EVALUATION OF LONG-TERM TREATMENT OF ESSENTIAL HYPERTENSION WITH GUANFACINE

M. HIGUCHI, A. OVERLACK & K.O. STUMPE

Medizinische Universitäts-Poliklinik, 5300 Bonn 1, Wilhelmstrasse 35–37, FRG

1 Twenty-two patients with moderately severe essential hypertension were treated for a period of 12 months with guanfacine (BS 100–141), a new centrally-acting antihypertensive agent. A twice daily schedule was followed and the dose range of guanfacine was 1–8 mg daily.

2 In twenty patients satisfactory blood pressure responses (diastolic pressure below 95 mmHg) were achieved in both the supine and the standing position. Pulse rate decreased slightly, though not significantly.

3 Tolerance to the pressure-lowering effect of the drug developed during the third or fourth month of therapy. This could be overcome by either increasing dosage or adding a diuretic.

4 All patients reported side-effects, mainly dryness of the mouth and fatigue. These side-effects became less or disappeared at the end of 3 months. Rebound hypertension on discontinuation of therapy occurred in two patients.

5 Plasma concentrations of noradrenaline and adrenaline as well as plasma renin activity were decreased after 1 week of treatment with the drug.

6 Guanfacine in conjunction with a diuretic is a useful drug in the long-term treatment of hypertension. Reduced central sympathetic outflow may be the major mechanism underlying the antihypertensive effect of the drug.

Introduction

GUANFACINE (BS 100–141; *N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride) is a new antihypertensive agent that is thought to reduce sympathetic tone by stimulation of the α -adrenoceptors in the central nervous system (Bream, Lauener, Picard, Scholtysik & White, 1975; Scholtysik, Lauener, Eichenberger, Bürki, Salzmann, Müller-Schweinitzer & Waite, 1975). It has been used alone or in conjunction with other antihypertensive drugs such as diuretics, vasodilators or β -adrenoceptor-blockers for the treatment of hypertension of various degrees of severity (Seedat, 1978; Kirch & Distler, 1978; Röckel, Sabel & Heidland, 1978). This study was designed to evaluate the long-term antihypertensive effect of guanfacine and to determine whether tolerance to the pressure-lowering effect of the drug develops. In addition, we investigated sympathetic nervous system function during short-term treatment by measuring plasma concentrations of catecholamines in some of the patients.

Methods

Subject selection

The study population comprised 24 males and 3 female patients with mild to moderate essential hypertension (WHO stage I or II). They ranged in age from 25–54 yr and had not taken antihypertensive drugs previously. All patients were selected at random from the outpatient department at the Medical University Policlinic Bonn. Average blood pressures on several outpatient visits were above 155 mmHg systolic or 100 mmHg diastolic, or both. Each subject signed an informed consent form after the nature of the study and its attendant hazards had been fully explained. All patients were on unrestricted diet, but they were asked not to increase their salt consumption.

Study design

This was a single-blind study starting with a 2–3 weeks placebo period. Thereafter, treatment

commenced with guanfacine, the initial daily dose ranging from 1–3 mg. In all patients a twice daily schedule was followed. The dosage was increased at weekly intervals until a satisfactory therapeutic effect (diastolic pressure below 95 mm Hg) was obtained or the maximum dose of guanfacine 8 mg daily was reached. When tolerance to the antihypertensive effect of the drug occurred, the dose was increased ($n=10$ patients) or a diuretic (hydrochlorothiazide 50 mg, amiloride 5 mg) ($n=12$ patients) was added. During the first 2 months of therapy blood pressure was monitored weekly, allowing untoward side-effects to be closely observed. Thereafter, measurements were performed at monthly intervals.

Sympathetic nervous system function was evaluated in a group of eight hypertensive patients by measuring plasma concentrations of noradrenaline before and after treatment with guanfacine. Blood samples were obtained in the supine position 60 and 120 min after administration of a single dose of guanfacine 5 mg as well as after 1 week of treatment with a daily dose of guanfacine 4 mg. In addition, plasma concentration of adrenaline and plasma renin activity were determined in the same patients.

Analytical methods

Arterial blood pressure was measured using a mercury sphygmomanometer (13-cm cuff), and the readings were taken in the supine and the standing position. Plasma noradrenaline and adrenaline concentrations were measured by the radioenzymatic method of Da Prada & Zürcher (1976). Plasma renin activity (PRA) was determined using the method of Haber, Koerner, Page, Kliman & Purnode (1969), followed by radioimmunoassay of angiotensin I generated during a 3-h incubation period. Statistical analysis was performed using paired-data analysis and correlation coefficients.

Results

Blood pressure and heart rate responses to long-term treatment

Of the 27 patients, 22 (19 males and 3 females) successfully completed the study according to the protocol (Table 1). The other patients dropped out for reasons independent of the trial after a treatment period of 3–12 weeks. Ten patients were treated for a period of 12 months with guanfacine alone. In these patients, blood pressure was satisfactorily controlled by a mean daily dose of guanfacine 2.8 mg during the first 4 months. To maintain blood pressure control, dosage had to be increased to 5.1 mg (range 2–12 mg) from the beginning of month 5 (Figure 1a). In the other 12 patients, mean daily dose of guanfacine was

Figure 1 Mean $\pm$ s.e. mean blood pressure ($\blacksquare$ supine, $\square$ standing) and heart responses to long-term treatment with guanfacine. *a*, Ten patients were treated with guanfacine alone. *b*, Twelve Patients were treated with guanfacine plus a diuretic. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

3.1 mg throughout the study. However, to overcome tolerance to the pressure-lowering effect of the drug, a diuretic had to be added from the beginning of the month 5 (Figure 1b). In the two groups of patients, the maximum antihypertensive effect of the drug was evident within the first 2–3 weeks of treatment. Mean systolic and diastolic blood pressures at the end of the fourth month of therapy were significantly higher than the corresponding values at the end of the first month of therapy (Figure 1).

Table 1 Details of patients who participated in the guanfacine study

Number of patients*	22
Male	19
Female	3
Average age	42.5 yr
Average dose/daily:	
Months 1–4	2.8 (3.1)† mg
Months 5–12	5.1 (3.1) mg
Duration of therapy	12 months

*Patients who completed the study.

†Values in brackets refer to 12 patients who in addition to guanfacine received diuretic treatment from the beginning of month 5.

In the two groups, heart-rates decreased slightly, though not significantly. During the second placebo period at the end of the trial, blood pressures and heart rates rose in most patients to near the pretreatment values. In two patients, however, the increase in blood pressure exceeded pretreatment values considerably, and the patients complained of throbbing headache suggesting rebound hypertension. These two patients were being treated with guanfacine and a diuretic.

Effect of short-term treatment on arterial pressure, plasma noradrenaline, adrenaline and plasma renin activity (PRA)

Following a single oral dose of guanfacine 5 mg, plasma concentrations of noradrenaline decreased significantly within the first 60 min after administration of the drug (Figure 2a). There was a further reduction in plasma noradrenaline after 120 minutes. Plasma concentration of adrenaline decreased slightly, though not significantly. PRA was significantly reduced 120 min after administration of guanfacine (Figure 2b). All three parameters showed a significant decrease after 1 week of treatment with the drug. The changes in hormone concentrations were accompanied by a small but significant decrease in arterial blood pressure both after the single dose and the 1 week of treatment. Reductions in heart rate were inconsistent and not significant.

Side-effects

Frequency and intensity of adverse reactions are summarized in Table 2. During the first 4 weeks of treatment all patients complained of side-effects. The most common reactions were fatigue and dryness of the mouth. During the course of treatment all of the side-effects decreased in severity. No significant changes were found in laboratory values.

Figure 2 Effect of a single dose and of 1 week of treatment with guanfacine on (a) plasma noradrenaline (●) and adrenaline (○), (b) PRA, (c) blood pressure and (d) heart rate in eight patients with essential hypertension. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Discussion

The present and previous investigations (Kirch & Distler, 1978; Seedat, 1978) have shown that guanfacine alone or in combination with other antihypertensive agents is effective in patients suffering from sustained essential hypertension. In almost all of the patients treated, satisfactory blood pressure responses were achieved in both the supine and the standing position without any orthostatic reaction. However, during the course of 1 year of treatment it became clear that in most patients tolerance to the pressure-lowering effect of the drug developed. This occurred usually during the third or fourth month of therapy and could be overcome by either increasing the dosage or adding a diuretic.

Table 2 Side-effects noted during treatment with guanfacine

Daily dose	Group I (n=10)						Group II (n=12)					
	2.8 mg			5.1 mg			3.1 mg			3.1 mg + Diuretic		
Week	1	2	3	1	2	3	1	2	3	1	2	3
Score*	1	2	3	1	2	3	1	2	3	1	2	3
Dryness of the mouth	5	5	0	6	2	0	5	1	0	7	0	0
Fatigue	7	3	0	6	0	0	4	0	0	6	1	0
Constipation	0	2	0	3	0	0	2	0	0	5	0	0
Weakness	4	0	0	2	0	0	0	0	0	2	0	0
Impotence	0	0	0	2	0	0	3	0	0	3	0	0

*Score 1=mild; 2=moderate; 3=drug withdrawn.

Similar findings have been reported by others (Kirch & Distler, 1978; Röckel *et al.*, 1978; Seedat, 1978).

To prevent tolerance during long-term treatment, it seems advisable to use guanfacine in conjunction with a diuretic, a procedure which also achieves blood pressure control with relatively small doses of guanfacine and reduces the incidence of side-effects. The present data show that guanfacine has a relatively long duration of action and can thus be administered easily on a twice daily schedule. This long duration of action may also account for the small incidence of rebound hypertension after withdrawal of the drug.

An increase in the blood pressure above initial values occurred in two patients who had been treated with daily doses of 6 and 8 mg, respectively, and had also received a diuretic for 7 months. As blood pressure was not measured on the first 1 or 2 days after interruption of the active treatment, it cannot be excluded that an early withdrawal reaction occurred in other patients.

All patients in the present study reported side-effects, mainly dryness of the mouth and fatigue. These adverse reactions usually became less or disappeared at the end of 3 or 4 months.

The present results do not enable us to draw any conclusion regarding the mechanisms underlying the antihypertensive effect of guanfacine. From animal data it seems that the drug lowers arterial blood

pressure by stimulating α -adrenoceptors in the central nervous system, thereby reducing central sympathetic outflow (Scholtysik *et al.*, 1975). The present finding of a marked decrease in plasma noradrenaline concentration shortly after administration of the drug is in accordance with this proposed mechanism of action. However, the plasma concentration of adrenaline also tended to be lower 2 h after the administration of guanfacine and was significantly reduced after 1 week of treatment. Thus, the reduction in noradrenaline may be in part due to an adrenal effect of the drug.

PRA also decreased in most of the patients. Because this was a normal-renin group, where a predominance of β -receptor activity may be present (Stumpe, Kolloch, Vetter, Gramann, Krück, Ressel & Higuchi, 1976), the reduction in PRA may have been due to depressed sympathetic activity. The decreases in hormone concentrations were associated with reductions in heart rate and arterial blood pressure, possibly indicating depressed activity of cardioexcitatory and bulbar vasoconstrictor centres. Further study is necessary to define the long-term effects of guanfacine on the relationship between changes in hormone concentrations and arterial pressure in these patients.

We thank Sandoz AG, Basel, Switzerland, for generous supplies of guanfacine (BS 100-141).

References

- BREAM, J.B., LAUENER, H., PICARD, C.W., SCHOLTYSIK, G. & WHITE, T.G. (1975). Substituted phenylacetylguanidines: A new class of antihypertensive agents. *Arzneimittel. Forschung.*, **25**, 1477-1482.
- DE PRADA, M. & ZÜRCHER, G. (1976). Simultaneous radioenzymatic determination of plasma and tissue adrenaline, nor-adrenaline and dopamine within the femtomole range. *Life Sciences.*, **19**, 1161-1174.
- HABER, E., KOERNER, T., PAGE, L.B., KLIMAN, B. & PURNODE, A. (1969). Application of radioimmunoassay for angiotensin I to the physiologic measurement of plasma renin activity in normal human subjects. *J. clin. Endocrin.*, **29**, 1349-1355.
- KIRCH, W. & DISTLER, A. (1978). Antihypertensive effect of *N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride. A double-blind cross-over trial versus clonidine. *Int. J. clin. Pharmac.*, **16**, 132-135.
- RÖCKEL, A., SABEL, B. & HEIDLAND, A. (1978). Therapie der essentiellen und renalen Hypertonie mit BS 100-141 (Guanfacinum). *Herz-Kreislauf.*, **3**, 136-142.
- SCHOLTYSIK, G., LAUENER, H., EICHENBERGER, E., BÜRKE, H., SALZMANN, R., MÜLLER-SCHWEINITZER, E. & WAITE, R. (1975). Pharmacological actions of the antihypertensive agent *N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride (BS 100-141). *Arzneimittel. Forschung.*, **25**, 1483-1491.
- SEEDAT, Y.K. (1978). Long-term treatment of hypertension with guanfacine (BS 100-141) alone and in combination therapy. *Curr. ther. Res.*, **24**, 288-298.
- STUMPE, K.O., KOLLOCH, R., VETTER, H., GRAMANN, W., KRÜCK, F., RESSEL, Ch. & HIGUCHI, M. (1976). Acute and long-term studies of the mechanisms of action of beta-blocking drugs in lowering blood pressure. *Am. J. Med.*, **60**, 853-865.