Oxidation phenotype and metiamide metabolism

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Metiamide was originally introduced as a histamine H_2-antagonist but it was subsequently withdrawn as its clinical use was associated with the occurrence of a few cases of agranulocytosis (Burland, Sharpe, Colin-Jones, Turnbull & Bowskill, 1975; Forest, Shearman, Spence & Celestin, 1975). Whether or not the dyscrasia is associated with idiosyncrasies in the metabolism of metiamide is not known.

In this communication we report the metabolism of [^{14}C]-metiamide in human subjects previously phenotyped as extensive (EM) or poor (PM) metabolizers of debrisoquine, guanoxan and phenacetin (Sloan, Mahgoub, Lancaster, Idle & Smith, 1978).

Eight healthy adult male volunteers, comprising four EM and four subjects were given orally [^{14}C]-metiamide (50 mg, 10 μCi). Bulked 0–24 h urines were analysed for metiamide and its metabolites (see Taylor, 1973) by thin-layer chromatography and radiochromatogram scanning.

Recovery of [^{14}C] was significantly different ($P < 0.05$) between phenotypes, EM subjects eliminating 77.9 ± 3.1% (mean ± s.d.) and PM subjects 70.1 ± 7.2% of the dose in the 0–24 h urine. All urines revealed four major [^{14}C] peaks on radiochromatography. By comparison with authentic standards, these corresponded to metiamide, metiamide sulphoxide, hydroxymethylmetiamide and unidentified polar material. The quantitative aspects of the metabolism of metiamide in both phenotypes are given in Table 1. Mean phenotype elimination of metabolites was as follows: metiamide (EM, 45.2 ± 6.4%; PM, 36.0 ± 6.6%; $P < 0.05$), metiamide sulphoxide (EM, 8.2 ± 1.4%; PM, 6.1 ± 0.4%; 2 $P < 0.05$), hydroxymethyl-metiamide (EM, 6.7 ± 1.8%; PM, 4.6 ± 0.8; $P < 0.05$) and the polar material (EM, 17.8 ± 4.0%; PM, 23.3 ± 3.4%; $P < 0.05$).

The findings indicate that there occur small but significant inter-phenotype differences in the metabolic handling of metiamide. The possible significance of this in relation to metiamide-induced agranulocytosis remains to be assessed.

Table 1 Urinary Metabolites of Metiamide in Human Phenotypes

		% Dose excreted as:				
Subject	*Phenotype**	*Metiamide*	*Sulphoxide*	*Hydroxymethyl*	*Unidentified*	*Total*
1	EM	38.8	10.1	9.1	18.4	76.4
2	EM	53.3	7.3	6.0	12.6	79.2
3	EM	41.6	8.4	6.8	17.6	74.4
4	EM	47.2	6.9	4.9	22.4	81.4
Mean ± s.d.		45.2 ± 6.4	8.2 ± 1.4	6.7 ± 1.8	17.8 ± 4.0	77.9 ± 3.1
5	PM	30.9	6.1	3.4	21.7	62.1
6	PM	38.8	6.4	4.9	19.7	69.8
7	PM	44.0	6.4	5.1	24.1	79.6
8	PM	30.4	5.6	5.1	27.6	68.7
Mean ± s.d.		36.0 ± 6.6	6.1 ± 0.4	4.6 ± 0.8	23.3 ± 3.4	70.1 ± 7.2

* Phenotyped according to Mahgoub *et al* (1977).

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