Application of the phenotyped panel approach to the detection of polymorphism of drug oxidation in man

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We have recently described the occurrence among Caucasians of a genetically determined polymorphism in respect of the alicyclic hydroxylation of the antihypertensive drug, debrisoquine (Mahgoub, Idle, Dring, Lancaster & Smith, 1977). About 6% of British Caucasians exhibit a defect for this reaction (PM phenotype) while the remainder are extensive hydroxylators of the drug (EM phenotype). Subsequently, it has been shown that PM subjects are also relatively defective in respect of the oxidative de-ethylation of phenacetin and the aromatic hydroxylation of guanoxan (Sloan, Mahgoub, Lancaster, Idle & Smith, 1978). It is obviously important to ascertain the types of oxidative reaction in man which may exhibit polymorphism. Rather than carrying out large population studies we have been examining the oxidative metabolism of a range of drugs in subjects of known oxidation phenotype with respect to debrisoquine hydroxylation.

In this paper we describe the metabolism of phenytoin and tolbutamide in two panels each of 4 subjects, one panel (A) consisting of individuals of EM phenotype and the second (B) of PM phenotype.

Fasted subjects were each given orally either phenytoin (200 mg) or tolbutamide (1 g) and serial urine samples collected for up to 48 h after dosing. The urine samples were analysed for p-hydroxyphenytoin (PHP) after phenytoin and carboxy-tolbutamide (CT) after tolbutamide administration, these being the main products of oxidative metabolism of the two drugs. From the data the appropriate rate constants for formation were calculated and are shown in Table 1.

Oxidation phenotype status had a marked effect upon the metabolism and elimination kinetics of phenytoin. EM subjects hydroxylated the drug more rapidly ($kf_{PHP} = 0.029 \pm 0.007\ h^{-1}$) than PM subjects ($kf_{PHP} = 0.016 \pm 0.003\ h^{-1}$; $2P < 0.01$). There was also a significant difference in the half-time for urinary elimination of the drug (EM $T_{\frac{1}{2}} = 41.8 \pm 12.8$ h; PM $T_{\frac{1}{2}} = 83.8 \pm 18.3$ h; $2P < 0.01$). By contrast the oxidative metabolism of tolbutamide does not appear to be significantly different between the two panels.

It is suggested that the phenotyped panel approach is a convenient procedure for detecting the types of oxidative reaction which may exhibit polymorphism in man.

Table 1 Rates of Oxidation and Half-times for Elimination of Phenytoin and Tolbutamide in Subjects of known Oxidation Phenotype

			Phenytoin		*Tolbutamide*	
	Subject	*Phenotype*	kf_{PHP} (h^{-1})	$T_{\frac{1}{2}}$ (h)	kf_{CT} (h^{-1})	$T_{\frac{1}{2}}$ (h)
Panel A	1	EM	0.034	30.5	0.093	12.2
	2	EM	0.025	36.5	0.140	11.9
	3	EM	0.021	60.1	—	—
	4	EM	0.036	40.2	—	—
	Mean		0.029	41.8	0.117	12.3
	± s.d.		±0.007	±12.8	±0.033	±0.5
Panel B	5	PM	0.011	108.9	0.080	13.6
	6	PM	0.019	63.5	0.102	10.6
	7	PM	0.016	81.9	—	—
	8	PM	0.016	81.7	—	—
	Mean		0.016	83.8	0.091	12.1
	± s.d.		±0.003	±18.3	±0.016	±2.1

Phenotyped according to Mahgoub *et al.* (1977). EM = extensive oxidizer, PM = poor oxidizer of debrisoquine kf_{PHP} and kf_{CT} are the minimum estimates of the apparent first-order rate constants for the formation of p-hydroxyphenytoin and carboxy-tolbutamide respectively. $T_{\frac{1}{2}}$ is the half-time for the elimination of drug in urine as its respective oxidative metabolite.

References

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Polymorphic hydroxylation of debrisoquine in Ghanaians

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The alicyclic hydroxylation of debrisoquine exhibits genetic polymorphism in Caucasians (Mahgoub, Idle, Dring, Lancaster & Smith, 1977). About 5–6% of British White Caucasians are defective in respect of this reaction (PM phenotype) while the remainder (EM phenotype) extensively 4-hydroxylate the drug. One feature of polymorphisms of drug metabolism reactions is that there can occur considerable inter-ethnic differences in the occurrences of the various phenotypes. Accordingly, we have been examining the metabolic hydroxylation of debrisoquine in a variety of different ethnic groups including, Egyptians, Nigerians, Gambians, Ghanaians, Malaysians and Chinese. In this communication we report on our studies with Ghanaians.

Eighty healthy Ghanaian medical students, male and female each took a single tablet of Declinax (10 mg debrisoquine) early morning after an overnight fast and the urine collected for a 0–8 h period. This was analysed by g.c. for debrisoquine and 4-hydroxydebrisoquine. A metabolic ratio was calculated for each subject this being derived as follows: % dose excreted unchanged/% dose as 4-hydroxydebrisoquine in the urine in the 0–8 h period. A frequency histogram was constructed from the results (Figure 1).

The data obtained indicates that the 4-hydroxylation of debrisoquine is polymorphic with an incidence of 'poor metabolisers' (PM) similar to that found for Caucasians. There is also an indication that the metabolic ratio frequency distribution in Ghanaians is trimodal, suggesting that homozygous and heterozygous EM subjects are distinguishable, a situation not evident with our Caucasian subjects (Figure 1).

Further studies revealed strong positive rank-correlation between the alicyclic and aromatic hydroxylation of debrisoquine in both Ghanaians and Caucasians ($r_{(s)} = 0.82$ and 0.83 respectively, $P < 0.01$) indicating the involvement of the same single gene in the two types of carbon-centre oxidation.

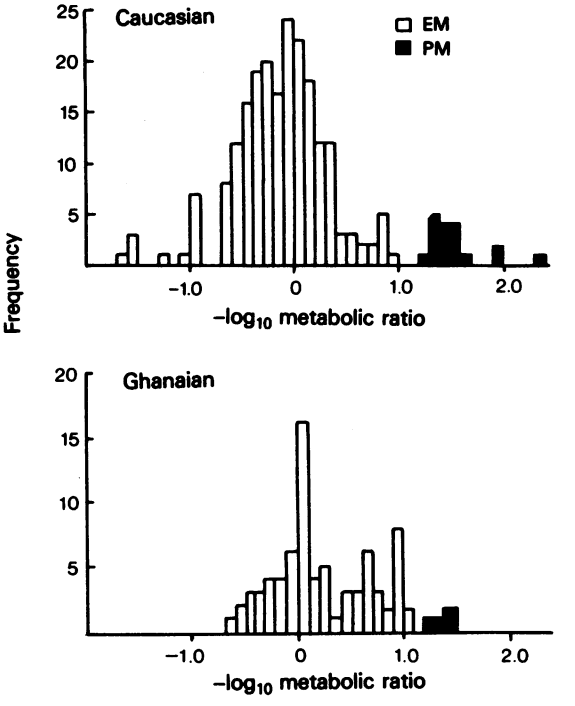

Figure 1 Frequency distribution of $\log_{10}$ metabolic ratios in Ghanaian and Caucasian study populations.

$$\left(\text{Metabolic ratio} = \frac{\%\text{ Dose eliminated as debrisoquine}}{\%\text{ Dose eliminated as 4-hydroxydebrisoquine}} \text{ in 0–8 h}\right).$$

Reference

MAHGOUB, A., IDLE, J.R., DRING, L.G., LANCASTER, R. & SMITH, R.L. (1977). Polymorphic hydroxylation of debrisoquine in man. *Lancet* **ii**, 584–586.