racemic form with, in addition, a biochemical investigation of monoamine oxidation to correlate with clinical effects.

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DRUG METABOLISM IN WHITE VEGETARIANS

Asian vegetarians metabolize antipyrine more slowly than Asians or Europeans who eat meat regularly (Mucklow, Caraher, Henderson & Rawlins, 1979; Fraser, Mucklow, Bulpitt, Kahn, Moulds & Dollery, 1978; Wilmana, Brodie, Mucklow, Fraser, Toverud, Davies, Dollery, Hillyard, McIntyre & Park, 1979). The dietary factors responsible for this effect have not been fully elucidated. We now wish to report a study of hepatic drug metabolism in white vegetarians, using antipyrine, paracetamol and phenacetin as probes of oxidation, conjugation and metabolism at first pass.

Nine white vegetarians (six males, three females; 23–40 years) agreed to participate. Seven were lactovegetarians and two were vegans. They had been vegetarians for a mean of 5.1 years (0.5–14 years). None had any clinical evidence of hepatic, haematological or renal disease and baseline haemoglobin, urea and electrolytes and liver function tests were all normal. None smoked cigarettes or were on regular medication. All were informed about the aims of the study and gave their written informed consent. The study had the approval of the Research Ethics Committee.

Each subject listed and weighed all food consumed in 1 week. Calculation of daily consumption of calories, fat, carbohydrate and protein was based on McCance & Widdowson's Composition of Foods (1978). The volunteers were studied on two occasions. On the first, antipyrine 600 mg and paracetamol 1.5 g were taken together and on the second, phenacetin 900 mg was ingested, both following an overnight fast. Unstimulated salivary samples were taken at 0, 2, 3, 5, 8, 12, 24 and 32 h for antipyrine and paracetamol measurements. In the phenacetin study, plasma was obtained for analysis at 0, 0.5, 1, 2, 3, 4 and 5 h after ingestion of the drug. Antipyrine and paracetamol were measured using specific gas chromatographic methods (Fraser, Mucklow, Murray & Davies, 1976; Prescott, 1971). Phenacetin

Table 1 Antipyrine, paracetamol and phenacetin metabolism in white vegetarian and non-vegetarian subjects (mean ± s.e. mean)

	Antipyrine		*Paracetamol*		*Phenacetin*	
	$T_{\frac{1}{2}}$ (h)	*Cl* (*ml min*$^{-1}$ *kg*$^{-1}$)	$T_{\frac{1}{2}}$ (h)	*Cl* (*ml min*$^{-1}$ *kg*$^{-1}$)	$T_{\frac{1}{2}}$ (h)	*AUC* (μg *min ml*$^{-1}$)
Vegetarians	11.8 ± 0.7	0.7 ± 0.06	2.8 ± 0.2	3.6 ± 0.3	1.04 ± 0.2	191 ± 71
	n = 9		n = 9		n = 8	
Non-vegetarians	10.4 ± 0.4	0.7 ± 0.03	2.4 ± 0.1*	4.1 ± 0.1	0.9 ± 0.06	291 ± 42
	n = 60		n = 60		n = 12	

*$P < 0.05$.

was assayed by high performance liquid chromatography using a modification of the method of Duggin (1976) with 4-bromoacetanilide as internal standard. Half-life ($T_{\frac{1}{2}}$) was calculated by least squares regression analysis, apparent volume of distribution (aV_d) by back extrapolation of the terminal β phase of the concentration-time curve, clearance (Cl) from the expression of $Cl = 0.693/T_{\frac{1}{2}} \times aV_d$ and area under the concentration time curve (AUC) by the trapezoidal rule and extrapolation to infinity.

The results are displayed in Table 1. Comparison is made with results obtained from our previous studies in white, non-vegetarian healthy Londoners using identical protocols and methodology. The antipyrine and paracetamol data in these subjects have been reported elsewhere (Dollery, Fraser, Mucklow & Bulpitt, 1979). The twelve meat-eating subjects taking phenacetin were all non-smokers aged between 22–38 years.

Comparison of pharmacokinetic values for vegetarians and non-vegetarians are shown in Table 1. Half-lives of all three drugs were slightly longer in the vegetarians but only the data for paracetamol attained statistical significance ($P < 0.05$). These differences were all very small and white vegetarians would appear to metabolise antipyrine, paracetamol and phenacetin similarly to non-vegetarians. Thus, the substantial prolongation of antipyrine half-life (16.3 ± 0.8 h; Wilmana *et al.*, 1979) and reduction in clearance (0.91 ± 0.07 ml min^{-1} kg^{-1}; Mucklow *et al.*, 1979) found in vegetarian Asians remains unexplained. Mucklow *et al.* (1979) found a highly significant difference between the daily protein intake of Asian vegetarians (51.9 ± 4.5 g) and non-vegetarians (77.8 ± 3.7 g). However, the correlation with animal fat intake was even stronger and these authors suggested that this explained the low antipyrine clearances. In a later study involving isocaloric substitution of vegetable fat for animal fat (and *vice versa*), they were unable to confirm this (Mucklow, Caraher, Idle, Rawlins, Sloan, Smith & Wood, 1980).

Our white vegetarians had a low intake of animal fat but the daily protein consumption (78 ± 4.5 g) was similar to that of non-vegetarians (78 g per day—based on McCance & Widdowson's Composition of Foods, 1978). This would suggest that the low protein content of the Asian vegetarian diet may be responsible for the differences in drug handling between Asian and white vegetarians. The prolonged antipyrine half-lives found in vegetarian Asians are of the same order as that in volunteers on a low protein diet (Kappas, Anderson, Conney & Alvares, 1976) and malnourished children (Homeida, Karrar & Roberts, 1979). Dietary protein supplementation in these subjects to give a normal protein intake reduced the antipyrine half-lives to similar values to those found in white vegetarians in this study.

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ACETANILIDE PHARMACOKINETICS IN KWASHIORKOR

There has recently been considerable interest in drug metabolism in patients with kwashiorkor. It has been demonstrated that in the acute phase of the disorder both polymorphic acetylation (Buchanan, Eyberg & Davis, 1979a), and antipyrine oxidation (Narang, Mehta & Mathur, 1979; Krishnaswamy & Naidu 1977; Buchanan, Eyberg & Davis 1979b) are impaired. Further evidence of impaired hepatic microsomal oxidation in kwashiorkor has been sought in the present study, using acetanilide as a model substrate.

Five children (aged 16.2 ± s.d. 5.8 months), with kwashiorkor as defined by the Wellcome Classification (FAO/WHO 1971) were studied after informed consent had been obtained from their parents, on admission to hospital (body weight 6.3 ± s.d. 1.5 kg) and subsequently after a 21 day period of nutritional rehabilitation (body weight 6.8 ± s.d. 1.3 kg). The study received prior approval from the University of Witwatersrand Ethical Committee. The patients were receiving no other drugs at the study times except oral potassium supplements. Acetanilide (50 mg/kg metabolically active mass) was administered after 4–6 h fast, and venous blood samples (3 ml) were obtained at 1, 2, 3, 4 and 6 h via an indwelling cannula. Plasma was separated and stored at −20°C until analysis in duplicate by flame ionization gas liquid chromatography. Phosphate buffer (0.5 ml) was added to 0.5 ml plasma, and the acetanilide was extracted into 2.5 ml ethyl acetate (containing 2 mg/l butyranilide as internal standard). After mixing and centrifugation, 2.3 ml of the ethyl acetate was transferred to a clean tube, evaporated to dryness, and the residue

Table 1 Acetanilide pharmacokinetics in the five patients studied

	On admission				*On recovery*			
Patient number	V_d (*l*)	$T_{\frac{1}{2}}$ (*h*)	k_{el} (h^{-1})	*Cl* ($l\,h^{-1}$)	V_d (*l*)	$T_{\frac{1}{2}}$ (*h*)	k_{el} (h^{-1})	*Cl* ($l\,h^{-1}$)
1	4.85	6.45	0.11	0.52	5.92	2.05	0.34	2.00
2	4.85	4.36	0.16	0.77	8.10	2.14	0.32	2.62
3	5.17	2.74	0.25	1.31	4.64	1.69	0.41	1.90
4	4.95	2.39	0.29	1.43	6.65	1.50	0.46	3.07
5	6.58	7.95	0.09	0.57	6.00	1.56	0.44	2.66
Mean	5.28	4.78	0.18	0.92	6.26	1.79	0.39	2.45
s.e. mean	0.33	1.07	0.04	0.19	0.56	0.13	0.03	0.22

V_d = apparent volume of distribution.
$T_{\frac{1}{2}}$ = half-life.
k_{el} = elimination rate constant.
Cl = plasma clearance.