The Effects of Functional Adaptation of Residual Nephrons on the Urinary Excretion of Drugs

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In patients with chronic renal failure due to glomerulonephritis, pyelonephritis or polycystic kidneys the urinary clearance of free chloramphenicol (C_{CHL}) was depressed proportionally to GFR (C_{In}). The ordinate intercept of the regression line of C_{CHL} on C_{In}, however, consistently was positive (+3 to +5 ml/min). The fractional excretion of chloramphenicol in renal failure increased from its normal value of 50 percent as an exponential function of the decrease of GFR, and as a linear function of the fractional excretion of water or of sodium. Dietary sodium restriction had no influence on C_{CHL} in the patients, while water diuresis, in normal subjects, enhanced the urinary excretion of chloramphenicol. The data suggest that chloramphenicol is reabsorbed by back-diffusion and that increases of the rate of flow of urine and tubular fluid prevent back-diffusion.

Nephron loss is associated with an adaptive decrease in tubular sodium reabsorption in residual nephrons [1,2,3,4]. Adaptive changes in the tubular transport of sodium (together with increased plasma urea levels in advanced stages of renal diseases) induce diuresis which, in turn, may influence the excretion of many substances.

This paper reports studies on the influence of adaptive decreases of tubular sodium and water reabsorption on the urinary excretion of drugs. Chloramphenicol was used as a test substance for this purpose because its urinary excretion is influenced by osmotic diuresis in subjects with normal renal function.

MATERIAL AND METHODS

Renal excretion and serum concentrations of chloramphenicol (CHL) were measured in 19 patients with chronic pyelonephritis, 16 patients with chronic glomerulonephritis and 15 patients with polycystic kidneys. The patients received a normal salt diet, a normal or limited amount of protein (depending on renal function) and liquids ad libitum. In addition, the urinary excretion of CHL was followed in 7 healthy volunteers after a water load (22 ml/kg) and in 10 subjects with chronic renal insufficiency under conditions of normal (108–134 mEq) and low daily salt (28–73 mEq) intake.

CHL was given either by sustained intravenous infusion expected to yield serum concentrations within the limits of 3–6 ng/L, or as a single oral dose of 1 g. Concentrations of CHL in serum and urine were assayed by the method of Levine and Fischbach [5]. Simultaneously, we measured inulin clearance [6] and sodium excretion.

RESULTS

In patients with renal failure, the renal clearance of CHL (C_{CHL}) decreased proportionally to the decrease of inulin clearance (C_{In}). There was no significant

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difference in this respect between patients with chronic pyelonephritis, glomerulonephritis or polycystic kidney (Fig. 1). $C_{\text{CHL}}$ decreased less than $C_{\text{In}}$. Fig. 2 shows the relationship between the relative values of $C_{\text{CHL}}$ (expressed in percentages of the normal value of $C_{\text{In}} = 120 \text{ ml/min}$) and of $C_{\text{In}}$ (expressed also in percentages). The slope of the regression line was 0.8.

**FIG. 1.** Relationship between the urinary clearances of chloramphenicol ($C_{\text{CHL}}$) and of inulin ($C_{\text{In}}$). (For details see reference [7]).

**FIG. 2.** Relationship between the relative values of the urinary clearances of chloramphenicol and of inulin. (For details see reference [8]).
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In agreement with the latter observation, the fractional excretion of CHL, calculated on the basis of the filterable fraction of plasma CHL, increased exponentially with falling values of C_in. In subjects with normal GFR the fractional excretion of CHL ranged from 40 to 50 percent (net tubular reabsorption of 50 to 60 percent of the filtered load). In cases with very low C_in (about 10 ml/min) the fractional excretion of CHL was nearly 100 percent. The ratio C_CHL/C_in increased in linear relation to the fractional excretion of sodium (Fig. 3) and fractional excretion of water (r = 0.72, p < 0.001).

DISCUSSION

The data reported above suggest a relationship between the fractional tubular reabsorption of sodium and/or of water and tubular reabsorption of CHL, since the C_CHL/C_in ratio increased proportionally to the fractional excretion of sodium and of water. Obviously, this functional change in residual nephrons accounts for the slower decrease of C_CHL in comparison with the decrease of C_in.

The decrease of the tubular reabsorption of CHL might depend on the depression of sodium reabsorption itself, or reflect the increased rate of flow of urine and of tubular fluid.

To decide between these possibilities, we investigated the influence of water diuresis on the urinary excretion of CHL in healthy subjects: each subject was investigated twice, with a one-week interval, under conditions of low and of high urine flow. The results are summarized in Fig. 4. An increase in urine flow, without any significant change of urinary sodium excretion, entailed a significant rise of urinary excretion of CHL (p < 0.05). This finding suggests that an increased rate of flow of tubular fluid and of urine depresses the tubular reabsorption of CHL and that CHL reabsorption occurs, at least in part, at sites downstream from the “diluting segment” of the nephron.

These findings, however, do not rule out a possible effect of changes in tubular sodium transport. We, therefore, investigated a possible effect of low sodium intake
in 10 patients with chronic renal insufficiency. The urinary excretion of CHL was not significantly altered by a low sodium diet. CHL reabsorption, thus, did not appear to be linked to tubular Na transport.

The results obtained are compatible with the view that enhanced tubular fluid and urine flow in residual nephrons, due to an adaptive decrease of tubular sodium reabsorption, affects the urinary excretion of drugs reabsorbed in part or entirely by back-diffusion from tubular fluid [7,8].

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