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The effect of dosage on the bioavailability of chlorothiazide administered in solution

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Chlorothiazide in solution was administered at four dose levels to three healthy male volunteers under controlled conditions. Excretion data indicated that the drug was poorly absorbed from the gastrointestinal tract. The 24 h recovery of the drug from urine fell from 33 to 6% as the dose was increased from 0·21 to 1·75 g per 70 kg of body weight. The cumulative amount of sodium excreted could be correlated with the cumulative amount of drug excreted, rather than with the dose administered. The electrolyte excretion response intensity could also be correlated with the amount of drug excreted. There was a poor linear relationship between response intensity and drug excretion rate. After higher doses the data suggested that the response was in the non-linear section of the dose response curve.

While differences in the extent of absorption of thiazide diuretics have been attributed to differences in partitioning properties Dollery (1964) there is evidence that formulation factors influence the absorption of these agents (Tannenbaum et al 1968; Corrigan et al 1976). The purpose of the present study was to investigate the influence of dosage on the absorption of and pharmacological response to chlorothiazide administered orally in solution.

MATERIALS AND METHODS

Study design. Doses of 25, 18, 10, 3 mg kg^{-1} or a placebo were administered in a cross-over study to three healthy male subjects at not less than weekly intervals. Sodium intake was controlled by the administration of a 0·14% solution of sodium chloride, 300 ml as an initial loading dose and 100 ml h^{-1} up to 7 h post drug administration. This procedure was based on that outlined by Martz et al (1962) for estimating natriuretic activity and exploring dose response relationships. Total urine volumes were estimated after 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 5·0, 7·0 and 24 h and samples were refrigerated while awaiting analysis.

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Assay procedures. The modified Bratton-Marshall assay procedure as described by Baer et al (1959) was used to assay chlorothiazide in urine. Urine concentrations of sodium and potassium were measured, following suitable dilution, using atomic absorption spectrophotometry in the emission mode at 589 nm and 766 nm respectively.

Preparation of dosage form. Drug solutions were prepared immediately before use by dissolving chlorothiazide (generously supplied by Merck Sharpe and Dohme Ltd, Herts) in a sodium hydroxide solution and adjusting the pH to 10 as described by Charnicki et al (1959) for the preparation of an injection of chlorothiazide sodium.

RESULTS AND DISCUSSION

The average cumulative amounts of drug excreted following each dose are presented in Table 1. The amount of drug excreted tended to increase with dose, the increase being in rank order with the dose at the early times. However, in spite of an eight fold increase in the amount of drug administered, there was less than a twofold increase in the amount excreted after 24 h. Since chlorothiazide is excreted unchanged in the urine (Parke 1968), the cumulative amount excreted is a measure of the amount

Table 1. Average cumulative amounts of drug excreted (mg) following the administration of different doses of chlorothiazide in solution to three healthy male volunteers.

Average dose (g per 70 kg)	Time (h) 0·5	1·0	1·5	2·0	2·5	3·0	4·0	5·0	7·0	24·0
1·75	9·4	32·6	52·6	69·7	81·2	91·4	106·8	115·4	120·3	126·4
1·26	8·8	25·6	39·6	52·3	62·6	71·7	81·1	87·6	89·3	90·6
0·70	3·8	18·3	36·1	50·7	60·7	69·2	85·6	88·9	93·0	112·9
0·21	2·0	12·5	23·6	32·4	38·2	45·1	54·6	58·7	62·8	73·2

absorbed. The percentage of chlorothiazide recovered in urine in 24 h fell from 33% to 6% ($P < 0.05$) as the dose was increased from 0·21 to 1·75 g per 70 kg body weight. The drug was rapidly absorbed from solution, excretion being evident within the first half hour (Fig. 1). The average time of peak drug excretion was 1 h (range 0·5 to 2·0 h) and excretion was almost complete at 6 h. Young et al (1959) reported that maximum drug excretion occurred 2–4 h after oral administration of an unspecified dosage form. The more rapid absorption in the current work may have been due to the use of a solution of the drug.

The cumulative amounts of sodium excreted at sampling times during the 7 h post drug ingestion (the time during which sodium and water intake were controlled), were at all times in rank order with the dose. A similar trend was observed for combined cumulative sodium and potassium data. In contrast, although chlorothiazide administration increased both urine and potassium excretion, these responses were more variable and not in rank order with dose.

Martz et al (1962) related cumulative sodium excretion for the 5 h post chlorothiazide administration period to the oral dose. On increasing the dose from 250 to 500 mg they observed a 23% increase in cumulative sodium excreted after 5 h, a finding with which our data are consistent. The cumulative amounts of sodium excreted after 3, 5 and 7 h were plotted against the cumulative amount of chlorothiazide excreted in the same time period. The lines of best fit and coefficient of determination thus obtained are included in Table 2. A better linear relationship was obtained using cumulative drug excreted rather than dose administered as the independent variable. In addition the slopes of the lines of best fit are much greater, reflecting the higher sensitivity of the pharmacological response to the amount absorbed rather than the dose administered.

An alternative approach to the estimation of bioavailability which utilizes pharmacological response intensity [I] data has been developed by Smolen & Schoenwald (1971) where

$$I = \frac{R - Ro}{Ro} = \frac{\Delta R}{Ro} \quad .. \quad (1)$$

R is the response at any time following drug administration and Ro is the response at time zero. The theoretical basis for this approach has been outlined by Weigand & Jhawar (1976). The use of equation 1 is based on the assumption that placebo values vary randomly with time following administration. Because of the circadian rhythm evident in the parameters under study, change in response intensity at a given time was estimated relative to the placebo response at the same time. This approach gave better correlations for the intensity versus drug excretion data. The relationship between response intensity, as measured by either the area under the response versus time curve or the average maximum peak intensity, and the amount of drug excreted is shown in Fig. 2. Irrespective of which parameter was used, similar coefficients of determination were obtained (i.e. 0·969 and 0·960 respectively).

These results indicate that sodium excretion under controlled conditions may be useful in measuring chlorothiazide bioavailability. The relationship between response intensity and drug excretion rate was also examined. The average response intensity

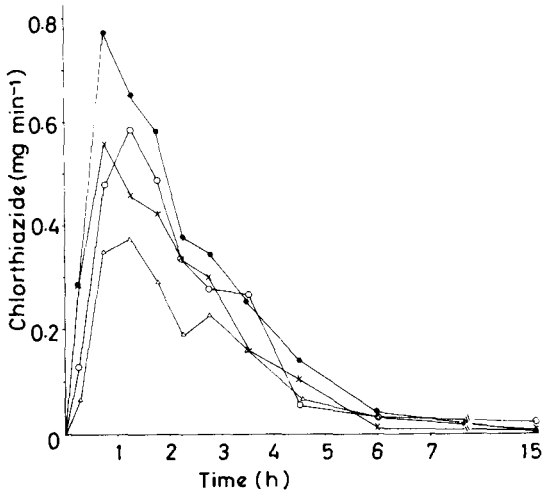

FIG. 1. Plot of the excretion rate of chlorothiazide (mg min^{-1}) versus time following administration of four different doses of chlorothiazide ● 25, X 18, ○ 10, △ 3 mg kg^{-1}.

Table 2. Relationships between cumulative amounts of sodium excreted (m mol) after 3, 5 and 7 h following four doses of chlorothiazide and (a) the dose administered (b) the cumulative amount of drug excreted.

	Time (h)	Intercept	Slope	Coeff. of deter.
a	3	44·7	0·039	0·680
	5	65·2	0·053	0·695
	7	81·3	0·059	0·703
b	3	21·5	0·99	0·940
	5	33·4	1·08	0·956
	7	45·9	1·14	0·966

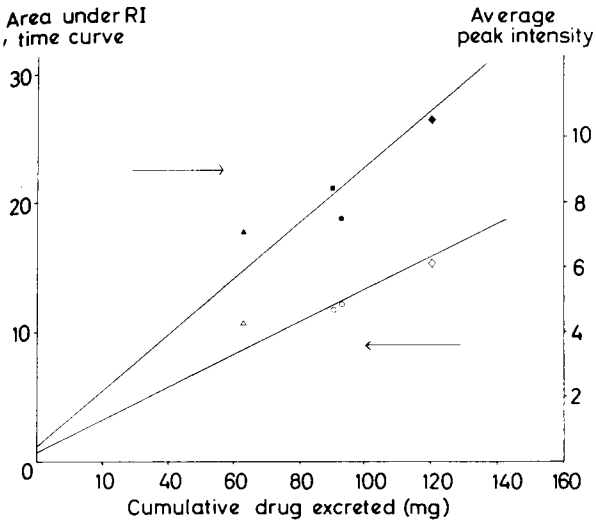

FIG. 2. Correlation between pharmacological response intensity i.e. area under the response intensity curve up to 7 hours (closed symbols), or average peak intensity (open symbols) and drug absorbed, as estimated from cumulative chlorothiazide excreted. ◆ ◇ 25, ■ □ 18, ● ○ 10; ▲ △ 3 mg kg^{-1}.

values obtained at each time are plotted against the corresponding drug excretion rate values for all four doses (i.e. 40 data points) in Fig. 3. Considerable scatter is evident about the trend line. Although Levy et al (1964), on the basis of diuretic response data obtained using mercaptomerin,

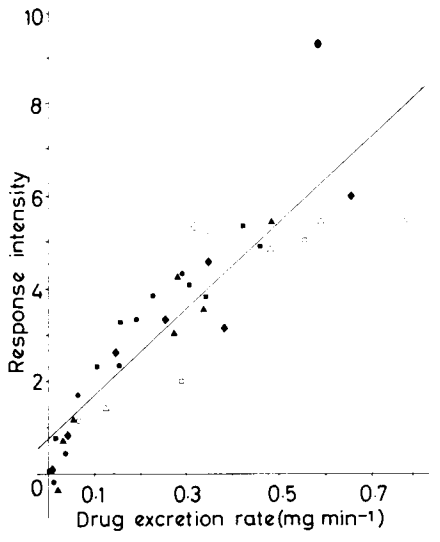

FIG. 3. Plot of response intensity versus corresponding chlorothiazide excretion rates. Pre-maximum drug excretion rate ○ 25, △ 18, □ 10, ◇ 3 mg kg^{-1}. Post-maximum drug excretion rate ● 25, ▲ 18, ■ 10, ◆ 3 mg kg^{-1}.

Table 3. The relationships between average response intensity and the corresponding drug excretion rate following four doses of chlorothiazide. Also included are the parameters obtained on combining all the data.

Dose (mg kg^{-1})	Intercept	Slope	Coeff. of deter.
25	0·566	9·36	0·6819
18	0·366	9·69	0·8131
10	— 0·030	10·37	0·9144
3	— 0·203	15·51	0·9554
Combined data	0·345	10·09	0·7837

suggested that post absorption sodium excretion rate correlated better with drug excretion rate, this effect was not evident in the present study. The intercepts, slopes and coefficients of determination obtained, for the combined as well as for the individual dose data, are summarized in Table 3. The decreases in coefficient of determination and slope, as well as the increase in intercept as dose administered was increased, suggests that the data points obtained at the higher doses are on the non-linear section of the dose response curve. Murphy et al (1961) reported chlorothiazide to be more effective when the dose is split into smaller units (e.g. 250 mg × 8) given intermittently than when administered as a single 2 g dose, a finding consistent with the current work.

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