Factors predisposing to postural hypotensive symptoms in the treatment of high blood pressure

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Symptoms due to orthostatic and exertional hypotension occurred in 23.4 per cent of 448 hypertensive patients treated with guanethidine, debrisoquine, or bethanidine. Symptoms were significantly more frequent in patients treated with guanethidine than in those treated with bethanidine or debrisoquine.

Women rather than men and patients with radiological evidence of cardiomegaly, electrocardiographic evidence of left ventricular hypertrophy, or ST/T wave changes, developed these symptoms significantly more often than other patients. A raised blood urea was found more frequently in patients with postural hypotensive symptoms.

Characteristically guanethidine produced early morning postural hypotensive symptoms, whereas hypotensive symptoms caused by bethanidine and debrisoquine occurred at other times of the day and particularly one to two hours after tablet ingestion.

Debrisoquine and guanethidine had a significantly greater negative chronotropic effect than bethanidine.

It is suggested that negative chronotropic effects of these drugs may potentiate hypotensive symptoms in patients with cardiovascular, renal, or cerebrovascular disease. It should be possible to minimize symptoms of postural hypotension by attention to predisposing factors and selection of treatment accordingly.

Treatment of hypertension with post-ganglionic sympathetic blocking drugs produces hypotension related to posture: this is both an inevitable consequence of their mode of action and a possible cause of troublesome side effects. In mild cases other drugs without orthostatic effects may be used, but treatment with post-ganglionic sympathetic blocking drugs may be essential for more severe hypertension, and debrisoquine, bethanidine, and guanethidine are the drugs most frequently employed. Debrisoquine and bethanidine are said to produce fewer orthostatic symptoms than guanethidine (Bath, Pickering, and Turner, 1967; Kitchin and Turner, 1966).

It was the aim of this study to determine the proportion of hypertensive patients on treatment with these drugs who suffered from postural symptoms and to identify any predisposing factors.

Method

Patients are reviewed at least every three months in the Sheffield Hypertension Clinic. The electrocardiogram, blood urea, and chest radiograph are repeated at

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yearly intervals. The patients in this study were seen between February 1972 and October 1972 (inclusive) by one observer. If at this visit they had been on hypotensive treatment for at least 18 months and complained of dizziness, whether this was orthostatic dizziness or not was identified by further questioning. Patients were considered to have symptoms of postural hypotension if at any visit there was a drop of systolic pressure of ≥ 30 mmHg (4.0 kPa) on standing from the supine position or on walking up and down 75 stairs (exertional hypotension), and if this drop of pressure was related to symptoms. Patients were not included if they complained of vertigo or dizziness, which was not clearly related to posture and/or exertion. Patients were also excluded if they were on more than one drug (with or without a diuretic). By these criteria all the patients eventually included in this study could be described as either symptomatic or asymptomatic in respect of dizziness related to orthostatic hypotension.

Only symptoms and blood pressure levels found at least 6 months after the initiation of therapy were recorded. Any patients in whom symptoms were thought to be caused by inappropriate timing of doses or excessive therapy were not included in the survey unless symptoms persisted after appropriate dose readjustments.

The age, height, weight, and blood pressure levels of each patient before and after treatment with debrisoquine, guanethidine, or bethanidine were recorded as well as the initial blood urea, the heart rate from the electrocardiogram, and electrocardiographic criteria of left ventricular hypertrophy (Sokolow and Lyon, 1949). ST/T wave changes were coded according to the revised Minnesota Code (Rose and Blackburn, 1968). Radiological evidence of cardiomegaly was defined as a cardiothoracic ratio of ≥ 1.2 . Dizziness was described as mild if it was recorded on at least three occasions after the first 6 months of treatment, but had disappeared by the date of the study; moderate if it had persisted up to this time; severe if it had been recorded on at least 6 occasions or blackouts had occurred; and disabling if treatment had had to be changed on its account.

From the last clinic review the lying and standing blood pressure levels and the heart rates were recorded, and also the blood urea, electrocardiographic changes, and the radiological heart size.

Results

There were 448 patients treated with post-ganglionic sympathetic blocking drugs; 205 were taking guanethidine, 158 bethanidine, and 85 debrisoquine. Results for patients with postural symptoms of different severity have been amalgamated for ease of presentation. For each drug patients have been divided into those with symptoms of postural hypotension and those without such symptoms. There were no significant differences in the mean supine and standing blood pressure levels and the average age and weight between these groups of patients before treatment (Table 1).

The mean heart rates of all groups were similar before treatment but afterwards there were significant differences. Debrisoquine and guanethidine slowed the resting heart rate by 16 per cent but bethanidine only slowed the heart rate by 5.6 per cent ($P < 0.01$). There were parallel effects on the standing heart rates, which for all groups were slightly higher than the supine heart rates.

Evidence of vascular and renal disease was significantly more frequent in all the symptomatic groups ($P < 0.01$). Cardiomegaly and electrocardiographic evidence of left ventricular hypertrophy were more often present in the symptomatic groups ($P < 0.01$). ST/T wave changes were more frequent in the patients with postural hypotensive symptoms, and pretreatment blood urea was significantly higher in this group ($P < 0.01$). After treatment symptomatic patients showed significantly greater rises of the blood urea and more frequent electrocardiographic evidence of left ventricular hypertrophy and radiographic evidence of cardiomegaly ($P < 0.01$). Women had postural symptoms relatively more frequently than men ($P < 0.02$) (Table 2).

No permanent complications of postural hypotension were detected. Angina frequently occurred in patients who also complained of postural symptoms (36, 34%), but angina rarely occurred at the same time as the hypotensive symptoms even if these occurred on exertion. However, in some patients before admission to the study it was noted that severe hypotensive episodes caused by inappropriate dose of drug were sometimes associated

TABLE 1 Blood pressure levels and heart rates of patients treated with post-ganglionic sympathetic blocking drugs

	Guanethidine		Debrisoquine		Bethanidine	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
No. of patients	145	60	70	15	128	30
Blood pressure (mmHg)						
before, supine	217/126	218/127	210/122	211/126	214/121	220/131
after, supine	175/100	178/101	168/100	168/98	172/102	184/98
Blood pressure (mmHg)						
before, standing	217/128	216/129	210/124	201/127	213/126	207/129
after, standing	160/94	159/96	160/96	147/98	156/96	159/99
Heart rate, before treatment (beats/min) (supine)*	74	77	75	85	78	80
Heart rate, after treatment (beats/min) (supine)*	63	63	64	68	73†	78†
Treatment period (yr)	5.7	5.5	2.2	2.5	2.9	3.0
Mean age (yr)	53.8	57.2	53.3	59.2	53.3	54.6
Weight (kg)	71.4	74.1	71.1	68.2	74.2	74.9
Daily dose (mg)	72.4	61.4	74.3	71.5	105.3	110.9

* Significant differences between average heart rates before and after treatment for the total groups of patients on guanethidine, debrisoquine, and bethanidine (grouped 't' test, $P < 0.001$).

† Significant differences between the average heart rates after treatment with bethanidine and the average heart rates after treatment with debrisoquine and guanethidine (grouped 't' test, $P < 0.01$).

Conversion factor from Traditional units to SI units: 1 mmHg $\approx$ 0.133 KPa.

TABLE 2 Factors associated with postural hypotensive symptoms

	Guanethidine Asymptomatic	Symptomatic	Debrisoquine Asymptomatic	Symptomatic	Bethanidine Asymptomatic	Symptomatic
No. of patients	145	60	70	15	128	30
Mean blood urea* (mmol/l) initially	6.1	6.5	5.7	6.4	5.8	6.4
Rise of blood urea* (mmol/l) after treatment	1.5	2.7	1.1	2.6	1.1	2.3
Initial cardiomegaly†	54 (37.2)	38 (63.3)	30 (42.9)	9 (60.0)	49 (38.3)	21 (70.0)
Persistent cardiomegaly after treatment†	52 (35.9)	45 (75.0)	29 (41.4)	12 (80.0)	47 (36.7)	26 (86.7)
Initial voltage criteria of left ventricular hyper- trophy†	25 (17.3)	34 (56.7)	12 (17.1)	6 (40.0)	14 (10.9)	17 (56.7)
Voltage criteria of left ventricular hypertrophy after treatment†	22 (15.2)	42 (70.0)	10 (14.3)	12 (80.0)	15 (11.7)	19 (63.3)
Initial electrocardiograms with ST/T wave changes†	44 (30.3)	26 (43.3)	17 (24.3)	8 (53.3)	17 (13.3)	13 (43.3)
Electrocardiograms with ST/T wave changes after treatment†	41 (28.3)	31 (51.6)	15 (21.4)	8 (53.3)	17 (13.3)	14 (46.7)
Men - total number } ‡	87	24	39	6	72	16
Women - total number }	58	36	31	9	56	14

* Significant differences between the total group with symptoms and the group without symptoms using grouped 't' test ($P < 0.01$).

† Significant differences between the total group with symptoms and the group without symptoms (using χ^2 test, $P < 0.01$).

‡ Significant differences between the total group with symptoms and the group without symptoms (using χ^2 test, $P < 0.02$).

Percentages are in parentheses.

Conversion factor from SI units to Traditional units: blood urea 1 mmol/l $\approx$ 6 mg/100 ml.

with angina and then hypotension and angina could be relieved by altering the medication.

There were differences between the drugs taken and the frequency of certain symptoms. Exertional hypotension was less frequent and less severe with bethanidine than with guanethidine, but unexpected diurnal or nocturnal orthostatic symptoms with bethanidine were significantly more frequent than

in those taking guanethidine or debrisoquine ($P < 0.02$) (Table 3).

Other differences did not attain statistical significance but bethanidine and debrisoquine rarely caused early morning hypotension if the medication was taken correctly; many patients, however, took their second dose of debrisoquine after 4.0 p.m. and readjustment was necessary. Patients on bethanidine

TABLE 3 Frequency of different types of postural hypotension and associated symptoms in patients treated with post-ganglionic sympathetic blocking drugs

	Guanethidine	Debrisoquine	Bethanidine
No. of patients with postural hypotensive symptoms	60	15	30
Exertional hypotensive symptoms	18 (30)	9 (60)	5 (17)
Early morning hypotensive symptoms	25 (42)	5 (33)	2 (7)
Blackouts or syncope	4 (7)	0	2 (7)
Intermittent claudication	3 (5)	1 (7)	2 (7)
Angina with hypotensive symptoms	5 (8)	1 (7)	3 (10)
Angina without associated hypotensive symptoms	23 (38)	5 (33)	8 (27)
Orthostatic hypotensive symptoms at any time of day	31 (52)	6 (40)	23 (77)*
Orthostatic hypotensive symptoms 1 to 2 hours after medication	0	4 (27)	4 (13)

* Significantly more frequent in the group of patients on bethanidine than in the group with postural hypotensive symptoms as a whole, using χ^2 test ($P < 0.02$).

Percentages are in parentheses.

showed striking diurnal variation of blood pressure and serial readings throughout the day confirmed postural hypotension related to the time of onset of symptoms.

Spreading the quantity of any drug over more than the recommended number of doses did not appear to relieve the patients' symptoms. A change of treatment from one post-ganglionic blocking drug to another because of postural symptoms was rarely beneficial, though this often altered the time of onset and type of symptoms. However, 6 patients on guanethidine had fewer symptoms when changed to debrisoquine.

Discussion

In this study, the groups of patients taking each of the three drugs were comparable as far as pre-treatment blood pressure levels and resting heart rate were concerned. They remained comparable when their mean post-treatment blood pressure levels, both lying and standing, were considered. The average pulse pressure was slightly lower in the group with postural symptoms. However, from the results of this study there is no evidence that postural hypotensive symptoms are just a reflection of a greater reduction of standing blood pressure in the affected group. Additional therapy consisted only of diuretics which were given to a similar proportion in each group (65%) and which would not account for the differences in symptoms. The different durations of treatment with each of the post-ganglionic sympathetic blocking drugs reflect the date of the introduction of the drug in the clinic, and though there are differences between drug groups there are no differences within each group.

However, when comparing asymptomatic with symptomatic patients in all three drug groups, the latter more often showed electrocardiographic evidence of left ventricular hypertrophy and ST/T wave changes and had radiological evidence of cardiomegaly. The renal status of symptomatic patients as judged by blood urea was worse. Women complained of symptoms proportionately more often than men. Patients with symptoms were older on average (though not significantly) than the asymptomatic patients. After treatment, certain differences persisted. There was less frequent improvement and more frequent deterioration in renal and cardiovascular parameters in symptomatic than asymptomatic patients. In the presence of a blood urea exceeding 16.6 mmol/l (100 mg/100 ml), there was often severe postural hypotension, particularly when guanethidine was the principal antihypertensive drug.

In comparison, during the same period of observation, other patients in the clinic treated with

alpha-methyldopa, reserpine, diuretics, and/or beta-receptor blocking drugs were examined, but less than 5 per cent had postural symptoms. Alpha-methyldopa and reserpine (less than 0.3 mg per day) had negligible effects on the heart rate.

Differences were also apparent between drug groups. More patients taking guanethidine (29%) were affected by postural symptoms than was previously suggested (Leishman and Sandler, 1967), whereas debrisoquine and bethanidine produced fewer severe side effects (18% and 19%, respectively). These figures may reflect either the differing kinetic properties of the drugs themselves or differences in their mode of action.

Guanethidine has the longest half-life of the three compounds, has a prolonged effect, and exerts a significant action in the early morning when hypotensive symptoms commonly occur. This effect might be potentiated by an early morning reduction in vascular volume (Cranston and Brown, 1963) or by an inhibitory effect of guanethidine on the diurnal rhythm of catecholamine excretion (Vyshnepolski, 1969).

Bethanidine is more rapidly absorbed and excreted (Doyle and Morley, 1965), causes a less smooth control of blood pressure throughout the day, and in this study often generated hypotensive symptoms between one or two hours after a dose. Debrisoquine was less prone to these drawbacks.

Pharmacodynamic factors may also be involved in the differences between the groups. Guanethidine depletes tissues of catecholamines and has negative inotropic effects (Richardson *et al.*, 1960; Gaffney, Braunwald, and Cooper, 1962; Kahler, Gaffney, and Braunwald, 1962). Debrisoquine and bethanidine do not deplete catecholamines significantly (Moe *et al.*, 1964; Boura and Green, 1963). Guanethidine is known to produce negative chronotropic effects but the effect of debrisoquine on the heart rate of hypotensive subjects is undocumented. The results presented here (Table 1) suggest that debrisoquine has a similar effect to that of guanethidine, but that bethanidine is less potent in this respect. These effects may be caused by blocking of beta-receptors (Kaldor and Juvancz, 1969), but they may also result from direct depression of pacemaker activity as has been shown for both reserpine and guanethidine (Innes, Krayner, and Waud, 1958). Compensation for venous pooling involves both alpha- and beta-sympathetic effects and the cardiac acceleration produced helps to maintain cardiac output. It is clear that, particularly among patients with severe cardiovascular disease, negative chronotropic effects may potentiate those of alpha-sympathetic blockade and accentuate symptoms of postural hypotension.

Treatment with beta-blocking drugs alone rarely produces postural symptoms and this suggests that such blockade only potentiates postural symptoms caused by other factors.

Many factors are, therefore, involved in the production of postural symptoms and many cannot be measured, e.g. the extent of cerebrovascular disease and psychological factors. Undoubtedly blocking the alpha-sympathetic response to standing, with resulting venous pooling, is the most important effect of post-ganglionic sympathetic blocking drugs. There may, however, be great differences in postural symptoms for similar orthostatic effects. In this comparison we have shown the importance of cardiac and renal function in predisposing patients to hypotensive symptoms.

The therapeutic choice between different post-ganglionic sympathetic blocking drugs may be influenced by the differences between debrisoquine, bethanidine, and guanethidine. Despite the greater frequency of side effects with guanethidine, consistent control of the blood pressure is better with this drug than with bethanidine, and single (or at most double) daily dose regimes are adhered to better than therapy given three times a day. Troublesome early morning hypotension with guanethidine may compel a change to bethanidine or debrisoquine if careful adjustment of dose has failed. However, severe orthostatic or exertional symptoms can often be relieved only by a change to a fundamentally different type of treatment. The factors examined in this study are easy to measure and may be used in the future to predict the predisposition of patients to postural hypotensive symptoms if they are treated with post-ganglionic sympathetic blocking drugs. Undoubtedly, such therapy is the most potent available and is often necessary in severely hypertensive patients. Wherever possible this type of treatment should be avoided in those predisposed to hypotensive symptoms.

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