MECHANISM OF ACTION OF AMINOPHYLLINE ON RENAL EXCRETION OF SODIUM, POTASSIUM, AND WATER IN PATIENTS WITH NEPHRITIS

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UDC 616.61-002-085.221-07:616.632-074

Intramuscular injection of 1 ml of 24% aminophylline into patients with nephritis and undisturbed kidney function increases the minute diuresis and excretion of osmotically active substances (sodium, potassium). Under conditions of antidiuresis endogenous creatinine clearance was unchanged, while in hydration it was lowered. Clearance of osmotically free water in the first case was lowered and in the second increased. The effect of aminophylline in increasing sodium excretion is due to a decrease in the proximal sodium reabsorption. Increased sodium loading of the distal nephron stimulated its distal reabsorption, which in turn increased the potassium excretion.

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Some investigators claim that aminophylline increases glomerular filtration and that the increase in sodium excretion is due to an increase in its filtration change [2, 8]. Others consider that the sodium-excreting effect of aminophylline depends on an increase in glomerular filtration and a decrease in the tubular reabsorption of sodium [4-7, 9, 11, 13, 15]; a third group [6, 7, 15] ascribe the leading role to a decrease in tubular reabsorption of sodium. Another extremely important problem is the degree to which the response to theophylline is modified in a pathologically changed kidney.

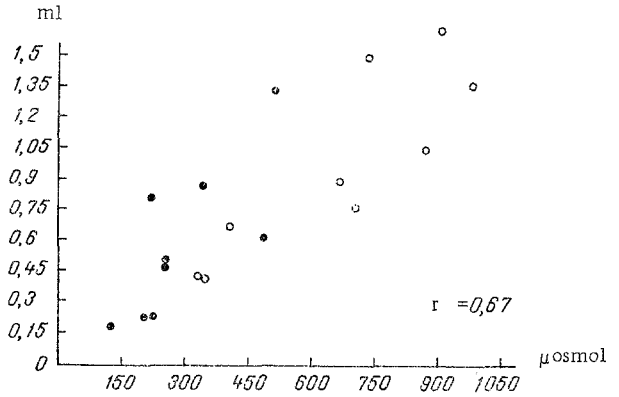

Fig. 1. Relationship between minute diuresis and excretion of osmotically active substances before and after injection of aminophylline. Black circles denote control period, unshaded circles 2 h after injection of aminophylline. Abscissa, excretion of osmotically active substances (in μosmol/min; ordinate, diuresis (in ml/min).

Because of absence of agreement in the literature on the nature of the sodium-excreting and diuretic action of aminophylline, the present investigation was carried out to study the mechanism of its action on the kidney.

EXPERIMENTAL METHOD

The investigation was carried out on 21 patients (14 men and 7 women aged from 17 to 55 years) with chronic glomerulonephritis or pyelonephritis with no signs of disturbance of kidney function (glomerula filtration over 60 ml/min, ratio between osmolarity of urine and osmolarity of plasma more than 1.5).

The patients were kept on a diet with considerable restriction of sodium chloride intake (reduced to 1.5 g/day). The investigations on 12 patients were carried out against a background of water diuresis, and on 9 patients during antidiuresis. Water diuresis was produced by taking water by mouth (20 ml/kg). Hyperhydration was maintained throughout the period of investigation. At the height of water

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TABLE 1. Effect of Aminophylline on Excretion of Water and Salts by the Kidney during Antidiuresis

Investigated indices of kidney function	Control period (60 min)	2 h after injection of aminophylline
Diuresis (in ml/min)	0.57 ± 0.12	1.17 ± 0.19 P < 0.01
Excretion of osmotically active substances (in μosmol/min)	287 ± 43.7	660 ± 82.2 P < 0.01
Sodium excretion (in μeq/min)	45.8 ± 14	136.4 ± 35.6 P < 0.05
Potassium excretion (in μeq/min)	40 ± 6.5	67.5 ± 11.9 P < 0.02
Reabsorption of osmotically free water (in ml/min)	0.39 ± 0.09	0.92 ± 0.14 P < 0.01
Endogenous creatinine clearance (in ml/min)	71.7 ± 10.3	76.2 ± 6.1 P > 0.7

TABLE 2. Effect of Aminophylline on Kidney Function during Hyperhydration

Investigated indices of kidney function	Control period (60 min)	2 h after injection of aminophylline
Diuresis (in ml/min)	7.2 ± 0.97	8.5 ± 1 P < 0.01
Sodium excretion (in μeq/min)	67.4 ± 11	107.3 ± 19.6 P < 0.01
Potassium excretion (in μeq/min)	95.5 ± 14.6	98.1 ± 14 P > 0.7
Sodium entering distal portions of nephron (in μeq/min)	944 ± 128	1133 ± 126 P < 0.01
Sodium reabsorption in distal portions of nephron (in μeq/min)	876 ± 117.5	1031 ± 116.6 P < 0.01
Clearance of osmotically free water (in ml/min)	5.57 ± 0.9	6.61 ± 0.91 P < 0.05
Endogenous creatinine clearance (in ml/min)	86.6 ± 9.2	69.7 ± 8.6 P < 0.01

diuresis aminophylline was given. The conditions of antidiuresis were produced by food and water deprivation for 12 h.

Samples of urine were collected over periods of 2 h before and after intramuscular injection of 1 ml 24% aminophylline solution. The concentration of sodium and potassium in the urine and blood plasma was measured by flame photometry, the osmolarity of the urine and plasma by a cryoscopic method using a semiconducting thermistor [1], and glomerular filtration by estimation of the endogenous creatinine clearance. Creatinine was determined by the method of Bonsnes and Toski [3]. The intensity of the color reaction was measured by a photoelectric colorimeter. Sodium reabsorption in the distal and proximal divisions of the nephron was calculated [14].

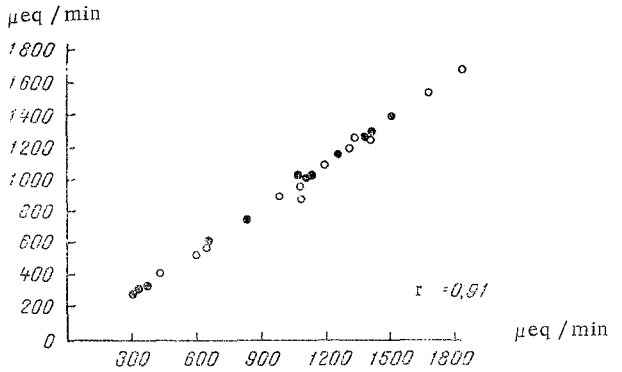

Fig. 2. Direct correlation between amount of sodium entering distal segments of nephron and distal reabsorption of sodium before and after injection of aminophylline. Legend as in Fig. 1. Abscissa, sodium entering distal segment of nephron (in μeq/min), ordinate, distal reabsorption of sodium (in μeq/min).

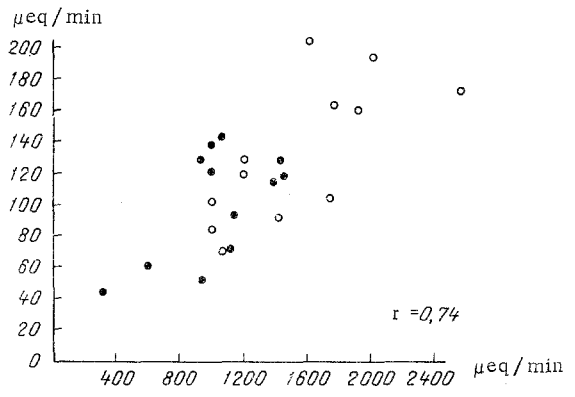

Fig. 3. Relationship between potassium excretion and distal sodium reabsorption before and after administration of aminophylline. Legend as in Fig. 1. Abscissa, distal reabsorption of sodium per 100 ml glomerular filtrate (in μeq/min); ordinate, potassium excretion per 100 ml glomerular filtrate (in μeq/min).

EXPERIMENTAL RESULTS

After injecting aminophylline into patients during antidiuresis, the diuresis, the excretion of sodium and potassium, and the reabsorption of osmotically free water were all increased (Table 1). On the average the diuresis was doubled, sodium excretion trebled, and potassium excretion doubled.

Injection of aminophylline against a background of water diuresis also increased the sodium excretion (Table 2) but had no appreciable effect on potassium excretion. The clearance of osmotically free water was definitely increased. The increase in sodium excretion produced by aminophylline was practically the same under the conditions of antidiuresis and hyperhydration.

Against the background of antidiuresis aminophylline caused no change in the endogenous creatinine clearance (Table 1), whereas during water diuresis the endogenous creatinine clearance was lowered (Table 2). This difference can be explained either by a true decrease in filtration or by a change in the ratio between creatinine secretion and reabsorption. The sodium excretion per 100 ml glomerular filtrate was definitely increased after injection of aminophylline during antidiuresis. Consequently, the effect of aminophylline in increasing sodium excretion is independent of changes in glomerular filtrate and is due to decreased tubular reabsorption of sodium.

After injection of aminophylline the amount of sodium entering the distal segment was increased (Table 2). Against the background of water diuresis aminophylline increased the clearance of osmotically free water, which can only have been due to an increase in the distal reabsorption of osmotically active substances and, in particular, of sodium. Consequently, the increase in sodium excretion caused by aminophylline depends on lowering of the proximal sodium reabsorption.

The increase in potassium excretion produced by aminophylline (per 100 ml glomerular filtrate) was the same during both antidiuresis and water diuresis. The increase caused by aminophylline in the volume of urine excreted during antidiuresis correlates directly (Fig. 1) with the increase in excretion of osmotically active substances ($r = 0.67$), and consequently it takes place by a mechanism of osmotic diuresis. This is in agreement with the fact that the increase in diuresis was accompanied by an increase in the reabsorption of osmotically free water. Against the background of hyperhydration the action of aminophylline on diuresis was particularly marked because as well as increasing the excretion of osmotically active substances, it also increased the clearance of osmotically free water.

The work of Gottschalk [12] has shown that increased sodium loading of the distal nephron leads to an increase in its distal reabsorption. In the experiments in which aminophylline was injected a direct correlation was in fact found between the amount of sodium entering the distal nephron and the distal sodium reabsorption ($r = 0.91$; Fig. 2). Berliner [10] found that the potassium secretion in the distal nephron takes place as a result of exchange for sodium. The increased excretion of potassium caused by aminophylline could therefore be explained by an increase in the distal reabsorption of sodium. A direct correlation

was in fact found between the effect of aminophylline in increasing potassium excretion and the increase in distal sodium reabsorption ($r = 0.74$; Fig. 3).

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