The relationship between the acetylator and the sparteine hydroxylation polymorphisms

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SUMMARY Thirty-eight healthy white British Caucasian subjects were hydroxylator phenotyped with sparteine and acetylator phenotyped with sulphadimidine. The results showed that there was no significant difference in the mean sparteine metabolic ratio between eight rapid acetylators extensive hydroxylators and 27 slow acetylators extensive hydroxylators.

There are two well known genetic polymorphisms of drug metabolism in man. The first governs the acetylation of isoniazid, sulphadimidine, hydralazine,¹ dapsone,² procaine amide,^{3,4} sulphapyridine,⁵ a reduced metabolite of nitrazepam,⁶ and a metabolite of caffeine.⁷ The N-acetyl transferase enzyme which exhibits polymorphic activity is cytosolic in liver and jejunal mucosa.⁸ The second governs the hydroxylation of debrisoquine,⁹ sparteine,¹⁰ phenacetin,¹¹ metoprolol,¹² propranolol,¹³ bufuralol,¹⁴ guanoxon,¹⁵ and perhexilene.¹⁶ The polymorphic enzyme is a liver P450.¹⁷

A population of healthy subjects has been examined for evidence of interaction between the two polymorphisms.

Materials and methods

Ethical clearance for these experiments was given by the Ethical Committee of the Mersey Regional Hospitals Board and all subjects also gave their informed consent. Thirty-eight healthy white British Caucasian subjects were investigated by means of two phenotyping procedures.

The acetylator phenotyping procedure was carried out with sulphadimidine¹⁸ and the hydroxylator phenotyping was carried out with sparteine.¹⁹ The two phenotyping tests were carried out at least ten days apart. The analytical procedures for the acetylator phenotyping²⁰ and hydroxylator phenotyping¹⁹ were carried out by means of standard published methods.

Results

The acetylator phenotyping information is shown in

fig 1. Ten rapid and 27 slow acetylators were found. The results from the subject with an unclear acetylator phenotyping result (a poor hydroxylator) were not considered further in the analysis.

The hydroxylator phenotyping information within both acetylator phenotypes is shown in fig 2. The

FIG 1 The acetylator phenotyping data on the 38 healthy volunteer subjects. The single subject with the anomalous result (a high acetylation percentage in urine and a low acetylation percentage in plasma) was not included in further analyses.

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FIG 2 The frequency distributions of $\log_{10}$ sparteine metabolic ratio in urine in subjects of both acetylator phenotypes.

mean $\log_{10}$ sparteine metabolic ratio for eight rapid acetylators and extensive hydroxylators was 1.9002 ± 0.1423 SEM, whereas the mean $\log_{10}$ sparteine metabolic rate for 27 slow acetylators and extensive hydroxylators was 0.0155 ± 0.0700 SEM. Comparison of these two means reveals $t=0.77$, and so with 33 degrees of freedom $p>0.05$.

Two rapid acetylator poor hydroxylators were identified as shown in fig 2.

Discussion

In this sample there were too few poor hydroxylators to be able to say whether or not the two polymorphisms are genetically independent.

The rapid acetylator extensive hydroxylators had a mean sparteine metabolic ratio which was not significantly different from that of the slow acetylator extensive hydroxylators. This finding is as expected since the biochemical transformations governed by the two polymorphisms are quite different. Sparteine hydroxylation is performed in the endoplasmic

reticulum in vivo (microsomes in vitro), while N-acetylation is a cytosolic activity.

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