THE EFFECT OF CARBONIC ANHYDRASE BINDING ON THE PHARMACOKINETICS OF CHLORTHALIDONE

G.D. Parr, B.A. Mulley, R.M. Rye, Postgraduate School of Studies in Pharmacy, University of Bradford, Bradford, BD7 1DP.

Chlorthalidone, a long-acting oral diuretic, has been used for several years in treating mild hypertension, oedema, and other associated disorders (Stenger et al 1959; Tweeddale et al 1977). However, little was known about the pharmacokinetics of the drug since a sensitive and specific assay was not reported until 1974 (Ervik and Gustavii). The biological half life is long and the published values vary widely within the range 35 to 80 hours (Fleuren and Van Rossum 1975; Riess et al 1977), but no explanation for either the variability or length of half life has been proposed to date.

Recent work on the distribution of chlorthalidone within blood (Collste et al 1976; Dieterle et al 1976) has shown that around 98% of the drug is bound to the enzyme carbonic anhydrase in erythrocytes. The amount of unbound chlorthalidone available in the plasma is therefore very small, and since glomerular filtration is by far the most important route of excretion (Fleuren et al 1979) the drug will have a long half life. In consequence, we considered that the amount of carbonic anhydrase within an individual's blood would be a significant factor governing the kinetics of chlorthalidone.

In order to elucidate this relationship the kinetics were investigated in six volunteers selected on the basis of their widely varying whole blood carbonic anhydrase levels. Carbonic anhydrase was estimated by the pH-stat method of Alsen et al (1973). Each subject received a single 25 mg oral dose of chlorthalidone and the kinetics were determined by urine analyses over a period of ten days using a modification of the chlorthalidone assay described by Riess et al (1977).

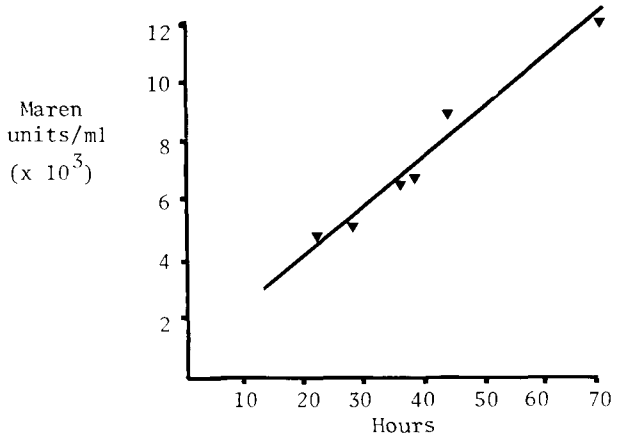

Figure 1. Graph of whole blood carbonic anhydrase concentration against half life of chlorthalidone.
$r^2 = 0.983$

Figure 1 shows a linear relationship between half life of chlorthalidone and whole blood carbonic anhydrase concentration, confirming our hypothesis that individual variations in the kinetics of the drug are largely controlled by levels of this enzyme.

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