EFFECT OF GUANFACINE ON BLOOD PRESSURE AND RENIN ACTIVITY IN HYPERTENSIVE PATIENTS

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- 1 The effect of treatment with guanfacine for 12 weeks on blood pressure and plasma renin activity was investigated in 24 hypertensive patients (WHO I-III).
- 2 Systolic, diastolic and mean blood pressure values underwent significant reductions with a constant dose of guanfacine 3 mg daily for 1 week: from 197/115/149 (systolic/diastolic/mean) mmHg before therapy to 166/97/126 mmHg. After 4 weeks of treatment at varying doses, the blood pressure decreased to 157/91/118 mmHg, and after 12 weeks of treatment it levelled off at 147/83/109 mmHg. Heart rate remained essentially unchanged throughout the observation period.
- 3 During exercise, blood pressure and heart rate increased to the same extent during therapy as before treatment. Orthostatic hypotension was not seen in any of the patients.
- 4 Renin values decreased under therapy from 3.3 to 2.3 ng ml⁻¹ h⁻¹, but at no time during treatment did this decrease correlate with that of blood pressure.
- 5 Guanfacine treatment was accompanied by relatively few and mild side-effects.

Introduction

In the majority of patients hypertension is caused by an increase in peripheral vascular resistance. The development of guanfacine (Estulic®), a phenylacetylguanidine derivative, affords the possibility of influencing blood pressure by way of total peripheral resistance without evoking unwanted reflex tachycardia (Dubach, Huwyler, Radielovic & Singeisen, 1977; Schäfer, Rauh & Rosenthal, 1979). Furthermore, this mode of action has given rise to the expectation that the renin-angiotensin system would not be activated, since it depends on neurogenic compounds (Zanchetti, Stella & Dampney, 1977). Against the background of these considerations the antihypertensive effect of guanfacine at rest and under ergometer stress conditions as well as its influence on plasma renin activity have been evaluated in the present study.

Methods

Twenty-six patients (aged 26-68 yr, mean 52 yr; 11 male, 15 female) participated in an open clinical trial. Two patients dropped out at an early stage and were not included in further evaluation. Five patients suffered from renal, and 21 from essential hypertension (WHO stage I-III). Hypertension was known to have existed for a maximum of 3 years.

All patients were informed of the experimental

design and participated voluntarily according to the Helsinki declaration. In a placebo phase of 14 days a blood pressure reading of at least 160/100 mmHg had to be present on 3 consecutive days. The patients then received guanfacine for a period of up to 3 months which was followed by another 2 weeks with placebo.

Therapy was started uniformly with 1 mg guanfacine three times daily. In the titration phase the patients came at weekly intervals for measurements of blood pressure and pulse rate. If these weekly visits revealed unsatisfactory blood pressure responses, the dose was increased. As soon as an effective maintenance dose was reached it was adhered to for the remaining period.

Further follow-up visits were arranged at 14-d intervals; and these served simultaneously for inquiring about subjective side-effects. In the subsequent placebo phase blood pressure and pulse rate were checked 3 and 7 days after discontinuation of therapy.

At the end of each placebo and therapy phase a modified Schellong test (Jarmatz, de Marées & Kunitsch, 1976) and an ergometer test (on average 50 W over 6 min) were performed. Blood and urine samples were collected for measurements of blood count, urine analysis, blood glucose, potassium, urea, uric acid, serum creatinine, renin and creatinine clearance. Plasma renin was measured using the

method of Haber, Koerner, Page, Kliman & Purnode (1969). Patients' data were averaged and standard deviations computed.

Results

Dosage, which was titrated individually, was in the range of 3–40 mg daily (average 6 mg daily). Twelve patients received only 3 mg daily for 4 weeks, and six of these continued on 3 mg daily for a total of 12 weeks. Values for systolic, diastolic and mean blood pressures, and for pulse rate are listed in Table 1 for the entire trial period.

Within a therapy period of 1 week, blood pressure fell by 31/18/23 mmHg (systolic/diastolic/mean), corresponding to a lowering of blood pressure by 15% on a mean daily dose of 3.4 mg. The responder rate at this point and with this dose amounted to 48%. A further decrease in blood pressure during the following 4 and 8 weeks was statistically significant when compared with the 1-week value ($P=0.02$; $P=0.01$). These decreases were 40/24/31 mmHg and 44/28/35 mmHg, that is, blood pressures were 21% and 23% lower than initial values. Dosages at these points averaged 5.9 and 8.0 mg daily, respectively,

with responder rates of 79% and 83%. Two patients had to be withdrawn from the study, as they did not display a blood pressure response. During the second placebo phase blood pressure increased slowly within 3 days but returned to initial values after 1 week. Heart rate remained essentially unchanged throughout the observation period.

A subgroup of 12 patients was treated with 3 mg guanfacine daily for a period of 4 weeks. Initial blood pressure values of 192/111/145 mmHg (systolic/diastolic/mean) dropped significantly after 1 week to 157/92/120 mmHg and further decreased on average by another 5 mmHg on each of the three subsequent weekly follow-up visits. Heart rate varied only slightly from the initial value. The responder rate in this group averaged 58% after 1 week and 92% after 4 weeks. After 4 weeks blood pressure readings were 151/87/114 mmHg (Figure 1). During the course of treatment an increase in the dose of guanfacine was necessary even in some patients in this group, to meet response criteria.

In the six patients treated for over 12 weeks with the uniform dose of 3 mg daily, blood pressure differences compared with the initial value were 47/23/33 mmHg after 1 week, 52/33/40 mmHg after 4 weeks, and 50/30/38 mmHg after 12 weeks (Table 2).

Table 1 Blood pressure (mmHg) and heart rate (beats/min) responses during oral application of placebo and guanfacine to 24 patients

		Systolic	Blood pressure Diastolic	Mean	Heart rate
8 days before	mean	193.7	111.2	145.9	74.7
guanfacine	s.d.	15.7	10.2	10.9	10.8
4 days before	mean	194.8	110.8	146.1	73.7
guanfacine	s.d.	24.8	15.9	18.6	8.4
Basal	mean	196.9	115.0	149.4	74.8
value	s.d.	16.7	9.0	10.3	7.8
After	mean	166.1	97.4	126.5	74.0
1 week of guanfacine	s.d.	20.2	13.0	15.1	4.8
After	mean	162.0	94.3	122.7	74.0
2 weeks	s.d.	18.1	13.0	14.6	5.7
After	mean	160.7	94.5	122.3	71.6
3 weeks	s.d.	20.6	14.6	16.7	7.7
After	mean	156.7	90.7	118.4	72.6
4 weeks	s.d.	17.9	15.6	16.0	7.2
After	mean	150.6	87.1	113.8	74.8
6 weeks	s.d.	18.4	10.1	13.1	8.1
After	mean	152.6	86.6	114.3	74.0
8 weeks	s.d.	17.5	12.4	13.2	6.8
After	mean	145.8	81.7	108.6	73.2
10 weeks	s.d.	14.9	9.4	9.4	5.4
After	mean	146.6	82.5	109.4	72.5
12 weeks	s.d.	15.8	9.3	9.7	7.4
3 days after	mean	177.6	102.1	133.8	73.6
stopping guanfacine	s.d.	17.5	14.6	14.7	6.3
7 days after	mean	197.9	113.4	148.9	78.2
stopping guanfacine	s.d.	26.6	13.3	18.2	7.2

Figure 1 Behaviour of systolic (●), diastolic (■), and mean blood pressures (○) in 12 patients treated with a constant dose of guanfacine 3 mg daily over 4 weeks (mean $\pm$ s.d. response). Note the number of responders at the corresponding weeks of treatment.

An ergometer test performed during the placebo phase in 18 patients demonstrated an increase in systolic blood pressure of 43 mmHg, in diastolic blood pressure of 19 mmHg and in heart rate of 34 beats/minute. These exercise-induced increases remained essentially unchanged during maintenance therapy, that is in week 12 of treatment (41/20 mmHg, 30 beats/min), and at the end of the second placebo phase (35/18 mmHg, 28 beats/min) (Figure 2, Table 3).

Circulatory behaviour during the orthostasis test (Jarmatz *et al.*, 1976) did not differ noticeably from the placebo phase (Figure 3). During therapy, plasma renin activity decreased from 3.1 ± 2.4 to 2.2 ± 1.2 mg

Figure 2 Changes in systolic (SBP) and diastolic (DBP) blood pressures and heart rate (HR) during exercise (bicycle ergometry, 50 W/6 min) in 18 patients at the end of the two placebo periods (open) and after 12 weeks of treatment with guanfacine (hatched) (mean values $\pm$ s.d.).

$\text{ml}^{-1} \text{h}^{-1}$ ($P \leq 0.02$) at the end of therapy. The degree of change correlated directly with the initial value: the higher the initial value, the more pronounced the suppression of renin activity ($r=0.85$, $P=0.01$) (Figure 4). No correlation could be demonstrated, however, between plasma renin activity and blood pressure before and after antihypertensive therapy with guanfacine. Creatinine clearance increased significantly from 1.38 to $1.61 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$

Table 2 Blood pressure (mmHg) and heart rate (beats/min) responses before and during treatment with guanfacine 1 mg three times daily to six patients for up to 12 weeks

		Weeks			
		0	1	4	12
Systolic BP	mean	196.7	150.0	145.0	146.7
	s.d.	6.8	13.8	11.8	18.3
Diastolic BP	mean	112.5	90.0	81.7	82.5
	s.d.	6.1	11.4	14.4	12.9
Mean BP	mean	147.9	115.2	108.3	109.5
	s.d.	5.7	11.7	12.8	13.6
Heart rate	mean	75.3	72.0	72.0	72.0
	s.d.	4.7	5.1	10.1	8.0
Responders			4	6	5

($P \leq 0.002$). Other laboratory values did not display any abnormalities during therapy. In particular potassium remained unchanged.

Subjective side-effects were noted in 11 patients. Those most frequently encountered were dry mouth, constipation and fatigue; these disappeared towards the end of the study. There was no correlation between daily dosage and the incidence of side-effects. Incidence and intensity of side-effects is shown in Table 4. Discontinuation of therapy was necessary in two patients because of bradycardia.

Discussion

Like clonidine, guanfacine is a centrally-acting α -mimetic antihypertensive agent. α -adrenoceptor stimulation of the vasomotor centre reduces the activity of the sympathetic nervous system and this induces a lowering of blood pressure (Saameli, Scholtysik & Waite, 1975). Pharmacological studies have shown that the mode of action of clonidine differs from that of guanfacine in some respects. In contrast to clonidine, guanfacine does not bring about a reduction in dopamine turnover in the corpus striatum (Scholtysik, Lauener, Eichenberger, Bürki, Salzmann, Müller-Schweinitzer & Waite, 1975). The pharmacodynamic differences are complemented by clinical-therapeutic ones, which find their expression in the mode and the intensity of side-effects. Fatigue and rebound phenomena following guanfacine treatment are less pronounced than after clonidine (Kleinlogel, Scholtysik & Sayers, 1975; Kirch & Distler, 1978; Kugler, Seus, Krauskopf, Brecht & Raschig, 1980).

As evidenced by our studies, treatment of hypertensive patients for 3 months with guanfacine effectively lowers blood pressure, with a responder rate of 83% after 8 weeks. The relatively low dose of 3 mg daily leads within 1 week to a well-tolerated blood pressure reduction of about 17%. Blood pressure changes during ergometry are noteworthy as the

Figure 3 Orthostatic blood pressure responses in 24 patients with (hatched) and without (open) guanfacine therapy (mean values $\pm$ s.d. of systolic (SBP) and diastolic (DBP) blood pressures).

increase is the same as during the placebo phase. After treatment with clonidine, however, Lund-Johansen (1974) found an increase, which exceeded the blood pressure response during the control period.

No symptomatic rebound phenomenon was noted during a 2-week observation period with placebo after the 3-month period of treatment. Nevertheless in one patient treated with guanfacine 21 mg daily blood pressure increased to 230/150 mmHg during the first 3 days after discontinuation of the drug

Table 3 Blood pressure (mmHg) and heart rate (beats/min) at rest and during bicycle ergometry (50 W/6 min) in 18 patients at the end of the two placebo periods and after 12 weeks of treatment with guanfacine

		Placebo		Guanfacine		Placebo	
		At rest	Stress	At rest	Stress	At rest	Stress
Systolic BP	mean	186.4	229.2	147.2	187.8	194.7	229.4
	s.d.	14.6	19.8	13.7	14.1	23.0	25.4
	min/max	160/220	185/260	130/170	165/230	160/230	185/250
Diastolic BP	mean	110.3	129.2	80.3	103.3	111.9	130.0
	s.d.	6.3	10.5	7.4	5.9	10.2	14.3
	min/max	100/120	110/145	70/95	90/110	95/125	105/150
Heart rate	mean	75.1	109.2	73.4	103.3	75.8	104.1
	s.d.	7.7	11.8	7.8	8.7	5.7	11.0
	min/max	64/90	92/140	60/88	88/120	68/84	88/120

Figure 4 Plasma renin activity in 24 patients before and after 12 weeks of treatment with guanfacine, $y = 1.03x + 1.69$; $r = 0.85$.

(initial value 210/140 mmHg). Despite these high values there were no concomitant symptoms which could be related to symptomatic activation. The 21 mg dose and that of 40 mg in another patient were well tolerated, and in no instance were the biochemical laboratory tests in a pathological range; in both patients creatinine clearance increased from 2.26 and 0.92 to 2.51 and 1.21, respectively.

Side-effects such as dry mouth and fatigue were also observed during treatment with clonidine. Direct comparative studies have shown that they are less pronounced with guanfacine (Kleinlogel *et al.*, 1975; Kirch & Distler, 1978; Kugler *et al.*, 1979). Neither subjective nor objective signs of orthostatic hypotension were observed during treatment with guanfacine.

To what extent guanfacine treatment induces tachyphylaxis cannot be stated at this point. However, in 3 out of 12 patients, treated during the first 4 weeks with a uniform dose, an increase in dosage was necessary. From this it can be concluded that in a certain percentage of patients a loss of effectiveness during treatment with guanfacine

occurs, which can be offset by increasing the daily dose or by adding a diuretic. The decrease in plasma renin activity found during therapy can be explained to a certain extent by this fact (Röckel, Sabel & Heidland, 1978).

These results, however, are at variance with recent data postulated by Schoeppe & Brecht (1980), demonstrating that in acute experiments guanfacine significantly suppresses plasma renin activity within a time span in which the only mechanism of action possible is a direct influence of the drug on the renin-angiotensin system, that is, by way of reduced sympathetic activity. The importance of this apparently direct influence on plasma renin and the extent of tachyphylaxis must be assessed in further studies.

No correlation between renin suppression and blood pressure reduction during guanfacine therapy could be demonstrated, and this is similar to findings with clonidine (Fyhrquist, Kurppa & Huuskonen, 1975; Weber, Case, Baer, Sealey, Drayer, Lopez-Ovejero & Laragh, 1976; Karlberg, Nilsson & Tolagen, 1977). On the other hand, these results are at variance with those of Niarchos, Baer & Radichevich (1978), but this could be due to the short duration of treatment implemented by Niarchos *et al.* (1978) (only up to 10 days).

In conclusion it can be stated that antihypertensive therapy with guanfacine generally leads to an effective and rapid result, which is accompanied by relatively few and mild side-effects.

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Table 4 Side-effects observed in 11 patients after treatment with guanfacine

Side-effects	Number of patients	Severity
Bradycardia	2	Severe
Dryness of mouth	7	Moderate
Constipation	7	Moderate
Fatigue	3	Mild to moderate
Headache	1	Mild

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