DRUG RESISTANCE, INAPPROPRIATE DOSING AND NON-COMPLIANCE IN HYPERTENSIVE PATIENTS

J.H. SILAS, G.T. TUCKER & A.J. SMITH

University Department of Therapeutics; Royal Hallamshire Hospital, Sheffield S10 2JF

- 1 From an understanding of the biological fate and hypotensive effect of debrisoquine (D) we have assessed the relative importance of true drug resistance, inappropriately low dosage and non-compliance as causes of apparent resistance to treatment with this drug.
- 2 Among 37 hypertensive patients prescribed D, eleven (30%) were non-compliant on the day of testing.
- 3 Non-compliance was found in 64% of patients with poor blood pressure control but only 15% of patients with intermediate and good blood pressure control ($P < 0.02$).
- 4 Five patients received doses which were too low for pharmacological effect while in a further five an increase in dose may have improved blood pressure control.
- 5 Resistance to D was uncommon indicating that non-compliance and inadequate dosing are the major causes of apparent resistance to treatment with this compound.

Introduction

An unsatisfactory response to antihypertensive treatment may result from true drug resistance, inadequate dosing or irregular tablet taking (non-compliance). Knowledge of the relationship between the biological fate of debrisoquine (D) and its hypotensive effect has enabled us to examine the importance of these determinants of response in a sample of hypertensive patients using measurements of the drug and its major metabolite in a single urine collection.

During the administration of a fixed dose of debrisoquine, the urinary recovery of the unchanged compound varies widely between patients but not in individual subjects dosed on several occasions (Silas, Lennard, Tucker, Smith, Malcolm & Marten, 1977; Silas, 1978). The major determinant of debrisoquine availability is the extent of its metabolism and not the amount absorbed, (Silas, 1978). In 28 supervised and compliant in-patients (mean $\pm$ s.d. age 53 ± 8 years; 16 men) receiving 10–120 mg (mean $\pm$ s.d. 50 ± 23 mg) debrisoquine daily for between 2 months–6 years ($\pm$ diuretics) there was an inverse correlation between the percentage of the daily dose recovered in 24 h urine as the major metabolite 4-hydroxydebrisoquine (HD) and that recovered as unchanged debrisoquine (Figure 1). During chronic treatment the effect of debrisoquine on standing blood pressure was correlated with the 24 h urinary recovery of unchanged drug (Figure 2). Therefore, it is possible to

predict that in a patient with a pretreatment diastolic blood pressure of 148 mm Hg, a 24 h urinary debrisoquine recovery of 70 mg would be associated with a fall in standing diastolic blood pressure to about 100 mm Hg. In contrast, a 24 h urinary debrisoquine recovery less than 11 mg/24 h is not associated with statistically significant change in blood pressure (Silas *et al.*, 1977).

These observations were used to draw up the following definitions.

Definitions

Non-compliance Patients were considered non-compliant if the co-ordinate of the percent of the *prescribed* daily dose recovered in a 24 h urine as HD% and D% fell below the 95% confidence limit shown in Figure 1.

Resistance Patients in whom treatment was associated with a 24 h urine debrisoquine recovery greater than 70 mg were considered resistant to debrisoquine. Few patients present with a diastolic blood pressure greater than 148 mm Hg.

Inadequate dosage This was defined as a 24 h urine debrisoquine recovery less than 11 mg/24 h, not due to non-compliance.

Figure 1 Correlation between the percent of the oral dose recovered in 24 h urine as 4-hydroxydebrisoquine (HD) and debrisoquine (D) in compliant in-patients receiving 10–120 mg debrisoquine daily ($\pm$ diuretic). The regression line ($r = -0.83$, $P < 0.001$) and the lower 95% confidence limit are indicated. The latter was essentially linear.

Methods

Patients and protocol

The above criteria were used to characterize 37 hypertensive out-patients (mean $\pm$ s.d. age 55 ± 11 years 23 men) prescribed D with or without another hypotensive agent (β -adrenoceptor blocker $n=5$, diuretic $n=22$, methyldopa $n=1$). The mean $\pm$ s.d. dose for all out-patients (82 ± 80 mg) was not significantly different ($P > 0.1$) from that given to the in-patients described above. In 29 out-patients the daily dose was 10–120 mg (mean $\pm$ s.d. 47 ± 27 mg) but the remainder were prescribed larger doses (mean $\pm$ s.d. 208 ± 82 mg). Although our definitions were derived from data obtained in patients receiving up to 120 mg D daily, we have included eight out-patients who were prescribed higher doses. This can be justified since we have shown (Silas, Lennard, Tucker, Smith, Malcolm & Marten, 1978) that increasing dose tends to be associated with a small increase in the proportion of D recovered in the urine which will decrease the chance of wrongly diagnosing non-compliance. Also the definition of true resistance is based entirely on the total D recovered. Patients selected were regular attenders at the Hypertension

Figure 2 Correlation between the mean daily urinary recovery of debrisoquine and the change in standing mean blood pressure in patients receiving 20–120 mg debrisoquine daily. The intercept was not significantly different from zero. $r = -0.82$, $P < 0.001$ $y = -6.039 - 0.649x$.

Clinic and they completed a 24 h urine collection which was subsequently assayed for D and HD by gas-liquid chromatography (Lennard, Silas, Smith & Tucker 1977).

Blood pressure control

This was assessed retrospectively from the four most recent visits to the Clinic. A standard mercury sphygmomanometer was used although observations were not always made by the same physician. Blood pressure control was defined arbitrarily from phase IV diastolic blood pressure as follows:

Good control: standing diastolic blood pressure ≤ 100 mm Hg on 3–4 visits

Intermediate control: standing diastolic blood pressure ≤ 100 mm Hg on 2 visits

Poor control: standing diastolic blood pressure ≤ 100 mm Hg on < 2 visits.

Results

Blood pressure control was good in 21 patients, intermediate in 5 and poor in 11 (Table 1).

Eleven patients were noncompliant with therapy (30%) (Figure 3). The blood pressure was poorly controlled in seven of these, and they represented 64% of patients with poor blood pressure control. The remainder of this non-compliant group comprised 15% of patients with intermediate or good

Figure 3 Co-ordinates of percent *prescribed* oral daily debrisoquine dose recovered in the urine as 4-hydroxydebrisoquine (HD) and debrisoquine (D) in 37 hypertensive out-patients whose blood pressure control was good (●), intermediate (◐) or poor (○). By definition, points below the lower 95% confidence line indicate non-compliant patients.

blood pressure control. Absolute noncompliance (no drug in the urine) was noted in only one subject.

Inadequate dosing was found in five patients; in two of these it was associated with poor blood pressure control. Blood pressure control was good in the remainder but all were receiving other drugs.

Eight patients were prescribed daily doses of between 140–340 mg of D. Of these, two were non-compliant and both had poor blood pressure control. Only four subjects were found to be relatively resistant to D (urinary D recoveries of 106–225 mg/24 h) but in three of them good blood pressure control had been achieved.

Discussion

Although our patients attended the hypertension clinic regularly, 30% were noncompliant with treatment on the day of testing and this rather than drug resistance was the major cause of poor blood pressure control. Previous attempts to assess compliance have used tablet counts, random blood and urine analysis of drug or a riboflavin marker (Crooks & Parkin, 1977). Tablet counts require long-term assessment and are subject to error if the patient has more than one source of medication. Random analysis of drug or marker provides 'all or none' results which lead to underestimation of non-compliance. Poor correlations have generally been observed between these estimates of compliance and blood pressure control (Alderman & Ochs, 1977; Taguchi & Freis, 1975). The advantages of our method of assessing compliance are underlined by the fact that analysis of urine for the presence or absence of debrisoquine would have failed to diagnose non-compliance in all but one subject.

Some of the compliant subjects were prescribed homeopathic doses of debrisoquine. This was associated with poor blood pressure control in two, while in three patients good blood pressure control was due to other drugs. Inappropriate combination therapy is to be discouraged as polypharmacy is more often associated with noncompliance (Weintraub, Au & Lasagna, 1973) and the therapeutic effect of

Table 1 Incidence of non-compliance, inadequate dosing and resistance in hypertensive outpatients treated with debrisoquine

<i>Patients</i>		<i>Non-compliance*</i>	<i>Inadequate dose</i>	<i>'Therapeutic' range**</i>	<i>Resistance</i>
Total	37	11 (30)	5 (13)	17 (46)	4 (11)
Good control	21	3 (14)	3 (14)	12 (57)	3 (14)
Intermediate control	5	1 (20)	0	4 (80)	0
Poor control	11	7 (64)	2 (18)	1 (9)	1 (9)

Figures in parentheses indicate percentages

* The incidence of non-compliance was significantly higher in patients with poor blood pressure control than in those with intermediate and good control (Chi-square 6.065, $P < 0.02$)

** Urinary debrisoquine excretion 11–70 mg/24 h

antihypertensive drugs appears to be additive rather than synergistic (Pearson, Bending, Bulpitt, George, Hole, Williams & Breckenridge, 1976; Petrie, Galloway, Webster, Simpson & Lewis, 1975).

Only four patients were resistant to debrisoquine and this could be overcome by using very large doses. The reasons for their resistance are unclear but fluid retention and tolerance (Kitchen & Turner, 1966; Jackson, 1972) are possibilities. Retrospective analyses (Silas, 1978) lend no support to this explanation and we agree with the view (Jackson, 1972; Turner, White & Benton, 1976) that tolerance is not a cause of resistance to debrisoquine. An

objective assessment of resistance to other antihypertensive agents has not previously been reported. When using debrisoquine it is clear that true resistance is rare and that apparent resistance to treatment can be overcome by improving compliance and by adjusting dose to suit individual requirements. This is important since debrisoquine is still used in hypertensive patients already receiving other drugs (Turner *et al.*, 1976; Editorial, 1976), particularly in those with severe hypertension.

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