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ENVIRONMENTAL FACTORS AFFECTING PARACETAMOL METABOLISM IN LONDON FACTORY AND OFFICE WORKERS

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1 Paracetamol elimination was measured, using serial saliva samples, in 114 London factory and office workers, 76 Whites and 38 Asian immigrants.

2 Use of social drugs such as alcohol, tobacco and the oral contraceptive varied considerably within the sample, being appreciably greater in White subjects.

3 Paracetamol clearance was 21% slower in Asians than in Whites and half-life 18% longer. The total range of clearance was 1.86–6.78 $ml\,min^{-1}\,kg^{-1}$.

4 Clearance was slower in women than in men, increased with increasing alcohol intake and cigarette consumption, and was more rapid in those women using the oral contraceptive. The effects of alcohol and the oral contraceptive were also found in White subjects alone.

5 The variables found to correlate independently with paracetamol clearance accounted for only 27% of the total sample variance, however, and are unlikely to be the major determinants of paracetamol elimination in man.

Introduction

The wide variation in the rate of drug metabolism in man is one of the major reasons for inter-individual variability in response to drugs. Evidence for variation in oxidation rates is considerable (Loeser 1961; Hammer & Sjoqvist, 1976; Vesell, 1972) and it has been possible to identify numerous factors, both genetic and environmental, which contribute to this variation (Alexanderson, Evans & Sjoqvist, 1969; Alvares, 1978; Conney, 1967; Fraser & Dollery, 1978; Vesell, 1972). Although the initial phase of biotransformation commonly involves some form of oxidation (Williams, 1959), many drug molecules take part in primary synthetic reactions with endogenous conjugating agents. The extent of, and reasons for, variability in the rate of drug conjugation are much less precisely defined than is the case for drug oxidation.

The present study was undertaken to examine variation in the rate of drug conjugation in a sample of healthy individuals drawn from an urban population and to assess the relative importance of different factors associated with this variation. Paracetamol (acetaminophen) was used as a model drug since it is metabolized largely by primary conjugation to glucuronide and sulphate conjugates (Cummings, King & Martin, 1967). This study also involved simultaneous measurement of drug oxidation rate in the same subjects, using antipyrine as a model, and the results of that investigation have been reported separately (Fraser, Mucklow, Bulpitt, Kahn, Mould & Dollery, 1979). The close correlation between plasma and saliva concentrations of both antipyrine (Fraser, Mucklow, Murray & Davies, 1976) and paracetamol (Glynn & Bastain, 1973) made it possible to measure elimination of both drugs using serial saliva samples.

Methods

Subjects and procedure

Letters were written to the personnel managers of 25 large London firms requesting co-operation in the study. Four firms agreed to allow an approach to be made to their employees, who were then circulated with an explanation of the nature and purpose of the study. For a number of reasons a purely random sample could not be made and volunteers were

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invited to indicate their willingness to take part by giving signed, informed consent. Liver, heart or thyroid disease, any chronic illness, a history of jaundice, use of sedatives and other regular medication were contraindications to inclusion in the study.

In order to obtain a uniformly distributed sample, volunteers were stratified for sex and age (18–30, 31–40, 41–50 and 51–60 years). As there was an excess of women aged 18–30 and 31–40, subjects were randomly selected from the volunteers in those two categories. The distribution by sex and age is shown in Table 1. Almost two-thirds of the sample were female, with a predominance of younger people, reflecting the distribution of the employees of the four factories.

A total of 114 subjects were studied, covering all personnel from manager to messenger, and divided equally between office and factory workers. There were 76 Whites (of similar ethnic origin) and 38 Asians, and 18 of the latter were factory workers from a single firm.

Weights and heights of all subjects were recorded. A history was taken of all socially used drugs, i.e. cigarettes, alcohol, coffee, tea and the contraceptive pill. Subjects were classified as smokers or non-smokers and the number of cigarettes per day was recorded. Alcohol consumption was estimated as drinks per week, one half-pint of beer being equated with a standard measure of spirit, sherry or glass of wine (approximately 12 g of alcohol) (Laurence, 1973). A coffee/tea score of 'cups of coffee per day + 0.6 × cups of tea per day' was obtained (Nagy, 1974), and use of the contraceptive pill was recorded.

Diet was classified as vegetarian or non-vegetarian. Only 9 (24%) of the Asians were non-vegetarian, and only one White subject was a vegetarian. Some Asians ate meat only occasionally and were classified as vegetarian. The quantity of dairy products and egg eaten varied considerably among vegetarians but no attempt was made to assess this further.

On arrival at work after an overnight fast each subject received 1500 mg (three 500 mg tablets) of paracetamol and 600 mg of antipyrine orally, accompanied by 150 ml of drinking water. No food or drink were permitted until after the first saliva sample was obtained. Samples were collected at 2, 3, 5, 8, 24 and 32 h, salivary flow being stimulated by a piece of Parafilm (Gallenkamp). After the particulate matter in the sample had settled, the supernatant was decanted, and the 3, 5 and 8 h samples divided into two portions. The 2, 3, 5 and 8 h samples were analysed for paracetamol and the 3, 5, 8, 24 and 32 h samples for antipyrine. Blood samples were taken by venepuncture on the second day of the study for total protein, albumin, bilirubin, alkaline phosphatase and aspartate transaminase estimations. Four subjects declined blood sampling and their values were set to the mean for males or females in the subsequent analysis. Subjects were requested not to drink alcohol or take analgesics for 24 h before, or during the study.

Paracetamol estimations were performed by a gas chromatographic method (Prescott, 1971). Elimination half-lives ($T_{\frac{1}{2}}$) were estimated from the log saliva concentration: time plot, using the method of least squares and assuming a one-compartment model (Perucca & Richens, 1979).

The saliva paracetamol concentration at zero time (C_0) was obtained by back extrapolation of the terminal regression line. Total body clearance was calculated using the formula:

$$\text{Clearance} = \frac{0.693.\ \text{Dose}}{T_{\frac{1}{2}}.C_0.\text{body weight}}\ \text{ml min}^{-1}\,\text{kg}^{-1}$$

Serum samples were analysed using a Technicon SMA plus autoanalyser. Multiple regression analysis were carried out using a stepwise regression programme (Biomedical Computer Programme BMD 02R). Differences between groups were tested for significance using Student's *t*-test.

Table 1 Distribution by age and sex of 114 London subjects

Age group (years)	*Males (number)*	*Females (number)*	*Totals*
18–30	20	31	51
31–40	7	21	28
41–50	12	12	24
51–60	4	7	11
Totals	43	71	114
Mean age	35.1	32.8	33.6

Results

The anthropometric and biochemical indices of nutritional status are shown in Table 2, according to sex and ethnic origin. Whites were taller and heavier than Asians but ponderal indices showed no significant difference. Women had a lower haemoglobin than men ($P<0.001$) and Asian women had significantly lower values than White women ($P<0.005$). Serum albumin was also significantly lower in Asians than in Whites ($P<0.02$) but there were no significant differences in globulin, bilirubin, alkaline phosphatase or aspartate transaminase.

The use of social drugs differed considerably in the two ethnic groups (Table 3). Asians used all these drugs to a lesser extent than Whites. Only one Asian woman smoked, only three drank alcohol and only two used the contraceptive pill.

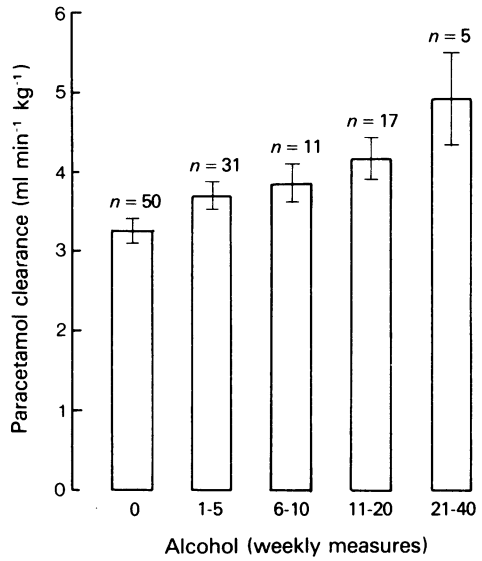

Figure 1 Paracetamol clearance in 114 subjects in relation to weekly consumption of alcohol.

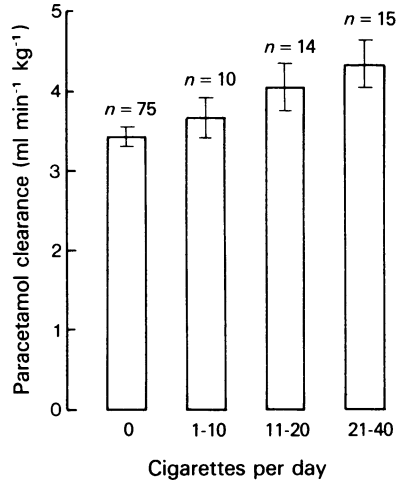

Figure 2 Paracetamol clearance in 114 subjects in relation to daily number of cigarettes smoked.

Paracetamol clearances, half-lives and volumes of distribution are shown in Table 4. The range of clearance for the whole sample was 1.86 to 6.78 ml min^{-1} kg^{-1}. The mean clearance in Asians was 21% slower than in Whites and the mean half-life 18% longer. Clearance (mean $\pm$ s.d.) was faster in men (3.94 ± 1.07 ml min^{-1} kg^{-1}) than in women (3.45 ± 1.16) ($P < 0.05$) but half-life did not differ significantly. There was no significant difference in the volume of distribution of paracetamol either between Whites and Asians or between men and women.

The data were further analysed to see if the apparent racial difference in paracetamol elimination could be explained by differences in alcohol intake, cigarette consumption, use of the contraceptive pill and diet. Mean paracetamol clearance was significantly faster in those who took alcohol (3.94 ± 1.05 ml min^{-1} kg^{-1}) than in those who did not (3.25 ± 1.16) ($P < 0.005$) and faster in smokers (4.06 ± 1.1) than in non-smokers (3.42 ± 1.11) ($P < 0.005$). Figures 1 and 2 show the graded increase in clearance with increasing alcohol and cigarette usage. Figure 3 shows the difference in clearance between women who used the oral contraceptive and women who did not, use of alcohol and tobacco being similar in the two groups. Mean clearance was 30% faster in pill-users ($P < 0.02$).

Analysis of clearance according to the presence or absence of meat in the diet differed little from the analysis according to race, the vegetarians being

Table 2 Nutritional indices of 114 Londoners, by sex and ethnic origin (mean values)

	Males		*Females*	
	Whites (n=*34*)	*Asians* (n=*9*)	*Whites* (n=*42*)	*Asians* (n=*29*)
Weight (kg)	74.0	63.9	62.1	56.5
Height (cm)	176	168	163	157
Ponderal index (Wt/ht^2 : g/cm^2)	2.39	2.26	2.35	2.28
Albumin ($g\ l^{-1}$)	47.1	46.4	45.4	44.2
Globulin ($g\ l^{-1}$)	28.5	31.1	28.7	29.5
Haemoglobin ($g\ 100\ ml^{-1}$)	15.0	14.4	13.2	12.0

Table 3 Social drug use among 114 London subjects, by sex and ethnic origin

	Males		Females	
	Whites (n=*34*)	Asians (n=*9*)	Whites (n=*42*)	Asians (n=*29*)
Smokers	14	2	22	1
Number of cigarettes per day (mean)	20.9	10.0	19.9	—
Users of alcohol	28	2	31	3
Number of alcohol measures per week (mean)	12.0	6.5	7.5	2.0
Coffee/tea index per day (mean)	5.5	2.6	5.1	2.3
Users of contraceptive pill	—	—	12	2

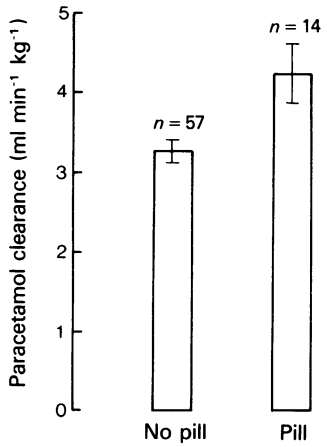

Figure 3 Paracetamol clearance in 71 women according to use of the oral contraceptive pill.

almost all Asian. Clearance was faster in the 84 subjects who ate meat regularly (3.84 ± 1.1 ml min^{-1} kg^{-1}) than in the 30 vegetarians (3.07 ± 1.09) ($P < 0.005$).

Multiple regression analysis

First order correlation coefficients for paracetamol clearance and 10 observed variables reached a significant level ($P < 0.05$) as shown in the correlation matrix (Table 5). These variables were: weekly alcohol intake and race ($P < 0.001$); diet, smoking status, number of cigarettes per day and height ($P < 0.01$); globulin, coffee/tea index, oral contraceptive usage and sex ($P < 0.05$). However, many of these variables correlated significantly with each other and stepwise multiple regression analysis was therefore performed to identify the independent correlates.

Table 4 Paracetamol clearance, half-life and volume of distribution for 76 Whites, 38 Asians, and all 114 London subjects

	Whites	*Asians*	*All subjects*
Clearance (ml min^{-1} kg^{-1})			
Mean	3.90	3.10**	3.63
s.d.	1.07	1.11	1.15
Half-life (h)			
Mean	2.36	2.78*	2.50
s.d.	0.51	0.87	0.68
Volume of distribution (l kg^{-1})			
Mean	0.78	0.74	0.77
s.d.	0.23	0.33	0.27

Significance of difference between Asians and Whites: **$P < 0.001$, *$P < 0.01$.

In view of the apparent racial difference in paracetamol clearance, separate analyses were carried out for Whites, Asians and all subjects together. Table 6 shows the independent correlates identified in these analyses with their partial regression coefficients and, for each analysis, the multiple correlation coefficient and its square. The constants for the multiple regression equation are also shown.

Amongst all 114 subjects, paracetamol clearance increased with increasing alcohol intake and cigarette consumption and fell as ponderal index increased. Although generally slower in women than in men, clearance was significantly faster in those women who used the oral contraceptive. In view of its close association with social drug usage, race could not be excluded with any certainty from the multiple regression equation. Nevertheless, it is of interest that both alcohol and the oral contraceptive were also identified as independent correlates with clearance in Whites alone. Analysis of Asians alone revealed only height as an independent correlate but social drug usage was minimal in this small group of subjects. In no single analysis did the variables included in the multiple regression equation account for more than 27% of the total variance in paracetamol clearance.

Discussion

This heterogeneous population sample, drawn from an urban community and comprising two distinct ethnic groups, made it possible to assess the effects of a variety of environmental factors upon paracetamol elimination. The differences in haemoglobin and albumin concentrations between Whites and Asians suggested that the Asian diets, largely lactovegetarian, were less nutritious than the diets of the White subjects. The Asians used alcohol, tobacco, caffeine-containing beverages and the oral contraceptive much less commonly and to a lesser extent than the Whites.

The use of total body clearance as the dependent kinetic variable in the statistical analyses requires qualification. There is evidence (Rawlins, Henderson & Hijab, 1977) of presystemic hepatic (first-pass) elimination of paracetamol after an oral dose and, were it to be substantial, this would render the calculation of total body clearance, following oral administration, invalid as an index of the rate of drug metabolism. However, the proportion of an oral dose eliminated at the first-pass declines with increasing dosage to around 12% at doses of 1000 mg or greater. Moreover, Perucca & Richens (1979) have shown

Table 5 Correlation matrix

	Race	Sex	Age	Weight	Height	Ponderal index	Haemoglobin	Albumin	Globulin	Smoking	Number of cigarettes	Alcohol	Coffee/Tea	Pill	Diet	Half-life	Clearance
Race	1.000	0.205*	−0.163	−0.387*	−0.420*	−0.143	−0.354*	−0.216*	0.162	−0.392*	−0.341*	−0.418*	−0.523*	−0.151	0.803*	0.294*	−0.337*
Sex		1.000	−0.081	−0.522*	−0.685*	−0.073	−0.586*	−0.342	−0.001	−0.049	−0.026	−0.296*	−0.087	0.291*	0.218*	0.136	−0.203*
Age			1.000	0.235*	0.067	0.249*	0.054	−0.099	0.129	0.108	−0.014	−0.109	0.144	−0.206*	−0.148	−0.078	−0.063
Weight				1.000	0.661*	0.732*	0.402*	0.249*	0.012	0.098	0.136	0.292*	0.249*	−0.109	−0.311*	−0.374*	0.080
Height					1.000	−0.021	0.466*	0.365*	−0.099	0.115	0.102	0.386*	0.183	−0.040	−0.349*	−0.254*	0.285*
Ponderal index						1.000	0.108	−0.004	0.125	0.030	0.098	0.041	0.180	−0.092	−0.094	−0.297*	−0.144
Haemoglobin							1.000	0.262*	−0.172	0.190	0.177	0.286*	0.249*	−0.142	−0.326*	−0.051	0.135
Albumin								1.000	0.096	0.119	0.093	0.292*	0.014	0.073	−0.231*	−0.290*	0.117
Globulin									1.000	−0.248*	−0.195*	−0.286*	−0.050	0.167	0.214*	−0.077	−0.222*
Smoking										1.000	0.846*	0.341*	0.439*	0.125	−0.431*	−0.167	0.268*
Cigs/day											1.000	0.294*	0.547*	0.107	−0.364*	−0.180	0.299*
Alcohol												1.000	0.120	0.037	−0.351*	−0.169	0.390*
Coffee/Tea													1.000	0.059	−0.512*	−0.154	0.210*
Pill														1.000	−0.042	−0.084	0.202*
Diet															1.000	0.235*	−0.298*
Half-life																1.000	−0.283*
Clearance																	1.000

*Significance of r values $r > 0.184$ $P < 0.05$, $r > 0.240$ $P < 0.01$, $r > 0.304$ $P < 0.001$

that, in healthy volunteers, paracetamol is poorly extracted by the liver (extraction ratio 0.17) and that systemic clearance can be satisfactorily estimated following an oral dose. Since paracetamol is eliminated almost entirely by conjugation (Cummings *et al.*, 1967), the rate of disappearance of unchanged paracetamol was assumed to reflect the overall rate of conjugation.

Previous investigations of paracetamol clearance in small numbers of healthy volunteers (Shively & Vesell, 1975; Rawlins *et al.*, 1977; Perucca & Richens, 1979; Fulton, James & Rawlins, 1979) have revealed mean values between 20 and 50% greater than the mean clearance of our White subjects and approximately double that of our Asians. The explanation for these differences is not immediately apparent. Fulton and her colleagues (1979) found significantly lower values among elderly patients but age did not emerge as a significant correlate with clearance in our study, despite an age range between 18 and 60 years. A third possibility is that concentrations of paracetamol in saliva were consistently greater than those in plasma, resulting in overestimates of C_0 and underestimates of clearance. The study of Glynn & Bastain (1973), although limited, gave little support to this suggestion and our own preliminary studies indicated that saliva and plasma concentrations did not differ significantly. A preliminary study in three subjects (Fraser, 1976) provided no evidence that simultaneous ingestion of antipyrine modified the rate of paracetamol elimination and we do not consider this a likely explanation.

The apparent racial difference in mean paracetamol clearance was partly related to the contrasting use of social drugs such as alcohol, tobacco and the contraceptive pill, all of which were identified as independent correlates with clearance.

Continued use of alcohol is known to result in induction of microsomal drug oxidation in man (Vesell, Page & Passananti, 1971) and, since UDP glucuronyl transferase is an inducible microsomal enzyme, it is possible that glucuronidation is similarly altered, but there is no other evidence to support this.

The apparent effect of cigarette smoking upon paracetamol clearance can be more easily explained. Cigarette smoke contains polycyclic hydrocarbons which are powerful enzyme inducers. UDP glucuronyl transferase activity in the presence of a wide range of substrates is increased in rats by pretreatment with the polycyclic hydrocarbon, 3-methylcholanthrene (Hamada & Gessner, 1975; Wishart, 1978a), while Uotila & Marniemi (1976) have demonstrated increased glucuronidation of 4-methyl-umbelliferone in rat lung, following inhalation of cigarette smoke for one hour. Thomas, Zeitz & Beaubien (1977), however, found a slight reduction in paracetamol glucuronidation in rats pretreated with 3-methylcholanthrene, in sharp contrast to the appreciable increase following pretreatment with phenobarbitone.

Paracetamol clearance in our female subjects was faster in those taking the steroidal oral contraceptive. This finding is of interest since antipyrine clearance was reduced in these subjects when compared with other women (Fraser *et al.*, 1979). The effect of oral contraceptives upon drug conjugation has not been studied directly in man or in animals and experiments with other steroids have produced conflicting results. Wishart (1978b) showed that dexamethasone stimulated the increase of UDP glucuronyl transferase activity in foetal rats, but Bolanowska &

Table 6 Independent correlates with paracetamol clearance

Subjects	*Correlates*	*Partial regression coefficients*	*Constant*	*Multiple R*	R^2
All (114)	Alcohol (measures week^{-1})	0.04**			
	Oral contraceptive	0.73*			
	Cigarettes (cigs day^{-1})	0.02*	4.64	0.52	0.27
	Sex	−0.45*			
	Ponderal index (g cm^{-2})	−0.62*			
Whites (76)	Alcohol (measures week^{-1})	0.04***			
	Oral contraceptive	0.78*	2.67	0.44	0.19
Asians (38)	Height (cm)	0.05*	−5.68	0.39	0.15

*$= P < 0.05$, **$= P < 0.005$, ***$= P < 0.001$
Oral contraceptive = 1 for non-users, 2 for users
Sex = 1 for men, 2 for women

Gessner (1978) found that prednisolone, testosterone and, to a lesser extent, oestrone and oestradiol inhibited paracetamol glucuronidation in rat liver microsomal incubations.

Analysis of men and women together showed that paracetamol clearance was faster in men. A similar sex difference exists in UDP glucuronyl transferase activity for certain substrates in Wistar rats (Winsnes, 1971) but there are no studies in man which are sufficiently large for comparison.

The inverse correlation between ponderal index and paracetamol clearance is similar to that found in the case of antipyrine clearance (Fraser *et al.*, 1979). There is no obvious explanation for these findings.

This is the first study of paracetamol kinetics in a population sample of healthy volunteers and its major findings suggest that environmental factors may modify the conjugation of paracetamol. However, the multiple regression equation accounted for only 27% of the total variance in paracetamol clearance, and it is therefore unlikely that the individual environmental factors measured in this study are the major determinants of paracetamol conjugation in man.

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