Paracetamol Metabolism in African Villagers

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1 Paracetamol clearance has been measured from serial serum samples in 49 healthy black Africans from a village in Southern Africa.
2 The subjects are minimally exposed to known environmental inducing or inhibiting agents and the staple diet consists of maize cereal and greens.
3 The mean clearance ($\pm$ SD) was 4.98 ± 1.61 ml min^{-1} kg^{-1}, which is significantly faster than the values found in previous investigations with paracetamol in whites and Asian immigrants in London. The mean half-lives were fairly similar but the apparent volumes of distribution were also found to be larger in the present study.
4 The ethnic difference in paracetamol kinetics identified in this study is possibly genetically controlled.

Introduction

It has been suggested that environmental factors may modify the conjugation of paracetamol (Mucklow *et al.*, 1980). The rate of disappearance of paracetamol from plasma can be assumed to reflect the overall rate of conjugation; about 55% of a therapeutic dose appears in urine as the glucuronide and about 30% as the sulphate conjugate (Kalow, 1982). Although paracetamol is subject to first-pass elimination this assumption remains valid because the proportion conjugated presystemically is only about 12% at doses of 1 g or greater (Mucklow *et al.*, 1980). The latter authors compared paracetamol elimination in a heterogeneous population sample, drawn from an urban community and comprising 76 whites and 38 Asian immigrants in London. Paracetamol clearance was 21% slower in Asians than in whites and half-life 18% longer. The apparent racial difference in mean paracetamol clearance was suggested to be partly related to the contrasting use of social drugs such as alcohol, tobacco and the contraceptive pill and to the presence or absence of meat in the diet. Asians used all these drugs to a lesser extent than whites and 29 (76%) of them were vegetarian.

The present study was undertaken to examine the rate of drug conjugation in a sample of traditionally living black Africans with low protein intake and minimal exposure to environmental chemicals. Antipyrine metabolism was studied simultaneously, the results of which will be the subject of a separate report.

Methods

Subjects and procedure

Tshikundamalema is a small village in an enclosed valley of the Republic of Venda in Southern Africa. The inhabitants of this very poor developing community have recently been the victims of a devastating drought of three years duration. As a consequence farming with peanuts and maize became impossible and the number of livestock raised was greatly reduced. The mashonza or tree worms which ordinarily serve as an additional source of protein have also practically disappeared from their diet. Food is mainly maize cereal, with a protein content of only about 8.8%, together with greens (merôho) consisting of veld flora, spinach and cabbage. Beef and chicken, when available, are added to this to make a stew. The only sources of alcohol are mabundu and mahapé, the former being a sour fermented maize porridge with very low alcohol content and the latter a brewed beer with an alcohol content of 3 g/100 ml or less. Tobacco use is confined to an occasional cigarette.

The protocol for this study was approved by the ethical committee of the University of Pretoria. Using an interpreter, the nature of the study was explained to each volunteer subject, whereafter each signed consent to take part. None showed evidence of liver or renal disease and all were in good health and receiving no regular medication.

Weight and height were measured and all volunteer subjects were questioned about use of alcohol and caffeine-containing beverages. A diet history was obtained from each subject by a qualified dietician. No attempt was made to quantify the food intake as the retrospective dietary assessments gleaned through an interpreter were considered to be too inaccurate. Rather, an attempt was made to record the frequency with which supplemental protein was taken with the staple diet of maize and greens. Milk was never drunk as such but added to tea and coffee or taken over porridge and usually only one egg is eaten per occasion.

A total of 50 subjects (35 women) were admitted to the study. After an overnight fast each subject received 600 mg (two 300 mg capsules) of antipyrine and 1500 mg (three 500 mg tablets) of paracetamol, followed by a glass of drinking water. No food or drink was permitted for a further 2 h. At regular times after drug administration ($t = 1, 2, 3, 5, 8, 24$ and 32 h) blood samples from a forearm vein were collected for later drug analysis. The 1, 2, 3, 5 and 8 h samples were analysed for paracetamol.

At 1 h blood was also taken for blood chemistry and haemoglobin estimations. The subjects were requested not to drink alcohol for 24 h before or during the study.

Paracetamol analysis

Serum paracetamol concentrations were determined by reverse-phase high-performance liquid chromatography with a 25 cm Spherisorb 5 μm ODS column preceded by a 4 cm guard column with the same packing. The paracetamol was eluted isocratically with 6% (v/v) acetonitrile and 94% (v/v) 0.05 M-phosphate buffer, pH 3.0, with detection at 247 nm and column temperature 37°C.

Interpretation of results
A one-compartment model was assumed and the concentration at zero time (C_o) and the elimination half-life were estimated. The apparent volume of distribution (V_d) was calculated as dose/C_o, while total body clearance, adjusted for weight, was calculated by using the formula

$$\text{clearance} = \frac{0.693 \cdot \text{dose}}{T_{1/2} \cdot C_o \cdot \text{body weight}} \text{ ml min}^{-1} \text{ kg}^{-1}$$

Statistical methods
Means and standard deviations were calculated for paracetamol clearance, half-life and volume of distribution and are shown on Table 2.

Differences between groups were tested for significance by Student's *t* test. More sophisticated statistical analyses on this type of data have been criticized in the literature (Vesell & Penno, 1983).

Results

Compliance was optimal except for one female volunteer subject who apparently did not swallow the paracetamol tablets. The data from 49 subjects (34 women and 15 men) could therefore be analysed. The mean age for women and men were, respectively, 28.3 (range 20–57) and 28.5 (range 20–52) years. Clinically the nutritional status of 38 subjects was considered to be good and that of the rest reasonable. The mean weight of the women was 51.57 kg and that of the men 55.20 kg. The mean height of the females and males was 1.6 m.

The intake pattern of animal protein, alcohol and tea and coffee is shown in Table 1. When meat is available it is added to the greens and served as a stew. Usually one egg is eaten per occasion and milk is only used with porridge and in tea and coffee. The diet was fairly uniform throughout the population sampled and the staple foods were maize cereal and greens.

With a mean value of 43.9 g/l the serum albumin was on the lower end of normal (range 43.0–54.0 g/l) and 19 subjects had values below the normal range. Seventeen had elevated alkaline phosphatase values but the mean bilirubin value of 7.0 μmol/l was similarly at the lower end of normal, coinciding with the lowest normal value (range 7.0–32.0 μmol/l). The mean total cholesterol was 3.61 mmol/l with the normal range for the laboratory being 3.5–7.2 mmol/l. The mean haemoglobin value was 14.4 g/100 ml with the lowest individual value being 11.5 g/100 ml.

No volunteer subject received long-term medication and the use of social drugs was minimal. No hormonal contraception control was practiced. Eleven admitted to smoking an occasional cigarette, but we observed no one smoking over the two-day trial period.

Table 1 Intake of animal protein, alcohol and caffeine-containing beverages

	Never	Once a month	Twice a month	Once a week	Twice a week	Every day
Protein intake						
Meat	**2**	**17**	23	5	3	—
Eggs	18	11	14	5	1	1
Milk	29	8	8	2	3	—
Alcohol consumption						
Mabundu	9	5	13	10	10	3
Mahapé	36	—	1	1	7	5
Use of tea and coffee	9	—	2	5	6	28

Mean values for paracetamol clearance, half-life and apparent volume of distribution are shown in Table 2 according to sex, alcohol consumption and serum albumin and alkaline phosphatase values. The only significant difference found was between mean clearance for men and women ($P < 0.01$).

Discussion

The subjects who took part in this study exist under 'near basal' conditions, i.e. a lifestyle which minimally, rather than moderately or heavily, exposes them to environmental inducing or inhibiting agents (Vesell & Penno, 1983).

Paracetamol seems to be a suitable probe drug for the study of hepatic conjugation reactions (Kalow, 1982) and the enzyme system mainly responsible for its clearance, i.e. for glucuronide formation, is inducible (Lecamwasam, 1975).

Mucklow *et al.* (1980) compared paracetamol elimination in 76 whites and 38 Asian immigrants in London. Paracetamol clearances (mean ± SD) were

Table 2 Paracetamol clearance, half-life and volume of distribution (mean ± SD)

Subjects	Clearance (ml min^{-1} kg^{-1})	Half-life (h)	Volume of distribution (l/kg)
49 volunteers	4.98 ± 1.61	2.33 ± 0.64	0.94 ± 0.19
34 women	4.52 ± 1.15	2.27 ± 0.68	0.87 ± 0.14
15 men	6.03 ± 2.01	2.38 ± 0.87	1.10 ± 0.21
18 with hypo- albuminaemia	5.16 ± 1.80	2.33 ± 0.66	0.96 ± 0.17
17 with raised alkaline phosphatase	4.62 ± 1.30	2.32 ± 0.53	0.89 ± 0.14
5 with daily alcohol consumption	5.69 ± 1.84	1.82 ± 0.58	0.86 ± 0.18

3.90 ± 1.07 ml min^{-1} kg^{-1} for whites and 3.10 ± 1.11 ml min^{-1} kg^{-1} for Asians. The contrasting use of social drugs such as alcohol, tobacco and oral contraceptives could partially account for the apparent racial difference in mean paracetamol clearance. Although dietary differences existed between the two groups, analysis of their effect independent of race was impossible since all but one of the vegetarians were Asian and the non-vegetarians were nearly all white (Fraser *et al.*, 1979). Mucklow *et al.* (1980) concluded that the major findings of their study suggested that environmental factors may modify the conjugation of paracetamol.

In the present study the paracetamol clearance (ml min^{-1} kg^{-1} as mean $\pm$ SD) was 4.98 ± 1.61, which is significantly faster than in the studies quoted above ($P < 0.01$). However, the Asians (Mucklow *et al.*, 1980) and the Vendas are both practically lactovegetarian and use social drugs sparingly. The increased paracetamol clearance in the five subjects with a daily alcohol intake is in keeping with the known fact that continued alcohol use results in microsomal enzyme induction (Vesell *et al.*, 1971). Environmental factors may therefore modify the rate of conjugation of paracetamol. However, present knowledge would seem to support heritability as the major determinant of ethnic differences in conjugative clearance.

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