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Influence of urine pH and flow rate on the renal excretion of chlorpheniramine in man

SIR,—The renal excretion of amphetamine and methylamphetamine has been shown to be dependant upon the pH of the urine and is sufficiently pH-sensitive to reflect the diurnal rhythm of urinary pH (Beckett & Rowland, 1964, 1965; Beckett, Rowland & Turner, 1965). We now report that, using a specific assay for unchanged drug based upon gas liquid chromatography (Beckett & Wilkinson, to be published) the renal excretion of the antihistamine, chlorpheniramine and its (+) and (−) isomers, shows a dependance not only upon urinary pH but also upon the rate of urine flow.

The oral administration to normal male subjects, of an aqueous solution of 10 mg chlorpheniramine base as the maleate, resulted in a fluctuating excretion rate. The total amount of unchanged chlorpheniramine excreted in 24 hr was 4·5–11·5%. In contrast to the results reported for amphetamine and methylamphetamine (Beckett & Rowland, 1964; 1965; Beckett & others, 1965), maintaining the urine acid (pH 5·00 $\pm$ 0·50), or alkaline (pH 8·00 $\pm$ 0·50), by administration of ammonium chloride or sodium bicarbonate, respectively, did not abolish the fluctuations (see Fig. 1), although there was a difference in the total amount of drug excreted. When the urine was acid, 20·0–26·5% unchanged drug was excreted in 24 hr, whereas only 0·3–0·4% was excreted when the urine was alkaline.

Under constant acid urine conditions the fluctuations in the rate of excretion appeared to be related to changes in the rate of urine flow; a high flow rate resulted in a high excretion rate (see Fig. 1). The volume-dependent fluctuations were abolished when the urine flow rate was maintained above 150 ml/hr by water loading the subjects (see Fig. 1). Under these conditions the excretion rate decreased exponentially except for a rise 10–15 hr after administration of the dose; the reason for this departure from exponential excretion is under investigation. The excretion pattern of both the (+)- and (−)-isomers was similar to that of the racemate.

These results may be explained by assuming that the tubular epithelium of the distal convoluted kidney tubules is selectively permeable to the unionised base (Schanker, 1962). The rate of reabsorption of the drug from the tubular fluid will thus depend on the ratio of concentration of unionised base within the tubules and that in the peritubular fluid (Milne, Scribner & Crawford, 1958; Weiner & Mudge, 1964). The concentration of unionised base in the tubules may be altered by a change in the pH of the tubular fluid, as the pK_a of chlorpheniramine is 9·16 (Marshall, 1955), or by alteration in the fluid volume.

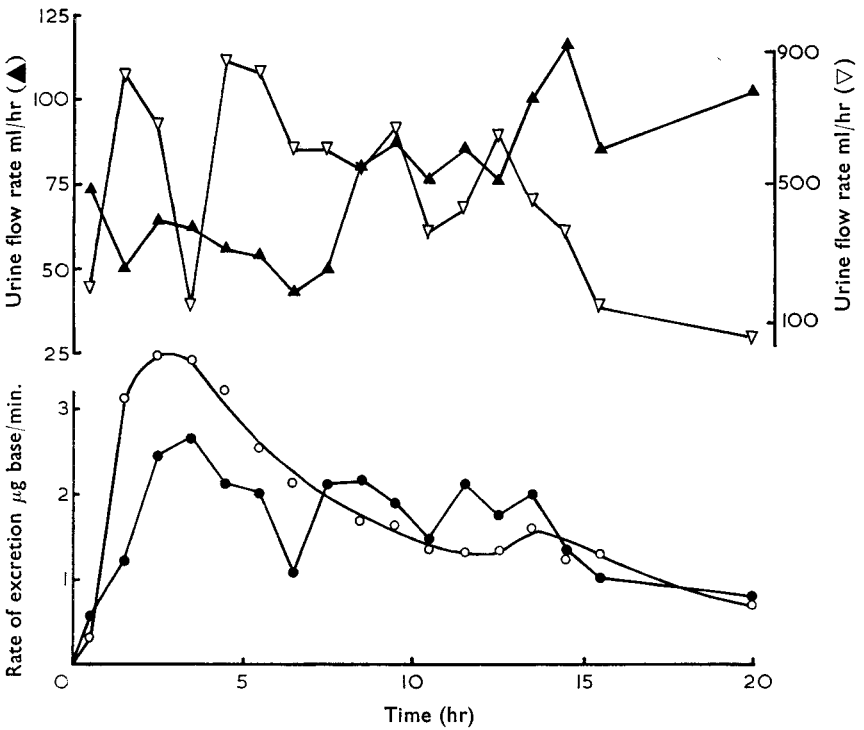

FIG. 1. The rate of excretion of chlorpheniramine and corresponding urine flow rates; conditions of normal flow rates (solid symbols) and high flow rates (open symbols). Subject G.R.W., urine pH 5·00± 0·50.

Abolition of the volume-dependent fluctuations in the excretion rate by water loading of the subjects suggests that there is a limiting ratio of concentration of unionised base in the tubular and peritubular fluids below which reabsorption is negligible.

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