A correlation between the response to debrisoquine and the amount of unchanged drug excreted in the urine

M. ANGELO, L.G. DRING, R. LANCASTER,* A. LATHAM & R.L. SMITH

Department of Biochemical and Experimental Pharmacology and Department of Clinical Pharmacology, St Mary's Hospital Medical School, London W2

The correlation between responsiveness to the adrenergic blocking agent debrisoquine and the amount of unchanged drug excreted in the urine has been investigated in normotensive subjects and in a number of hypertensive outpatients as part of a study on the therapeutic implications of metabolism of this hypotensive agent.

Preliminary experiments showed that single oral doses (40 mg) of [^{14}C]-debrisoquine were well absorbed (75% of ^{14}C was excreted in the urine in 24 h) and that the drug was metabolized by hydroxylation to an extent which appeared to vary between subjects (Angelo, Dring, Lancaster & Smith, unpublished data). To investigate a possible relationship between responsiveness and extent of metabolism in a larger group of subjects a g.l.c. method for the estimation of unchanged debrisoquine in urine was developed. This was a modification of the method of Hengstmann, Falkner, Watson & Oates (1974) and depends upon the hydrolytic conversion of debrisoquine to tetrahydroisoquinoline which is measured as its trichloroacetyl derivative on g.l.c. with electron capture detection using phenformin as internal standard.

For the purpose of this study the blood pressure of 10 normotensive subjects with normal renal function who had received 40 mg of debrisoquine orally was recorded lying down, standing and after walking 50 yards, using a random zero sphygmomanometer, at intervals for up to 48 hours. Urine samples were collected at similar intervals for measurement of their debrisoquine content. The blood pressure of the subjects was measured on a control day at the same times but in the absence of the drug.

There occurred a sevenfold range (8-58% of dose) in the amount of debrisoquine excreted in the urine unchanged. The mean of the standing blood pressure values obtained 2, 3, 4, 6, 8, 10 and 24 h after debrisoquine was compared to the values obtained at identical times on a control day and showed that the three subjects with a statistically significant ($P < 0.05$) hypotensive response excreted more unchanged debrisoquine (34, 51, 58% of the dose) than seven non-responders ($P < 0.005$) who excreted a mean of only 16% of the dose unchanged (range 8-28). The subject who excreted most unchanged drug had a standing mean blood pressure more than 2 s.d. below his control value 32 h after ingestion.

A number of hypertensive outpatients with normal renal function were treated with debrisoquine and the hypotensive response determined by comparing their pre-debrisoquine mean standing blood pressure with that found after the drug. The amount of unchanged debrisoquine excreted in the urine in the 24 h following drug administration was also determined. The range of percentage of the dose excreted unchanged in the urine (8-48%) was similar to that found in normotensive subjects and the correlation between response to the drug and the amount of unmetabolized drug excreted was better than between the response and the daily dose.

It is concluded that probably debrisoquine itself and not a metabolite is responsible for its hypotensive action and that the rate at which debrisoquine is metabolized is a major determinant of responsiveness to the drug. Inter-individual difference in response to the drug can be related to variations in the extent of metabolism and not to differences in absorption.

Reference

HENGSTMANN, J.H., FALKNER, F.C., WATSON, J.T. & OATES, J. (1974). Quantitative determination of Guanethidine and other Guanido-containing drugs in biological fluids by gas chromatography with flame ionization detection and multiple ion detection. *Anal. Chem.*, **46**, 34-39.