Journal of Pharmaceutical & Biomedical Analysis
Vol. 5, No. 1, pp. 45–49, 1987
Printed in Great Britain

0731–7085/87 $3.00 + 0.00

Short Communication

Better response to thiazides in blacks — lack of pharmacokinetic evidence with chlorothiazide

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Keywords: *Diuretic; chlorothiazide; bioavailability; pharmacokinetic; disposition.*

Introduction

Diuretics are commonly used in the management of hypertension. They are often preferred in mild cases and are almost always included when management requires a combination of drugs. As a group, the thiazides are probably the most widely used diuretics, being prescribed either alone or in various drug combinations such as 'Dyazide' (triamterene 50 mg + hydrochlorothiazide 25 mg; Smith Kline & French), 'Moduretic' (amiloride hydrochloride 5 mg + hydrochlorothiazide 50 mg; Merck Sharp & Dohme) and 'Inderetic' (propranolol hydrochloride 80 mg + bendrofluazide 2.5 mg; ICI). Hypertensive blacks have been reported to respond better than non-blacks to thiazide diuretics [1]. The possibility that a racial difference exists in the disposition of drugs has already been documented in respect of such drugs as sulphonamides, hydrazines, debrisoquine and metoprolol [2–9]. The purpose of this study was to examine the disposition of the prototype thiazide diuretic, chlorothiazide (CTZ), in blacks and to compare the results with those reported by other workers.

Materials and Methods

Ten healthy adult male non-smokers, who did not drink alcohol and were not on any medication, participated after informed consent. None had on any occasion within two months prior to this study taken the antimalarial 'Fansidar' (sulfadoxine 500 mg + pyrimethamine 25 mg, Roche) or any other sulphonamide. In none of them was there a history suggestive of allergy to sulphonamide.

After an overnight fast and an hour after taking 400 ml of water, each subject, immediately before drug ingestion, completely emptied his bladder and a sample of the voided urine was kept as a blank. At zero time, a tablet (500 mg) of CTZ ('Saluric',

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Merck Sharp & Dohme, Batch Number 22199) was crushed into fine powder and taken with an overall volume of 200 ml of water. An additional 200 ml of water was taken at 2 and 4 h after dosing, and nothing else was allowed orally until 4 h after dosing. At 2, 4, 6, 8, 12, 18, 24, 30 and 36 h after dosing, voided urine was collected, measured, and a sample kept frozen for analysis, commencing 48 h after dosing. Urine creatinine estimation was used to assess the completeness or otherwise of urine collection.

Chlorothiazide assay

The method of Baer *et al.* [10] as modified by Kauffman and Azarnoff [11] was employed for the assay of CTZ. A 2 ml aliquot of urine was acidified with 1 ml 0.1 M hydrochloric acid and extracted with 25 ml ethyl acetate by mechanical shaking for 30 min. The mixture was centrifuged and 20 ml of the organic phase evaporated to dryness. The residue was dissolved in 6 ml 1 M sodium hydroxide and extracted with 10 ml chloroform by shaking. A 5 ml aliquot of the aqueous phase was heated in a boiling water bath for 30 min to convert chlorothiazide to 6-amino-4-chlorobenzene 1,3-disulphonamide. After cooling the absorbance of the hydrolysate was measured at 520 nm, employing an SP8-100 UV/VIS Pye–Unicam spectrophotometer, to provide a determination of background absorbance. Diazotization of this solution was then carried out by the addition of 1 ml 6 M hydrochloric acid and 0.6 ml 0.1% sodium nitrite, and then the reaction was stopped after 3 min by the addition of 0.6 ml 0.5% sulphamic acid, which destroys excess nitrite. After a further 5 min, 0.6 ml 0.1% *N*-(1-naphthyl)-ethylenediamine dihydrochloride was added and 10 min later the absorbance of the chlorothiazide diazo derivative was measured at 520 nm. This determination was corrected by subtraction of the background absorbance obtained previously.

Recovery at concentrations of 160, 80, 40 and 20 μg ml^{-1}, (n = 5) were 98.5% ± 3.5; 97.4% ± 2.5; 96.5% ± 3.4; and 93.2% ± 3.5, respectively (mean ±R.S.D.).

Analysis of Data

Semilogarithmic plots of mean urinary excretion rate versus midpoint sampling time were interpreted on the basis of one compartment open model following rapid absorption. Regression analyses of the data for these plots were made with a model HP-IIC Hewlett–Packard programmable calculator, and the overall elimination rate constant, k, obtained from the slope of the line. Half-life ($t_{1/2}$) was calculated from the following equation:

$$t_{1/2} = \frac{0.693}{k} \text{ h}.$$

Results

Urine creatinine estimations in samples from each of the ten subjects indicated complete urine collection. The range of correlations between regression lines and experimental data for chlorothiazide excretion rates are given in Fig. 1, where (a) and (b) are the best and (c) and (d) the worst correlations.

Urinary excretion of CTZ summarized in Table 1 shows that over the period of 36 h, the mean urinary recovery was 61.61 mg, representing 12.32% of the orally administered dose. Half-life values ranged from 5.06 to 10.04 h with a mean of 7.43 h ± 1.55 (±S.D.)

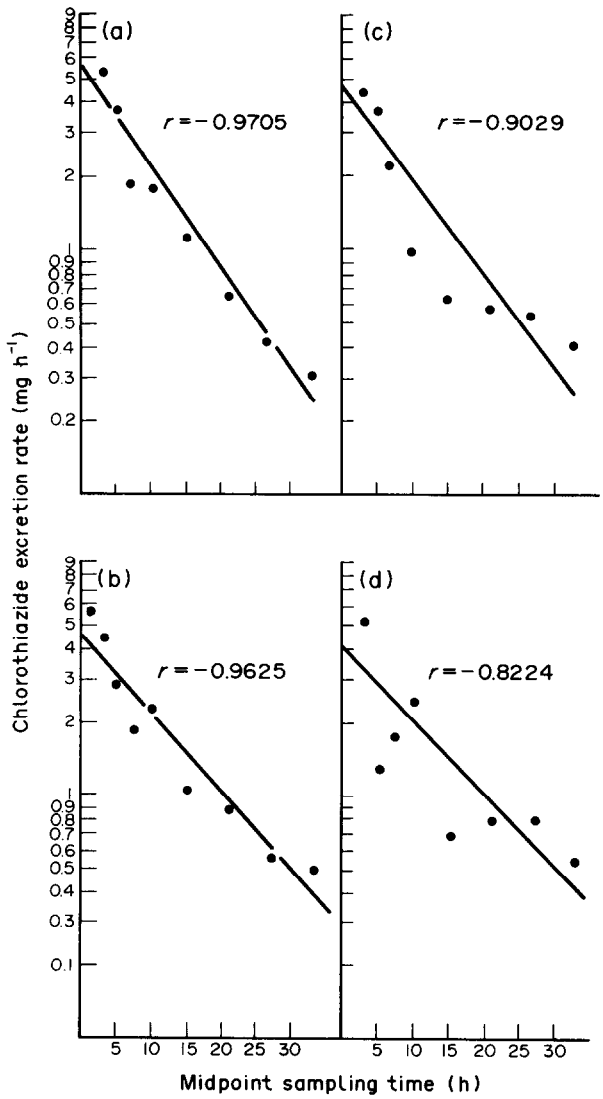

Figure 1
Semilogarithmic plots of mean urinary excretion rate of chlorothiazide against midpoint sampling time after oral ingestion of 500 mg crushed tablets by subjects, 4, 5, 8 and 6 (a, b, c and d respectively).

(Table 2). Maximum urinary excretion rate had a mean value (±S.D.) of 8.68 mg h^{-1} (±1.99) (range: 5.53–12.42 mg h^{-1}) attained at a mean period (±S.D.) of 1.6 h (±0.97) (range: 1.0–3.0 h).

Discussion

The facts that CTZ is not metabolized and the unchanged drug is essentially completely eliminated by the kidney [12, 13] make urinary excretion measurements adequate for the study of its bioavailability [14]. Over a 36 h period, the mean urinary

Table 1
Cumulative urinary excretion of chlorothiazide (CTZ) in ten healthy subjects after oral ingestion of 500 mg as suspension

Subject	Cumulative urinary excretion (mg)								
	2	4	6	8	12	18	24	30	36
1	24.84	43.68	52.19	58.05	63.51	67.70	69.48	70.68	71.82
2	16.29	27.38	40.15	49.82	57.12	66.77	74.61	79.64	83.62
3	10.01	28.85	39.01	42.82	49.24	55.03	58.06	59.96	61.43
4	15.84	26.51	34.12	37.82	44.82	51.53	55.37	57.88	59.70
5	11.06	19.84	25.53	29.30	38.26	44.49	49.82	53.14	56.15
6	16.13	26.53	29.11	32.59	42.41	46.50	51.16	55.96	59.22
7	16.93	28.56	37.01	41.05	48.22	50.92	53.14	55.17	56.92
8	16.89	25.54	33.10	37.05	41.46	45.24	48.65	51.88	54.27
9	10.01	24.10	28.78	31.66	36.43	39.56	41.86	43.80	44.94
10	11.26	33.91	38.50	46.96	53.89	60.36	63.42	65.48	67.98
Mean	14.93	28.49	35.75	40.71	47.54	52.81	56.56	59.36	61.61
S.D.	4.56	6.43	7.57	8.99	8.63	9.58	10.05	10.25	10.66

Table 2
Pharmacokinetic parameters of CTZ in ten healthy subjects each given 500 mg orally as fine particles

Subject	$t_{1/2}$ (h)	$\frac{dA_e}{dt_{max}}$ (mg h^{-1})	t_{max} (h)
1	5.06	12.42	1
2	8.77	8.15	1
3	6.36	9.42	3
4	7.07	7.92	1
5	9.36	5.53	1
6	10.04	8.07	1
7	6.30	8.47	1
8	7.88	8.45	1
9	6.60	7.05	3
10	6.86	11.33	3
Mean	7.43	8.68	1.60
S.D.	1.55	1.99	0.97

recovery of CTZ was 12.32% of the orally administered dose, and this confirms its poor bioavailability as reported by other workers [11–14]. Given that absorption characteristics and bioavailability of CTZ are at least partly controlled by the rate as well as the extent of its dissolution [15] this percentage obtained with a fine particle dosage form is consistent with the mean urinary recovery of 8.85 and 14.36% over the same 36 h period when it was given as tablets (Merck Sharp & Dohme) and solution, respectively [14].

The mean half-life of 7.43 h (Table 2) suggests that for bioavailability studies urine collection may have to be carried out, ideally, for about 52 h (seven times the half-life). This period is in agreement with Shah *et al.* [14] who suggested at least 48 h.

The mean maximum excretion rate, dA_e/dt_{max}, of 8.68 mg h^{-1} was attained at an average period (t_{max}) of 1.60 h (Table 2). Shah *et al.* [14] reported that after an oral intake of 500 mg solution, a mean maximum urinary excretion rate of 16.4 mg h^{-1} was

attained at an average time of 1.2 h. The corresponding values with tablets (Merck Sharp & Dohme) were 7.2 mg h^{-1} and 2.7 h. The differences in these three pairs of data are to be expected because absorption/elimination should be fastest with the solution, slowest with the tablets and intermediate with the fine particles used in this study.

The exact mechanism by which diuretics lower blood pressure is still uncertain. Two hypotheses — volume depletion and reduction in peripheral resistance — have been postulated and experimental data in support of both have been reviewed by Roberts [16]. Both mechanisms are probably operative but volume depletion is probably the more important factor at the initial stage and reduced vascular resistance later [17]. Whatever mechanism(s) is involved, however, it is generally agreed that the hypotensive effect of diuretics is primarily related to diuresis and natriuresis with the resultant depletion of body sodium stores [16, 17]. Natriuresis induced by CTZ has been reported to correlate well with its cumulative urinary excretion [18]. The 36 h urinary recovery values as well as other parameters of CTZ calculated in this study are consistent with those reported by Shah *et al.* [14], and unless the report by these workers was also on blacks the reported better response [1] to this group of drugs in blacks has, probably, no pharmacokinetic basis. It is, however, noteworthy that this finding with CTZ may not be applicable to all thiazides since others may be handled differently.

Acknowledgements: We are grateful to Merck Sharp & Dohme Ltd, Hoddesdon, Hertfordshire, UK and Associated Pharmaceutical Products Ltd, Lagos, Nigeria for providing us with chlorothiazide powder and tablets used for this work.

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[*Received for review 29 January 1985; resubmitted 13 June 1985*]