GUANFACINE: EFFECTS OF LONG-TERM TREATMENT AND WITHDRAWAL

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- 1 Guanfacine 3–6 mg daily lowered blood pressure in five essential hypertensives and also reduced saliva production.
- 2 Plasma and urinary noradrenaline values were significantly reduced throughout the 8–10 weeks of treatment.
- 3 On substitution of placebo tablets for guanfacine, blood pressure increased over a 2–4 d period to reach but did not significantly exceed pretreatment levels.
- 4 After withdrawal of guanfacine plasma noradrenaline standing was significantly higher than the pretreatment level ($P < 0.05$) after 4 days. Saliva production was significantly higher than the pretreatment level on day 3 and day 4 of withdrawal.
- 5 Guanfacine is an effective antihypertensive drug with a spectrum of actions similar to clonidine. However, in abrupt withdrawal blood pressure returned to the pretreatment level over a 2–4 d period.

Introduction

GUANFACINE (BS 100–141; N amidino-2(2–6 dichlorophenyl acetamide hydrochloride) lowers blood pressure in animals by acting on the central nervous system in a manner similar to that of clonidine (Scholtysik, Lauener & Eichenberger, 1975). Clinical studies have confirmed that the compound has a useful hypotensive action in man after oral dosing (Dubach, Huwyler, Radielovic & Singeisen, 1977; Seedat, 1978; Zamboulis, Reid & Hamilton, 1978). We have noted that the duration of action of guanfacine after a single dose is at least 36 h and that good blood pressure control can be maintained throughout the day with single daily doses in the evening (Zamboulis *et al.*, 1978). One of the limitations of clonidine therapy is its short duration of action and the occurrence of symptoms of anxiety, tremor, nausea, headache and insomnia within 12–24 h of the last dose of clonidine, often associated with increases in blood pressure up to or above pretreatment recordings (Hunyor, Hansson, Harrison & Hoobler, 1972; Reid, Wing, Dargie, Hamilton, Davies & Dollery, 1977). These withdrawal symptoms are associated with increased catecholamine release and excretion (Hököfelt, Hedeland & Dymling, 1970; Reid *et al.*, 1977). In the present study a group of patients with essential

hypertension were treated with guanfacine for 8–10 weeks. At the beginning and end of the investigation they were admitted to hospital to measure changes in blood pressure, urinary and plasma noradrenaline, and subjective and objective side-effects during blind substitution of placebo tablets for active drug.

Methods

Five essential hypertensives were investigated (four men, one woman) whose ages ranged from 56–64 years. The clinical features of the patients are summarized in Table 1. All patients gave their written informed consent to the procedure. The protocol was reviewed and approved by the Ethical Review Committee of the Royal Postgraduate Medical School and Hammersmith Hospital. They were admitted to hospital for 7 d for initiation of treatment and subsequently followed as outpatients. They were treated with oral guanfacine (Sandoz Ltd, Feltham) 3–6 mg (Table 2) once or twice daily as outpatients for at least 8 weeks before its withdrawal. Patients were then hospitalized for withdrawal of the drug. They remained ambulant and received a standard ward diet. For the first 24 h, measurements of blood pressure, heart rate and side-effects were made while the patients remained on their individualised guanfacine doses. The last dose was administered at 0900 h of the second day in hospital (time 0) and then

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the same number of identical placebo tablets was given under single-blind conditions for the following 96 hours.

Blood pressure was measured in duplicate using an automatic ultrasonic sphygmomanometer (Roche Arteriosonde 1217) after a minimum of 10 min resting supine in a quiet clinical laboratory. Supine heart rate was measured by counting the radial pulse at the wrist for 1 minute. The subject then stood erect and blood pressure was measured after 1 and 2 min standing. Heart rate was counted between 2 and 3 min standing. Lying and standing heart rate were measured before drug dosing and at 1 h intervals until 10 h and at 4 h intervals thereafter during the waking hours till 96 hours.

Sedation was assessed semiquantitatively using a visual analogue scale (Dollery, Dargie, Draffan, Davies, Dean, Reid, Clare & Murray, 1976). A 100 mm line was marked 'nearly asleep' and 'wide awake' at opposite ends. The subject was invited to mark the line at different times throughout the day. Sedation was measured as millimetres from awake. Saliva production was determined by change in weight of dental cotton rolls (Oratex Ltd) placed in the mouth for 1 min (Wing, Reid, Davies, Neill, Tippet & Dollery, 1977). Four cotton rolls were placed opposite the opening of the parotid duct and submandibular ducts for 1 min and then discarded. Four further fols, preweighed in a container, were inserted in the mouth for exactly 1 min and returned to the container which was then sealed. A further set

of preweighed rolls were then inserted and the procedure repeated. The mean change in weight of the dental rolls was taken as the saliva production and expressed as g/minute. Sedation and saliva flow were measured before drug dosing at 2-h intervals until 10 hours. Measurements were repeated on subsequent days between 1000 h and 1100 h and 1500 h and 1600 hours.

Venous blood was collected by direct puncture of a forearm vein, after at least 10 min rest in the supine position, into chilled tubes containing lithium heparin and stored on ice. Plasma was then separated by centrifugation at 4°C for 15 mins at 2000 rev/min in a refrigerated centrifuge. Plasma was stored at -20°C for up to 3 weeks before assay of noradrenaline using a sensitive radiometric method (Henry, Starman, Johnson & Williams, 1975). Urine collections (24h) were made into plastic bottles containing 100 ml 10% hydrochloric acid. Total volume was measured and an aliquot assayed for free urinary catecholamines by fluorimetry (von Euler & Lishajko, 1961). Plasma concentration of guanfacine was measured by mass fragmentography (GC-MS) in plasma collected before and after the last dose of guanfacine. Guanfacine was measured after extraction in diethylether and condensation with hexafluoroacetylacetone by Drs Morin and La Planche (Sandoz, Basel).

Results

Blood pressure and heart rate supine and after standing

Systolic and diastolic blood pressures (mean $\pm$ s.e. mean) in the supine posture before and throughout the study are shown in Figure 1. Values shown are the means of average blood pressures for each patient taken throughout the waking period from 0700–2300 h each day. After substitution of placebo for guanfacine a gradual elevation of the blood pressure was observed over the next 96 hours. There was an increase of 13/14 mm Hg (supine) and 33/16 mm Hg (standing) from the treated levels in the first 48 h, and the highest readings were recorded 54 and 78 h after withdrawal. There was also a gradual increase in heart rate from 54 to 70 beats/min in the supine position at the end of 96 h after withdrawal, whereas standing heart rate increased from 64 to 86 beats/minute.

Plasma and urine noradrenaline

Urine noradrenaline (Figure 2) fell from 71 to 22 μ g/24h ($P < 0.01$) after oral administration of guanfacine. It remained low during 8 weeks' treatment and after withdrawal of the drug it increased to 63 μ g/24h by day 4.

Table 1 Patients' pretreatment blood pressure levels and guanfacine dosage

Patient	Age	Pretreatment supine BP (mm Hg)	Guanfacine dose during long-term treatment
A	64	230/124	2 mg twice daily
C	54	214/114	3 mg once daily
D	53	224/123	3 mg once daily
E	58	190/130	3 mg once daily
F	63	160/100	2 mg once daily

Table 2 Plasma half-life ($\pm 95\%$ confidence limits) of guanfacine in five patients

Patient	Guanfacine plasma half-life (h)
A	29.9 $\pm$ 5.7
C	16.4 $\pm$ 6.4
D	19.5 $\pm$ 10.1
E	21.5 $\pm$ 14.3
F	34.4 $\pm$ 0.6

Between five and seven plasma samples were analyzed by mass fragmentography 2–22 h after the last dose of drug.

Figure 1 Mean ($\pm$ s.e. mean) supine systolic and diastolic blood pressures ($n=5$) before and after treatment with guanfacine. Outpatient follow-up and measurements after withdrawal are also shown. The time scale is interrupted as shown by the oblique parallel lines.

Figure 2 Mean ($\pm$ s.e. mean) 24-h urine noradrenaline ($\mu\text{g}/24\text{h}$) before and for 7d after treatment with guanfacine. Further observations are shown before and after withdrawal of guanfacine after 8–10 weeks' treatment as an outpatient.

Figure 3 Mean ($\pm$ s.e. mean) plasma noradrenaline lying supine ($\blacklozenge$) and standing ($\circ$) before and after treatment with guanfacine, and after withdrawal.

Supine plasma noradrenaline levels (Figure 3) which decreased from 0.29 to 0.06 ng/ml after treatment with guanfacine and remained low during chronic dosing for 8 weeks, increased to 0.56 ng/ml by the end of day 4. Standing plasma noradrenaline levels increased to 1.03 ng/ml by day 4 after withdrawal and were significantly greater than before treatment ($P < 0.05$).

Saliva production and sedation

Salivary flow (Figure 4) increased gradually from 0.51 to 1.36 g/min by day 4. Saliva flow was significantly higher on day 3 ($P < 0.05$) and day 4 ($P < 0.01$) after withdrawal than before starting treatment with guanfacine.

Sedation (assessed by visual analogue scaled) was

Figure 4 Mean ($\pm$ s.e. mean) saliva production (g/min) before and after treatment with guanfacine, and after withdrawal. $P < 0.05$; $**P < 0.01$.

noted after the first dose of guanfacine. There was a progressive reduction in sedation score during the chronic dosing in the inpatient and outpatient part of the study (Figure 5).

Plasma guanfacine

Plasma levels of guanfacine ranged from 5.4 to 8.8 ng/ml. Plasma levels in chronic treatment were directly related to daily dose, although there was some inter-individual differences. The decline in plasma concentration was followed after the last dose, the terminal elimination half-life ranging from 16.4 to 34.4 h (Table 2).

Discussion

In five essential hypertensive patients abrupt withdrawal of guanfacine resulted in a slow and gradual return of blood pressure to pretreatment levels by day 4. Although *all* patients had a mild headache by day 3 or 4, no patient noted this symptom in the first 48 h after withdrawal. The return of blood pressure to control levels was not accompanied by the symptoms which have been described after clonidine withdrawal. None of the patients complained spontaneously of flushing, sweating, anxiety, insomnia or agitation; nor were these elicited on direct questioning.

The increase in blood pressure was gradual and although the patients were ambulant, it did not exceed pretreatment levels by day 4. In contrast to a similar study with clonidine (Reid *et al.*, 1977), in none of the patients did the degree or the rate of the blood pressure increase necessitate premature termination of the withdrawal study. Urinary catecholamines fell during treatment with guanfacine and increased gradually to reach levels which were similar but not

Figure 5 Mean ($\pm$ s.e. mean) sedation score from visual analogue scales (mm from wide awake) before and after treatment with guanfacine, and after withdrawal.

higher than pretreatment by day 4. Plasma noradrenaline levels decreased during treatment with guanfacine, and increased after its withdrawal. However, standing plasma noradrenaline levels were greater by day 4 after cessation of guanfacine than before treatment ($P < 0.05$). The decrease in plasma and urinary noradrenaline levels on treatment is similar to that observed after clonidine (Hökfelt *et al.*, 1970; Reid *et al.*, 1977) and is consistent with a central sympathetic inhibitory action for guanfacine. The increase in standing plasma noradrenaline may indicate an increase in sympathetic activity at that time.

Salivary flow also increased after discontinuation of guanfacine and by day 4 exceeded by twofold the pretreatment control levels. Animal studies suggest that reduction in saliva production and resulting dry mouth is a central effect (Rand, Rush & Wilson, 1969) resulting from an interaction of clonidine with α -adrenoceptors in the central nervous system. An overshoot of saliva flow has not been reported before for clonidine. However, in our previous studies we did not examine saliva production during withdrawal (Reid *et al.*, 1977). If saliva flow is an index of the central α -adrenoceptor agonist actions of guanfacine the late (3–4d) appearance of increased saliva flow parallels the slow increase in blood pressure.

The slower recovery from the pharmacological effects of guanfacine than from those of clonidine may be related to the longer plasma half-life noted with guanfacine. In previous studies clonidine plasma concentration has been related to hypotensive effect (Wing *et al.*, 1977) and shorter durations of action

(8.8–18.2h) were noted in studies of clonidine withdrawal. Experimental studies in the rat confirm the relatively long duration of action and slow offset of effect of guanfacine (Barber & Reid, 1978).

In the absence of within-patient comparisons we can only suggest that the longer duration of action and longer time for recovery of blood pressure to baseline pretreatment levels may be of some clinical use. Although our results do not exclude the occurrence of withdrawal reactions and symptoms after guanfacine, they do suggest that the frequency of appearance of these symptoms within 12–24h of omitting therapy may be less than with clonidine. Neither these clinical studies nor studies on withdrawal in the rat (Barber, Zamboulis & Reid, 1978) support the observations of Oates, Stoker & Stokes (1979) that guanfacine in the rat frequently causes pronounced 'overshoots' in blood pressure.

However, our results suggest that even in the absence of blood pressure changes and subjective symptoms, biochemical indices show some evidence of increased sympathetic activity and may indicate that similar changes to those seen after clonidine withdrawal may occur after treatment with other centrally acting antihypertensives.

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