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ANTIPYRINE KINETICS IN NIGERIAN WOMEN IN CHRONIC RENAL FAILURE

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Summary

Antipyrine was given orally to five patients with Chronic renal failure and nine normal subjects. Plasma antipyrine levels were measured by high pressure liquid chromatography method, the plasma half-life of the drug was determined and used as an index of drug oxidation. The mean (±s.d.) plasma antipyrine half-life in patients with chronic renal failure (7·8 ± 2·6 h) was significantly shorter than in normal subjects (13·1 ± 2·3 h) ($P > 0·001$). There was no significant difference in the volume of distribution but there was a significant difference in the clearance in ml.kg^{-1}h^{-1} ($P < 0·001$).

The results suggest that oxidation of antipyrine by hepatic microsomal enzymes is increased in patients with chronic renal failure. The role of this in the apparent resistance among our patients to antihypertensive agents needs further study.

Résumé

De L'antipyrine fut donné à cinq personnes affligées d'un affaiblissement chronique de rein, et à neuf personnes normales. Des niveaux de l'antipyrine de plasma furent measurés grâce à une technique H.P.L.C.; la demi-vie de la drogue fut ainsi déterminée et employée comme indice d'exydation de la drogue. La moyenne (± d.s.) demi-vie de l'antipyrine de plasma chez les malades de l'affaiblissement chronique de rein (7·8 ± 2·6 h) fut, d'une manière significative, plus courte que chez les personnes normales (13·1 ± 2·3 h) ($P > 0·001$). Il n'y avait pas de différence significative de volume de la distribution, mais il y en avait de la dépuration de ml. kg^{-1}h^{-1} ($P < 0·001$).

Les résultats font creire que l'oxydation de l'antipyrine par des enzymes hépatiques microsomales est augmentée chez les malades de l'affaiblimmement chronique de rein. Son rôle dans la résistance apparente de nos patients aux agents antihypertensife éxige d'autre étude.

Introduction

Drug oxidation studies in chronic renal failure are relatively few. Letteri *et al.* (1971) showed that the plasma half-life of phenytoin is considerably shortened in chronic renal failure. Rasmussen *et al.* (1972) found similar shortening of digitoxin plasma half-life in some patients with chronic uraemia. Lichter, Black and Arias (1973) found that antipyrine plasma half-life in undialysed uraemic patients was significantly shorter, but not significantly different from that in normal subjects when the whole group of uraemic patients (dialysed and undialysed) was considered. Maddocks, Wake and Harber (1975) found the plasma half-life in patients with chronic renal failure significantly shorter than in normal subjects. The study reports our findings in Nigerian women in chronic renal failure. The study was carried out in women mainly because control subjects were more readily available.

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Methods

The study was carried out in the University College Hospital, Ibadan, in July 1980 and the samples transported, frozen, to the Royal Hallamshire Hospital in Sheffield, England, for analysis.

Five female patients in chronic renal failure and nine normal subjects, attending a gynaecology clinic at the University College Hospital, Ibadan, for secondary infertility, were studied. None of the patients had received any form of dialysis at the time of study. All the control subjects had normal haemoglobin, plasma creatinine and liver function tests. Informed consent was obtained from patients and controls.

Protocol

Following an overnight fast, each subject took 1·0 g antipyrine dissolved in 60 ml water by mouth. Plasma samples were obtained at 3-hour intervals up to 15 hours and a final sample at 24 hours.

Drug analysis

To 0·5 ml plasma were added 100 ml of 0·1 M NaOH, 25 µl aqueous phenacetin solution (100 µg/ml) as internal standard, and 1·0 ml dichloromethane (DCM).

Extraction was carried out in screw-cap culture tubes. Samples were mixed on a horizontal shaker for 5 min. They were then centrifuged for 10 min at 3000 rev/min. The upper aqueous layer was removed by suction and as much of the organic layer as possible transferred to a conical tube.

The solvent was evaporated off using a vortex evaporator at 35°C. The residue was taken up into 200 µl of methanol: water (1 : 1) mixture and 2·0 – 5·0 µl injected into a high pressure liquid chromatograph (HPLC).

The instrument used was a Waters Associates HPLC model 440 with an absorbance detector at wavelength 254 nM. The column was C18 organosilane in reversed phase; the eluting solvent was methanol: water (1 : 1) mixture at a flow rate of 1·8 ml/min. Peak-height ratios of antipyrine to phenacetin were measured.

Antipyrine half-lives were estimated by the method of least squares. Apparent volumes of distribution (V_d) were calculated from the dose and the estimated initial concentration (C_o), using the relation

$$V_d = \frac{\text{Dose}}{C_o}$$

and assuming instantaneous and complete absorption of an oral dose (Andreason & Vessel, 1974; Brodie & Axelrod, 1950). Clearances were calculated from the product of V_d and K_e, the elimination rate constant.

$$(\text{where } K_e = \frac{0{\cdot}693}{t\frac{1}{2}})$$

Results

Table 1 shows the clinical features of the patients in Chronic renal failure while Table 2 shows the individual pharmacokinetic data on patients and normal controls. The mean plasma half-life in the patients (7·8 ± 2·6 h) was significantly shorter ($P > 0{\cdot}001$) than in normal subjects (13·1 ± 2·3 h) The clearance in $L.h^{-1}$ was significantly greater in the renal patients ($P > 0{\cdot}025$) and this significance was greater ($P < 0{\cdot}001$) when the clearance was converted to $ml.kg^{-1}h^{-1}$ (29·9 ± 5 3 for normal subjects and 55·6 ± 11·9 for renal patients). There were no significant differences in the age, weight, concentration at zero hour and the volume of distribution.

Discussion

Antipyrine was used in this study because available evidence shows that it is eminently suitable for the investigation of oxidative drug metabolism. It is not appreciably bound to protein (Brodie & Axelrod, 1950), therefore altered protein binding in uraemia would not affect disposition, and its half-life is reproducible (Davies & Thorgeirsson, 1971).

Our findings in this study are in agreement with those of Lichter *et al.* (1975) who found no significant difference in intestinal absorption of antipyrine between control patients and non-dialysed uraemic patients, but found significantly shorter antipyrine half-life between the two groups. Maddocks *et al.* (1975), using intravenously administered antipyrine, also found a significantly shorter antipyrine plasma half-life in patients with chronic renal failure than normal subjects. These findings indicate tha patients with chronic renal failure oxidation antipyrine by hepatic microsomal enzymes

TABLE 1. Clinical features of uraemic patients

Patient	Sex	Age	Weight (kg)	Serum urea (mg/100 ml)	Serum creatinine (mg/100 ml)	Serum albumin (g/100 ml)	P.C.V. (%)	Medication
C.M.	F	35	54·5	188	16·1	2·9	22	α-methyl dopa, frusemide
A.K.	F	18	38·1	84	12·5	3·0	28	α-methyl dopa, frusemide, hydrallazine
G.O.	F	32	52·2	162	18·7	3·5	26	frusemide
Y.F.	F	20	52	54	12·6	2·2	25	frusemide
V.O.	F	52	50	81	12·4	3·7	30	hydroflumethiazide

TABLE 2. Individual pharmacokinetic data

Name Groups	Age	Sex	Weight (kg)	C_o (μg/ml)	$t^{1}/_{2}$ (h)	V_d (l)	V_d in (L/kg bd.wt.)	Cl ($l.h^{-1}$)	Cl ($ml.kg^{-1}h^{-1}$)
Controls									
F.	30	F	50·3	29·9	16·65	33·44	0·665	1·39	27·63
M.	27	F	49·6	31	13·38	32·26	0·650	1·67	33·67
O.	26	F	63·3	32·5	11·19	30·77	0·486	1·91	30·17
T.	26	F	67·1	29	12·11	34·48	0·514	1·97	29·36
B.	40	F	95·7	21·16	12·84	47·26	0·494	2·55	26·65
O.Y.	50	F	83·5	17·7	15·40	56·50	0·677	2·54	30·42
S.	20	F	48·9	41	15·75	24·40	0·499	1·07	21·88
O.G.	17	F	50·3	31·34	10·65	31·91	0·634	2·08	41·35
O.L	36	F	76·5	31	10·28	32·23	0·421	2·17	28·37
Mean	30·2±10·3		65·9±17·15	29·4±6·69	13·9±2·3	35·9±9·76	0·56±0·1	1·9±0·49	29·9± 5·35
Patients									
	32	F	52·2	37·53	7·97	26·64	0·510	2·32	44·44
O.M.	52	F	50	38·81	6·37	25·77	0·515	2·80	56·00
K.A.	18	F	38·1	42·51	7·11	23·52	0·617	2·29	60·10
E.A.	20	F	52	24·57	12·19	40·7	0·783	2·31	44·42
M.G.	35	F	54·5	33·8	5·16	29·59	0·543	3·97	72·84
Mean	31·4±13·6		49·4± 6·5	35·4±6·8	7·8±2·6	29·2±6·7	0·59±0·1	2·7±0·72	55·6±11·9

normal or increased.

The implication of our findings in the management of our patients needs further evaluation. Our patients, particularly those of them who were hypertensive, are often resistant to antihypertensive drug therapy. They either do not respond or require much higher dosages. How much of this is due to circulating substances in uraemia, to altered receptor sensitivities or to increased oxidative metabolism remains to be studied.

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