Table 3 Noradrenaline (NA) and adrenaline (A) (nmol/l plasma) in the upright position following institution and withdrawal of guanfacine

Subject	Day	Onset						Withdrawal				
		1	2	3	4	5	6	1	2	3	4	5
H.B.	NA	1.88	1.72	1.89	1.45	1.02	0.54	0.74	1.03		4.31	2.36
	A	0.34	0.39	0.26	0.18	0.25	0.15	0.19	0.32		0.31	0.40
S.S.	NA	1.03	2.06	1.50	0.64	0.96	0.63	1.33	2.14	2.25	1.64	2.17
	A	0.21	0.25	0.19	0.21	0.20	0.26	0.49	0.23	0.60	0.47	0.33
S.E.	NA	3.53	4.24	2.47	1.51	1.60	1.70	1.03	2.00	2.57	2.68	4.14
	A	0.29	0.42	0.32	0.22	0.22	0.19	0.40	0.56	0.82	1.67	0.31
M.N.	NA	6.50	6.80	7.39	5.27	3.72	2.11	2.19	3.11	5.89	7.12	9.65
	A	0.33	0.24	0.31	0.20	0.31	0.15	0.20	0.53	0.59	0.72	0.77
S.G.	NA	3.71	3.40	4.14	1.81	2.24	0.66					
	A	0.41	0.58	0.36	0.34	0.47	0.21					
Mean $\pm$ s.d.	NA	3.33	3.64	3.48	2.14	1.90	1.13	1.33	2.07	3.57	3.93	4.59
		± 2.1	± 2.04	± 2.41	± 1.82	± 1.13	± 0.72	± 0.63	± 0.85	± 2.02	± 2.38	± 3.52
	A	0.32	0.38	0.29	0.23	0.29	0.19**	0.32	0.41	0.67	0.82	0.45
		± 0.07	± 0.14	± 0.07	± 0.06	± 0.11	± 0.05	± 0.15	± 0.16	± 0.13	± 0.74	± 0.22

For detailed information about medication, see text. * $P < 0.05$; ** $P < 0.01$.

Figure 3 Columns as in Figure 1. PRA (mean $\pm$ s.d.) in supine position during onset ($n=5$) and withdrawal ($n=4$) of guanfacine treatment.

PRA. In this respect, our studies agree with the findings reported by Kirch & Distler (1978), who carried out a double-blind cross-over study with guanfacine v clonidine and came to the conclusion that no rebound phenomena occur following withdrawal of guanfacine. The effects of guanfacine on blood pressure and heart rate occur somewhat later than those of clonidine. After the withdrawal of clonidine, rebound phenomena occurred within 12–72h (Hökfelt *et al.*, 1970). It thus seems possible that withdrawal phenomena could occur somewhat later after guanfacine than after clonidine withdrawal and more prolonged follow-up studies would be desirable. However, we observed one patient for 144h after the withdrawal of guanfacine and saw no further increase in blood pressure and heart rate during the last 2d of observation.

The reduction in blood pressure and heart rate

following institution of guanfacine treatment was accompanied by a reduction in both plasma and urinary noradrenaline levels. This finding indicates that guanfacine inhibits sympathetic activity in the same way as clonidine does. The decrease in PRA—in spite of the lowering of systemic mean blood pressure—might also be the result of decreased sympathetic activity.

In most instances plasma and urinary catecholamine levels seem to show a very similar pattern, and this also seems to apply during treatment with clonidine (Hökfelt, Hedeland & Hansson, 1975). Thus, the finding in our studies that the withdrawal of guanfacine was followed by a gradual return of plasma noradrenaline levels to pretreatment values, whereas a slight overshoot was seen in urinary noradrenaline on day 4 without medication, cannot be readily explained.

Table 4 PRA ($\mu\text{g/l/3 h}$) in the upright position following institution and withdrawal of guanfacine

Subject	Day	Onset						Withdrawal				
		1	2	3	4	5	6	1	2	3	4	5
H.B.		3.4	3.9	5.7	5.1	5.2	5.3	0.8	1.8	1.8	2.5	2.3
S.S.			3.1	2.2	1.3	2.5	3.0		5.4	7.1	5.4	7.3
S.E.		1.5	2.6	4.1	3.7	3.3	3.5		4.3	8.1	8.3	4.5
M.N.		4.1	5.1	5.0	3.3	2.1	1.3	0.7	0.6	1.5	2.2	3.4
S.G.		6.8	8.6	5.3	3.8	2.7	0.7					
Mean $\pm$ s.d.		4.0 ± 3.0	4.7 ± 2.4	4.3 ± 1.5	3.4 ± 1.4	3.2 ± 1.2	2.2 ± 1.2		3.0 ± 2.2	4.6 ± 3.5	4.6 ± 2.9	4.4 ± 2.2

For detailed information about medication, see text.

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