Sulbenicillin-induced Kaliuresis in Man

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Abstract The mechanism of kaliuresis induced by massive antibiotic administration was studied using α -sulfbenzyl penicillin (SBPC). In experimental group ($n=8$), urinary electrolytes excretion were compared between following the infusion of 10 g SBPC in 200 ml water at a constant rate and following the infusion of 48 mmol of NaCl (equal to that contained in 10 g SBPC) in 200 ml water. For the control group, 96 mmol NaCl in 400 ml water was infused ($n=5$). In the experimental group, urinary Na (UNaV) and urinary K excretion (UKV) increased relative to the control period. In the control group, UKV was not increased although UNaV was increased ($p<0.05$). UKV following SBPC infusion was correlated with UNaV ($p<0.05$) and urinary SBPC excretion ($p<0.05$). The ratio of urinary anion gap to urinary cation [$1 - \{\text{urinary Cl concentration}/(\text{urinary Na concentration} + \text{urinary K concentration})\}$] was significantly increased following SBPC infusion ($p<0.005$) but not in the control group. This increase in anion gap is possibly due to urinary SBPC, which will be ionized over 90% as nonreabsorbable anion in maximally acidic urine. We conclude that the kaliuresis induced by massive SBPC administration in man is probably caused by the nonreabsorbable anion effect of SBPC itself.

Key Words: kaliuresis, nonreabsorbable anion, antibiotics, sulbenicillin.

Recently, treatment with massive doses (from 10 to 30 g per day) of antibiotics has been extensively applied to serious infections or infections in patients with malignant tumors. Several reports (BRUNNER and FRICK, 1968; HOFFBRAND and STEWART, 1970; TATTERSALL *et al.*, 1972; KLASTERSKY *et al.*, 1973; CABIZCA and DESSER, 1976; STAPLETON *et al.*, 1976; GILL *et al.*, 1977) describe hypokalemia developing in about 10% of the cases treated with massive antibiotic therapy.

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There are several causes of hypokalemia: potassium trapping by cells in cases of alkalosis, decreased intake, increased renal excretion and increased extrarenal losses. BRUNNER and FRICK (1968) suggested that renal potassium losses constituted the main cause of hypokalemia during "massive" sodium penicillin therapy. In their paper, urinary potassium excretion did not drop below 50–70 mmol/24 hr despite frank hypokalemia during sodium penicillin administration, while urinary potassium excretion fell below 40 or even below 20 mmol/24 hr in a few days even before hypokalemia developed in normal controls depleted of potassium by a potassium deficient diet (SQUIRES and HUH, 1959). In experiments using rats, LIPNER *et al.* (1975) suggested that a nonreabsorbable anion effect of the antibiotic may accelerate K secretion into urine.

In the present study, sulbenicillin (α -sulfobenzyl penicillin) (SBPC), manufactured by Takeda Chemical Ind., Ltd. in Japan with a similar structure and antibacterial spectrum to carbenicillin (α -carboxybenzyl penicillin) (CBPC), was given to healthy persons. Our results are compatible with the hypothesis that the nonreabsorbable anion effect plays an important role in loss of K in urine.

SUBJECTS AND METHODS

Subjects included 13 healthy volunteers (age, 48.9 ± 3.0 ; male, 6; female, 7). Eight subjects were given SBPC as the experimental group and 5 were given saline as the control group.

Table 1 shows the initial profiles of both the experimental and control groups. There was no significant difference between these two groups in serum creatinine,

Table 1. Comparison of clinical parameters.

Parameter	Control group (n=5)	Experimental group (n=8)
Age	45.0 $\pm$ 5.5	51.3 $\pm$ 3.4
Male/female	2/3	4/4
Serum Cr (mmol/liter)	0.071 $\pm$ 0.022	0.074 $\pm$ 0.019
UN (mmol/liter)	4.6 $\pm$ 0.6	4.4 $\pm$ 0.7
Na (mmol/liter)	141.4 $\pm$ 1.1	142.9 $\pm$ 3.2
K (mmol/liter)	3.9 $\pm$ 0.2	4.0 $\pm$ 0.2
Cl (mmol/liter)	104.6 $\pm$ 1.8	103.8 $\pm$ 3.7
Ca (mmol/liter)	2.33 $\pm$ 0.10	2.27 $\pm$ 0.12
Mg (mmol/liter)	0.82 $\pm$ 0.05	0.83 $\pm$ 0.06
P (mmol/liter)	0.99 $\pm$ 0.14	0.96 $\pm$ 0.10
Blood gas pH	7.40 $\pm$ 0.03	7.42 $\pm$ 0.03
HCO ₃ (mmol/liter)	23.9 $\pm$ 1.1	24.6 $\pm$ 1.1
C _{cr} (ml/min)	112.2 $\pm$ 14.3	117.6 $\pm$ 21.0

There were no significant differences in each parameters between the control group and the experimental group. Cr, creatinine; UN, urea nitrogen; C_{cr}, endogenous creatinine clearance. Mean $\pm$ S.D.

urea nitrogen (UN), Na, K, Cl, Ca, Mg, P, pH, or creatinine clearance. All studies were carried out in the morning in the fasting state. The subjects remained recumbent during the studies except when voiding. Room temperature was kept constant at 25°C.

Experimental group. Ten grams of SBPC (therapeutic dosage) contained 48 mmol of Na. In order to measure the effect of Na alone, 200 ml of 1.4% saline (room temperature, 48 mmol NaCl) was infused intravenously at a rate of 1.67 ml/min during the period of 9:00–11:00, and then 10 g of SBPC dissolved in 200 ml of distilled water were infused at the same rate during the period of 11:00–13:00. The blood samples were collected at 9:00, 11:00, and 13:00 for analyses of serum electrolytes, creatinine and pH. The urine was collected at 30-min intervals by voiding under liquid paraffin. The electrolytes, creatinine, total CO₂, titratable acid, ammonium, pH, and SBPC concentration were measured in the urine.

Control group. In order to evaluate whether 200 ml of NaCl solution, given prior to SBPC infusion, modified the effect of the SBPC on the urinary electrolytes, the control group was tested in the following manner. During the period from 9:00 to 13:00, 400 ml of 1.4% saline (96 mmol NaCl) were infused at the same rate as in the experimental group. Plasma and urinary Na, K, Cl, Ca, P, UN, creatinine, and uric acid were measured by auto-analyser (Olympus). In this system, creatinine was measured after dialysis (Jaffe's reaction). Magnesium was measured by Xylidil blue method. Urinary total CO₂ was measured by microgas analysis using Natelson's method. Urinary ammonium was measured by Conway's diffusion method. Concentration of sulbenicillin was measured by the cylinder-plate diffusion technique (YAMAZAKI *et al.*, 1975). Creatinine clearance was measured by endogenous creatinine clearance. Values are expressed as mean±S.D. Statistical evaluation of the data was performed using analysis of variance.

Table 2. Change in blood chemistry.

	Control group		Experimental group	
	Before	After	Before	After
Cr	0.071±0.022	0.074±0.020	0.074±0.019	0.076±0.016
UN	4.6 ±0.6	4.4 ±0.8	4.4 ±0.7	4.5 ±0.8
Na	141.4 ±1.1	142.0 ±1.8	142.9 ±3.2	143.4 ±4.0
K	3.9 ±0.2	3.8 ±0.1	4.0 ±0.2	3.8 ±0.2
Cl	104.6 ±1.8	106.0 ±2.1	103.8 ±3.7	102.1 ±2.8
Ca	2.33 ±0.10	2.39 ±0.08	2.27 ±0.12	2.30 ±0.15
Mg	0.82 ±0.05	0.86 ±0.09	0.83 ±0.06	0.85 ±0.10
P	0.99 ±0.14	0.95 ±0.15	0.96 ±0.10	0.93 ±0.12

The values of before infusion and those of following infusion were compared. There were no significant differences in each parameters by infusion. Each value is expressed as mm. Cr, creatinine; UN, urea nitrogen. Mean±S.D.

Table 3. Change in urinary parameters.

	Saline loading period				Control group: saline loading period Experimental group: SBPC loading period				Significance
	9:00- 9:30 (P ₁)	9:30- 10:00 (P ₂)	10:00- 10:30 (P ₃)	10:30- 11:00 (P ₄)	11:00- 11:30 (P ₅)	11:30- 12:00 (P ₆)	12:00- 12:30 (P ₇)	12:30- 13:00 (P ₈)	
SBPC (mmol/30 min)	—	—	—	—	0.58 ±0.16	1.50 ±0.29	2.36 ±0.32	2.81 ±0.27	—
Volume (ml/30 min)	C 41.1 ±18.9	90.7 ±28.8	101.4 ±23.4	103.0 ±17.0	94.1 ±24.2	96.9 ±22.7	95.7 ±21.2	93.7 ±18.5	N.S.
	E 47.0 ±13.4	86.9 ±23.6	99.5 ±20.1	82.6 ±13.7	88.3 ±26.0	96.8 ±31.7	92.5 ±20.9	101.5 ±25.7	N.S.
C _{cr} (ml/min)	C 112.2 ±6.4	108.0 ±6.4	111.2 ±7.2	108.0 ±9.7	108.2 ±7.2	109.2 ±7.4	110.0 ±9.1	107.0 ±10.0	N.S.
	E 117.6 ±7.4	108.7 ±10.5	120.2 ±13.9	114.0 ±15.8	114.0 ±15.8	110.5 ±10.9	101.6 ±6.0	103.4 ±7.4	N.S.
Na (mmol/30 min)	C 3.16 ±0.87	3.75 ±0.70	4.32 ±1.22	4.20 ±0.76	4.83 ±0.80	4.92 ±0.91	5.31 ±0.93	5.46 ±0.90	<i>p</i> <0.05
	E 3.40 ±0.93	3.49 ±0.76	4.77 ±1.30	5.23 ±1.18	6.01 ±1.04	6.88 ±1.44	9.00 ±1.66	9.37 ±1.46	<i>p</i> <0.01
K (mmol/30 min)	C 1.14 ±0.16	1.04 ±0.14	1.10 ±0.15	1.13 ±0.18	1.01 ±0.15	1.02 ±0.18	1.06 ±0.17	0.96 ±0.17	N.S.
	E 1.36 ±0.14	1.30 ±0.14	1.33 ±0.17	1.39 ±0.19	1.55 ±0.16	1.65 ±0.26	1.82 ±0.26	1.84 ±0.26	<i>p</i> <0.05
Cl (mmol/30 min)	C 3.54 ±0.92	4.11 ±0.90	4.47 ±0.75	4.41 ±0.77	4.98 ±0.81	5.07 ±0.79	5.52 ±0.81	5.55 ±0.80	<i>p</i> <0.05
	E 4.08 ±1.03	4.11 ±0.88	5.45 ±1.55	5.84 ±1.35	5.64 ±1.02	5.30 ±1.31	5.85 ±1.46	5.41 ±1.37	N.S.
Ca (mmol/30 min)	C 0.035 ±0.004	0.037 ±0.004	0.047 ±0.006	0.036 ±0.005	0.035 ±0.006	0.035 ±0.006	0.039 ±0.007	0.039 ±0.006	N.S.
	E 0.033 ±0.008	0.027 ±0.006	0.035 ±0.008	0.038 ±0.010	0.036 ±0.009	0.045 ±0.014	0.053 ±0.014	0.061 ±0.018	<i>p</i> <0.01

Mg (mmol/30 min)	C	0.049 ±0.005	0.050 ±0.003	0.048 ±0.003	0.044 ±0.002	0.047 ±0.002	0.046 ±0.002	0.046 ±0.003	0.041 ±0.002	N.S.
	E	0.046 ±0.007	0.042 ±0.005	0.045 ±0.008	0.047 ±0.007	0.049 ±0.005	0.048 ±0.007	0.057 ±0.012	0.058 ±0.012	N.S.
P (mmol/30 min)	C	0.395 ±0.068	0.422 ±0.053	0.471 ±0.041	0.448 ±0.045	0.483 ±0.036	0.490 ±0.039	0.498 ±0.043	0.480 ±0.040	N.S.
	E	0.376 ±0.060	0.378 ±0.062	0.451 ±0.056	0.419 ±0.051	0.439 ±0.075	0.387 ±0.057	0.385 ±0.035	0.402 ±0.036	N.S.
T-CO ₂ (mmol/30 min)	C	0.091 ±0.034	0.142 ±0.038	0.210 ±0.057	0.217 ±0.047	0.298 ±0.081	0.308 ±0.072	0.257 ±0.079	0.257 ±0.060	N.S.
	E	0.111 ±0.040	0.154 ±0.044	0.164 ±0.045	0.137 ±0.033	0.249 ±0.100	0.299 ±0.088	0.356 ±0.120	0.341 ±0.101	N.S.
TA (mmol/30 min)	C	0.26 ±0.03	0.30 ±0.04	0.24 ±0.05	0.26 ±0.04	0.27 ±0.05	0.26 ±0.05	0.22 ±0.04	0.27 ±0.06	N.S.
	E	0.36 ±0.12	0.34 ±0.08	0.36 ±0.07	0.36 ±0.07	0.34 ±0.10	0.27 ±0.07	0.30 ±0.08	0.29 ±0.09	N.S.
NH ₄ (mmol/30 min)	C	0.81 ±0.11	0.84 ±0.12	0.90 ±0.10	0.81 ±0.13	0.81 ±0.07	0.85 ±0.08	0.69 ±0.10	0.64 ±0.09	N.S.
	E	0.62 ±0.12	0.76 ±0.20	0.90 ±0.22	0.77 ±0.15	0.66 ±0.09	0.57 ±0.05	0.67 ±0.11	0.69 ±0.08	N.S.
pH	C	6.10 ±0.23	6.33 ±0.44	6.30 ±0.43	6.34 ±0.40	6.38 ±0.41	6.44 ±0.30	6.42 ±0.38	6.46 ±0.48	N.S.
	E	6.04 ±0.40	6.08 ±0.45	6.29 ±0.41	6.30 ±0.46	6.15 ±0.39	6.37 ±0.52	6.20 ±0.52	6.18 ±0.72	N.S.

Statistical analyses were performed between P₁-P₄ and P₅-P₈ using analysis of variance. C, control group—infusion of 96 mmol NaCl in 400 ml water from 9:00 to 13:00 hr; E, experimental group—infusion of 48 mmol NaCl in 200 ml water from 9:00 to 11:00 hr and infusion of 10 g SBPC in 200 ml water from 11:00 to 13:00 hr; (P), period of urine collection; C_{cr}, endogenous creatinine clearance; T-CO₂, total CO₂; TA, titratable acid; N.S., not significant. Mean ± S.D.

RESULTS

Change in blood chemistry (Table 2)

Blood parameters were measured during both periods in both groups. No changes between periods were observed.

Changes in urinary excretion of sulbenicillin, creatinine, electrolytes, and acid (Table 3)

Significance differences were determined between saline loading periods (P_{1-4}) and saline loading periods (P_{5-8}) in the control group or sulbenicillin loading periods (P_{5-8}) in the experimental group. Urine volume was constant during the experiment except period 1 (P_1) in both groups. This means that the difference between input and output was kept steady. There was no change in creatinine clearance between two periods in both groups. Sodium excretion increased gradually during the experiment in both groups. However, potassium excretion increased only in the experimental group. Chloride excretion increased in the control group but not in the experimental group. Calcium excretion increased in the experimental group but not in the control group. Magnesium, phosphate, total CO_2 , titratable acid, ammonium, and pH did not show any difference in either group.

Relationship among the urinary Na, K, and SBPC excretion in the experimental group

To determine the effect of SBPC on urinary Na and K excretion, the increment in P_5-P_8 from P_4 [ΔUNaV ($\mu\text{mol}\cdot\text{min}/\text{ml GFR}$), UKV ($\mu\text{mol}\cdot\text{min}/\text{ml GFR}$)] was studied. A significant correlation: $y=0.056x+0.10$, $x=\Delta\text{UNaV}$, $y=\Delta\text{UKV}$, $r=0.44$ ($p<0.05$), was obtained. The values were divided by GFR to determine the change per nephron.

A significant relationship was observed between the increments in urinary Na excretion [ΔUNaV ($\mu\text{mol}\cdot\text{min}/\text{ml GFR}$)] and urinary SBPC excretion [USBPCV ($\mu\text{mol}\cdot\text{min}/\text{ml GFR}$)] in P_5-P_8 compared with P_4 following the infusion of SBPC solution (Fig. 1a). As is evident from Fig. 1b, a significant correlation was also obtained between urinary SBPC excretion [USBPCV ($\mu\text{mol}\cdot\text{min}/\text{ml GFR}$)] and increments of urinary K excretion from P_4 following the infusion of SBPC solution.

To evaluate the amount of excreted undetermined anions, the so-called anion gap in urine was calculated as $[1 - \{\text{urinary Cl concentration}/(\text{urinary Na concentration} + \text{urinary K concentration})\}]$. As shown in Fig. 2, in the control group, the anion gaps are maintained at a value of 0.20 or lower. In the experimental group, the gaps increased stepwise and significantly during P_5-P_8 .

Fig. 1. Relationship among the urinary Na, K, and SBPC excretion in the experimental group. $U_{Na}V$, increments of urinary Na excretion using period 4 (P_4) as baseline; $U_{K}V$, increments of urinary K excretion using period 4 (P_4) as baseline; $U_{SBPC}V$, urinary sulbenicillin excretion.

Fig. 2. Effect of control solution or experimental solution on the urinary anion gap. Urinary anion gap was calculated as: $1 - \{\text{urinary Cl concentration} / (\text{urinary Na concentration} + \text{urinary K concentration})\}$. White columns indicate the values of control group. Shaded columns indicate the values of experimental group. Each value of P_5 , P_6 , P_7 , and P_8 was compared with that of P_4 . * $p < 0.05$, ** $p < 0.005$. Mean $\pm$ S.D.

DISCUSSION

In our experiments, urinary K excretion increased following the infusion of SBPC solution and was correlated with urinary SBPC excretion. Hypokalemia did not occur during the experiment probably because of the short duration of the experiment.

In considering factors that influence K excretion, the nature of the filtered anion load, the effect of Na load, the mineralocorticoid activity, the degree of urinary acidification, and the intratubular fluid flow in the distal tubule may be important (COHEN *et al.* 1981). Nonreabsorbable or poorly reabsorbable anions such as sulphate and bicarbonate are thought to enhance cation excretion such as potassium by increasing potential difference (intratubular negativity). Penicillin is secreted by the proximal tubule (EAGLE and NEWMAN, 1947). Like other penicillin derivatives, SBPC is filtered in part by the glomerulus and possibly secreted by the proximal tubule. SBPC can not be reabsorbed in the distal nephron because of its large molecular size, 458.42, which is slightly greater than that of mannitol. In addition, SBPC is a rather strong acid with a pK value of 2.7. This means that even in maximally acidic urine over 90% will be ionized. We observed that the urinary anion gap increased in our experiments following the SBPC infusion. Therefore, a fairly high percentage of anion in the urine was SBPC. It is presumed that SBPC accelerates urinary K excretion in man by the nonreabsorbable anion effect in the distal tubules.

To examine the effect of the increased potential difference in the distal tubules on K and H excretion, Na₂SO₄ loading test has been used (SELDIN *et al.*, 1967; CLAPP *et al.*, 1962). In their experiments, supraphysiologic amounts of mineralocorticoid are concomitantly administered to obtain the maximal effect of Na₂SO₄. Urinary pH decreased, and urinary K, H, and NH₄ excretion were increased. In animal experiments using CBPC, increases in urinary K and NH₄ excretion and lowering of urinary pH were observed (LIPNER *et al.*, 1975). In the experiment of Lipner *et al.*, the animals were fed a Na-free diet so that their endogenous mineralocorticoid activity was stimulated. In our experiment, endogenous mineralocorticoid activity was not stimulated and only urinary K excretion was increased. The difference between our results and the result of the animal experiments and Na₂SO₄ loading test in man might be due to the level of endogenous mineralocorticoid activity.

Mineralocorticoids are capable of exerting an influence on K and H transport in the cortical collecting tubule (SCHWARZ and BURG, 1978). However, it is unlikely in our experiment that the mineralocorticoid is the main factor of increased urinary K excretion (though aldosterone concentration was not measured) because urinary K excretion increases too quickly to be the result of aldosterone (FELDMAN *et al.*, 1972).

SBPC is a Na salt. However, this Na load was not the main cause of K

excretion in our experiments. The same amounts of Na were infused as controls. As shown, infusion of NaCl in the control group caused no significant increase in urinary K excretion in spite of an increase in urinary Na excretion. The failure of urinary K excretion to increase despite increased urinary Na excretion in control group may be due to the low correlation between Na and K excretion as shown by MALNIC *et al.* (1966a, b) or the nonstimulated condition of endogenous mineralocorticoid activity in our experiment.

When SBPC is excreted in the urine as a nonreabsorbable solute, osmotic diuresis may occur (BURG, 1981), and it is possible that an increased urinary K excretion is induced by augmented intratubular fluid flow (KHURI *et al.*, 1975). In our results, however, constant amounts of urine were excreted in both the control and experimental groups, except the first 30 min (P_1). It is not likely that osmotic diuresis is the main cause of increased urinary K excretion.

While it is not proved yet, some authors consider a redistribution of K in the body to be important as the cause of hypokalemia (TATTERSALL *et al.*, 1972). Another concept is a toxic effect of antibiotics on the cells (MONTGOMERIE *et al.*, 1968) including tubular cells.

We conclude that the kaliuresis observed by massive SBPC administration in man is probably caused by the nonreabsorbable anion effect of SBPC itself.

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