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POLYMORPHIC SULPHOXIDATION OF S-CARBOXYMETHYL-L-CYSTEINE IN MAN

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INTRODUCTION

A number of reactions involved in the metabolism of drugs are known to exhibit the phenomenon of genetic polymorphism. These include the acetylation of various sulphonamide and hydrazine drugs, the hydrolysis of esters such as succinylcholine and paraoxon, the glucuronidation of various substrates and the C-oxidation of such drugs as debrisoquine and guanoxan (1-3). The S-oxidation of metiamide has also been shown to be related to debrisoquine oxidation phenotype (4). The mucolytic drug, S-carboxymethyl-L-cysteine, [carbocysteine; carbocisteine; 'Mucodyne'; 'Mucolex'] is extensively metabolised in man to give eight metabolites, four of which are sulphoxides, in addition to trace amounts of urea and inorganic sulphate (5-7). Recent investigations in volunteer subjects have shown that there is a wide variation in the amount of the dose excreted in the urine as these sulphoxide metabolites (6) and preliminary studies have suggested that this difference in sulphoxide production may be associated with the genetically determined oxidation of debrisoquine (8). The possibility of a polymorphic distribution of sulphoxidation capacity within the population has now led to the investigation of the metabolism of S-carboxymethyl-L-cysteine in a larger number of subjects.

METHODS

One hundred and eighty one healthy British white volunteers, male and female, were recruited from the staff and students of St. Mary's Hospital Medical School, London and the Biochemistry Department of Birmingham University. None of these subjects (mean age 21.5 years) had been exposed to any recent drug medication. Each volunteer took two capsules each containing 375 mg of S-carboxymethyl-L-cysteine following a light breakfast. The bladder was emptied before dosing and thereafter all urine collected for the next 8 hours. The total urine volume was recorded and aliquots frozen until analysis which was undertaken as rapidly as possible after collection. Reference compounds were synthesised and the urine samples quantitatively analysed for the parent compound and its metabolites, including the sulphoxides [S-carboxymethyl-L-cysteine sulphoxide, N-acetyl-S-carboxymethyl-L-cysteine sulphoxide, S-methyl-L-cysteine sulphoxide, N-acetyl-S-methyl-L-cysteine sulphoxide] by methods previously described in detail (5-7).

From the results a 'sulphoxidation index' (SI) for each 0-8 hour urine was calculated as follows :

$$\frac{\%\text{ administered dose excreted as (parent compound + non-sulphoxide metabolites)}}{\%\text{ administered dose excreted as sulphoxide metabolites}}$$

It can be seen that a 'sulphoxidation index' of less than 1.0 indicates that more than 50% of the excreted dose was in the form of sulphoxide metabolites.

RESULTS AND DISCUSSION

The value of the 'sulphoxidation index' was found to be reproducible in 23 subjects on whom complete repeat tests were performed on two separate occasions. For 6 of these individuals the separation between tests was 30 months. Figure 1 shows a scattergram of the first estimate of SI against the second estimate of SI. The non-parametric Spearman rank correlation gives $r_s = 0.98$, $p < 0.001$. In addition, 3 individuals were challenged with the drug on 5 separate occasions over a period of 24 months and the values obtained for the SI were almost identical.

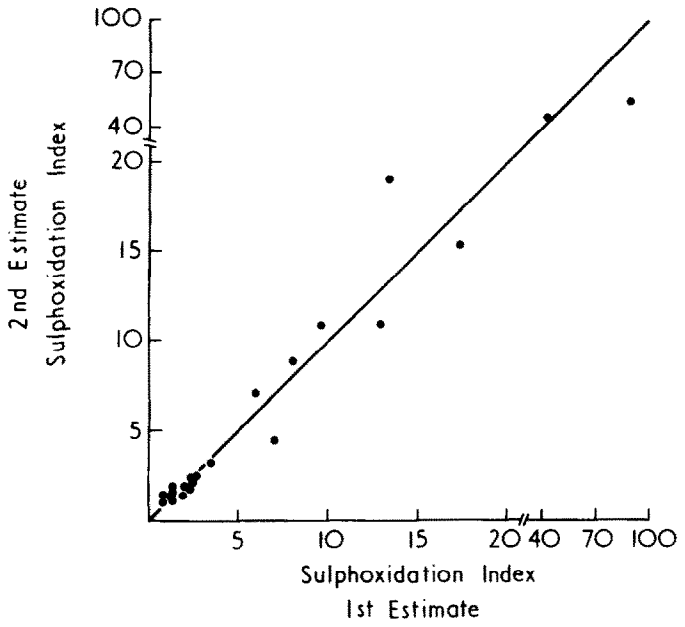

Figure 1. Repeat determinations of 'sulphoxidation index' carried out on separate occasions in 23 unrelated British white volunteers.

The distribution of 'sulphoxidation indices' for the 181 volunteers studied is shown in the form of a histogram (Figure 2) which relates these indices on an arithmetic scale against the number of individuals (frequency). The distribution obtained is not normal but discontinuous and askew. The population as a whole (181 subjects) eliminated a mean of 52.8% (S.D. $\pm$ 20.6) of the administered dose in the 0-8 hour urine of which 23.2% (S.D. $\pm$ 14.7) of that excreted was in the form of sulphoxide metabolites. However, inspection of the distribution showed that a small group of 21 individuals (11.6% of the total sample) displayed a relative impairment of sulphoxidation (SI > 20) giving a mean recovery of 47.4% (S.D. $\pm$ 19.4) with only 2.7% (S.D. $\pm$ 1.3) of the recovered dose as sulphoxides. The majority of individuals (63.5% of the total 181 volunteers) lay within the major population mode and had 'sulphoxidation indices' in the range of 0.7 to 5.0, excreting between 16 and 59% of the eliminated dose as sulphoxides.

Statistical analysis of the results showed that no significant correlation existed between the 'sulphoxidation index' or the percentage of the administered dose excreted as sulphoxide metabolites, and the total recovery, urine volume or age of the subject. In terms of impaired sulphoxidation both males and females were affected and were present in the volunteers recruited from both Institutes. This study suggests that a polymorphism exists

within the population with respect to sulphoxidation and that a substantial proportion of the population (ca 10%) has a reduced capacity to oxidise the sulphur atom of S-carboxymethyl-L-cysteine. Further investigations are now underway using appropriate family studies to determine whether or not this polymorphism is under genetic control.

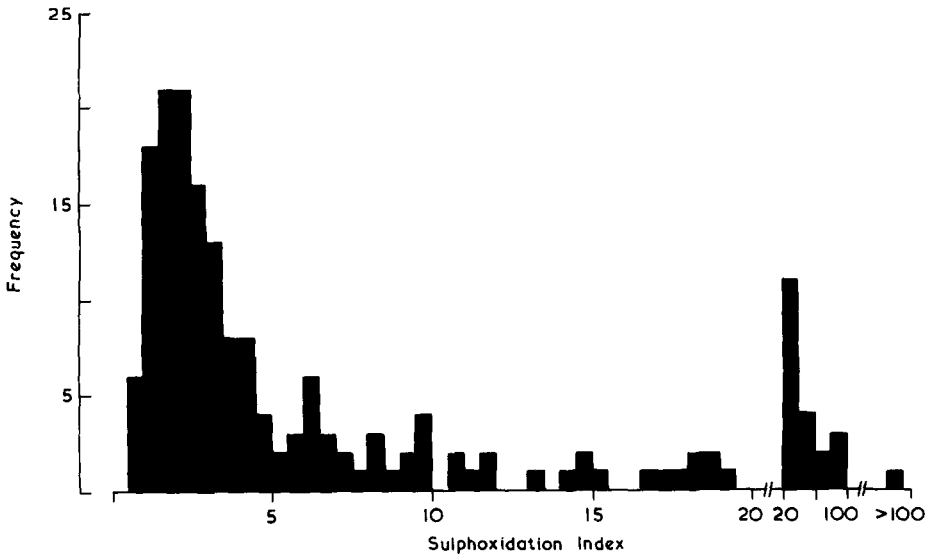

Figure 2. Frequency distribution of 'sulphoxidation index' in 181 unrelated British white volunteers.

If this impairment is true for the metabolic handling of other sulphur containing compounds it may be of considerable clinical interest and importance since several drugs (eg. phenothiazines, ethionamide) are metabolised to sulphoxides which are known to possess different pharmacological properties from the parent compounds (9,10). The reaction is also thought to be of importance in the metabolic activation and toxicity of certain sulphur containing drugs, particularly the thioamides (11).

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