Effect of Bucladesine Sodium on the Plasma Concentrations and Urinary Excretion of Purine Bases and Uridine

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To examine whether bucladesine sodium affects the plasma concentrations of purine bases (hypoxanthine, xanthine, and uric acid) and uridine, 100 mL of physiological saline containing bucladesine sodium (6 mg/kg weight) was administered intravenously to eight healthy subjects for 1 hour after overnight fast except for water. Blood was drawn 30 minutes before, and 30 minutes and 1 hour after the beginning of the infusion, and 1-hour urine was collected before and after the beginning of the infusion. Two weeks later, 100 mL of only physiological saline was administered under the same protocol. Bucladesine sodium decreased the plasma concentrations of hypoxanthine by 36% and by 37%, and of xanthine by 16% and 33%, and of uridine by 17% and 30%, 30 minutes and 1 hour after the beginning of the infusion, respectively, and increased the urinary excretion of hypoxanthine and uric acid by 140% and 30%, respectively, after the beginning of the infusion. However, it did not affect the plasma concentration of uric acid or the urinary excretion of xanthine, and the urinary excretion of uridine was less than 0.2 μmol/h before or after bucladesine sodium infusion. On the other hand, physiological saline alone did not affect any of the values described. These results suggest that bucladesine sodium acts on the secretory process of the renal transport of hypoxanthine, resulting in the increased urinary excretion of hypoxanthine, and further suggest that bucladesine sodium enhances the uptake of uridine in plasma to liver cells.

Bucladesine sodium (dibutyryl cyclic adenosine monophosphate [AMP]) passes easily into cells and then is converted to cyclic AMP, resulting in an increase in intracellular concentration of cyclic AMP. Many studies[1-6] have demonstrated that bucladesine sodium plays many roles in vivo, for example, increases in secretion of insulin, cardiac output, urine volume, and the blood concentration of renin. However, among the many effects of bucladesine sodium, the effect on heart was eagerly investigated and clinically identified in Japan.[1,3] Accordingly, bucladesine sodium has been used as a cardiotonic since 1984 in Japan.

Previous studies[7-9] have demonstrated that glucagon increased the urinary excretion of uric acid. Since uric acid is transported at the site of renal proximal tubules, but no glucagon receptor is present at the site, the result suggests that liver-derived factor under glucagon acts on the site of the proximal tubules. In other previous studies,[10-12] it has been demonstrated that cyclic AMP released from the liver by glucagon enhances the urinary excretion of sodium and inorganic phosphate. Since inorganic phosphate is also transported mostly at the site of renal proximal tubules, it has been suggested that cyclic AMP acts on the proximal tubules. If the liver-derived factor under glucagon is cyclic AMP, bucladesine sodium, similar to cyclic AMP, may affect the urinary excretion of uric acid at the site of the proximal tubules. However, it remains undetermined whether bucladesine sodium affects the renal transport of uric acid and that of oxypurines, which share a common transport pathway partly with uric acid.[13-16]

A recent study[17] demonstrated that glucagon accelerated Na-dependent nucleoside transport of uridine into liver cells in vitro by increasing cyclic AMP, suggesting that the Na-dependent nucleoside transport pathway is regulated by glucagon in the prereplicative phase soon after partial hepatectomy. Furthermore, it was also demonstrated that bucladesine sodium accelerated Na-dependent nucleoside transport of uridine into liver cells in vitro,[13] suggesting that cyclic AMP directly accelerated the Na-dependent nucleoside transport of uridine. These results suggest that bucladesine sodium affects the plasma concentrations of uridine in humans. However, it remains undetermined whether bucladesine sodium affects the plasma concentrations of uridine. To investigate these effects of bucladesine sodium described, we conducted the present study.

MATERIALS AND METHODS

Subjects and Protocol

Eight men aged 34 to 47 years (body weight, 49 to 75 kg) participated in the study after informed consent was obtained. These subjects had normal laboratory data. After an overnight fast except for water, urine was completely voided, followed by collection of the first 1-hour urine samples (first period). The first blood samples were drawn with heparinized syringes 30 minutes before the first urine collection. After the first urine samples were collected, 100 mL of physiological saline containing bucladesine sodium (6 mg/kg weight) (bucladesine infusion) was infused over 1 hour. The second urine samples were collected at the end of the infusion, and the second and third blood samples were drawn 30 minutes before and at the end of the infusion, respectively. Two weeks later, a control study was performed with intravenous administration of 100 mL of only physiological saline (control infusion). In the preliminary study, the administration of 10 to 12 mg of bucladesine sodium/kg weight did not increase significantly the urinary excretion of uric acid, because of bucladesine sodium-induced decrease in blood pressure in several cases. Therefore, in the present study, we administered a dose of bucladesine sodium (6 mg/kg weight) that does not significantly change blood pressure.

Blood and Urine Analyses

Plasma and urinary concentrations of hypoxanthine, xanthine, and uridine were determined using high-performance liquid chromatography (HPLC) as described previously.[18] In brief, the column was a Wakosil 5C-18 (4.6 × 250 mm; Wako Pure Chemicals, Osaka, Japan). The flow rate was 1 mL/min, and the mobile phase was 0.02 mol/L potassium phosphate buffer (pH 2.2). The concentration of uric acid in plasma and urine was measured by the uricase method using a

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Hitachi-736 autoanalyzer (Tokyo, Japan). Plasma concentration of bucladesine sodium was determined using HPLC as follows: the chromatographic system consisted of an LC-6A high-performance liquid chromatograph (Shimadzu, Kyoto, Japan), an SPD-6AV UV-VIS detector (Shimadzu), a CTO-6A (column oven) (Shimadzu), and a CR3A chromatopac recorder. The column was a Chemosorb 7scx (4.6 mm × 250 mm; Chemco Scientific, Tokyo, Japan), the column temperature, 50°C, the flow rate, 1.5 mL/min, and the mobile phase, 0.1 mol/L potassium phosphate buffer (pH 3.5) containing 1% methanol (vol/vol). The detection limit of bucladesine sodium was 0.4 μmol/L. Plasma was diluted two fold with distilled water and then filtered with Microcon 3-42403 (Amicon, Beverly, MA) using high speed micro refrigerated centrifuge Tomy, MR-150 (Osaka Japan). Twenty microliters of the filtrate was injected onto the column. Plasma concentrations of glucagon were measured by radioimmunoassay, using a Daiichi Glucagon Kit (Daiichi RI, Tokyo, Japan). The percentage ratios of uric acid clearance/creatinine clearance (fractional uric acid clearance), hypoxanthine clearance/creatinine clearance (fractional hypoxanthine clearance), and xanthine clearance/creatinine clearance (fractional xanthine clearance) were calculated using the plasma values 30 minutes before and after the beginning of bucladesine sodium infusion and the 1-hour urine values before and after the beginning of the infusion.

Chemicals

Bucladesine sodium was obtained from Daiichi. Other chemicals were purchased from Wako Pure Chemical.

Statistical Analysis

Values were expressed as the mean ± SD. The significance of differences between the variables was analyzed using a two-tailed, paired *t* test.

RESULTS

Plasma Concentration of Purine Bases and Uridine

Bucladesine sodium infusion decreased the plasma concentrations of hypoxanthine by 36% and 37%, of xanthine by 16% and 33%, and of uridine by 13% and 30% 30 minutes and 1 hour after the beginning of the infusion, respectively, but it did not affect the plasma concentration of uric acid (Table 1). On the other hand, infusion of only physiological saline (control infusion) did not affect the plasma concentrations of hypoxanthine, xanthine, uric acid, or uridine (Table 1).

Table 1. Concentration of Purine Bases and Uridine in Plasma (N = 8)

Infusion	30 Minutes Before Infusion	30 Minutes After Beginning Infusion	1 Hour After Beginning Infusion
Bucladesine sodium			
Hypoxanthine (μmol/L)	1.44 ± 0.26	0.92 ± 0.16†	0.90 ± 0.14†
Xanthine (μmol/L)	0.90 ± 0.20	0.76 ± 0.16*	0.60 ± 0.14*
Uric acid (μmol/L)	375 ± 60	375 ± 65	375 ± 65
Uridine (μmol/L)	4.14 ± 0.12	3.62 ± 0.22†	2.88 ± 0.24†
Control (physiological saline)			
Hypoxanthine (μmol/L)	1.34 ± 0.18	1.36 ± 0.20	1.28 ± 0.26
Xanthine (μmol/L)	0.86 ± 0.15	0.88 ± 0.17	0.82 ± 0.22
Uric acid (μmol/L)	369 ± 55	369 ± 56	369 ± 54
Uridine (μmol/L)	4.22 ± 0.41	4.20 ± 0.44	4.26 ± 0.38

*$P < .05$.
†$P < .01$.

Table 2. Urinary Excretion of Purine Bases and Uridine (N = 8)

Infusion	Preinfusion	Infusion
Bucladesine sodium		
Hypoxanthine (μmol/h)	4.62 ± 0.81	10.93 ± 1.96†
Xanthine (μmol/h)	3.92 ± 0.76	3.68 ± 0.66
Uric acid (μmol/h)	152 ± 48	198 ± 53†
Uridine (μmol/h)	ND	ND
Control (physiological saline)		
Hypoxanthine (μmol/h)	4.77 ± 0.72	4.55 ± 0.54
Xanthine (μmol/h)	4.02 ± 0.58	4.08 ± 0.75
Uric acid (μmol/h)	146 ± 49	147 ± 45
Uridine (μmol/h)	ND	ND

Abbreviation: ND, below the detection limit (0.2 μmol/h).
*$P < .01$.

Urinary Excretion of Purine Bases and Uridine

Bucladesine sodium infusion increased the urinary excretion of hypoxanthine and uric acid by 140% and 30%, respectively, but did not affect that of xanthine significantly, while the control infusion did not affect the urinary excretion of hypoxanthine, xanthine, or uric acid (Table 2). The urinary excretion of uridine was less than 0.2 μmol/h before and after bucladesine sodium infusion, as well as before and after the control infusion.

Creatinine Clearance and Fractional Clearance of Hypoxanthine, Xanthine, and Uric Acid

Although bucladesine sodium infusion did not affect fractional xanthine clearance significantly, it increased creatinine clearance by 6%, fractional hypoxanthine clearance by 238%, and fractional uric acid clearance by 23% (Table 3). On the other hand, the control infusion did not affect creatinine clearance or the fractional clearances of hypoxanthine, xanthine, and uric acid (Table 3).

Plasma Concentration of Bucladesine Sodium, Glucose, Insulin, and Glucagon

Bucladesine sodium infusion increased the plasma concentrations of bucladesine sodium from below the detection limit before the infusion to 6.2 ± 0.8 and 7.5 ± 0.9 μmol/L 30

Table 3. Creatinine Clearance and Fractional Clearance of Hypoxanthine, Xanthine, and Uric Acid (N = 8)

Infusion	Preinfusion	Infusion
Bucladesine sodium		
Ccr	100.4 ± 8.7	106.8 ± 5.8*
Fhx	55.6 ± 15.6	188.3 ± 46.0†
Fx	71.2 ± 17.5	80.6 ± 15.1
Fua	6.6 ± 0.9	8.1 ± 0.9†
Control (physiological saline)		
Ccr	100.7 ± 12.0	99.6 ± 7.3
Fhx	59.3 ± 15.7	56.3 ± 12.6
Fx	79.3 ± 22.7	79.7 ± 24.5
Fua	6.2 ± 0.9	6.5 ± 1.0

Abbreviations: Ccr, creatinine clearance; Fhx, fractional hypoxanthine clearance (hypoxanthine clearance/creatinine clearance × 100); Fx, fractional xanthine clearance (xanthine clearance/creatinine clearance × 100); Fua, fractional uric acid clearance (uric acid clearance/creatinine clearance × 100).
*$P < .05$.
†$P < .01$.

minutes and 1 hour after the beginning of the infusion, respectively (Table 4). It also increased the plasma concentrations of glucose by 81% and by 96%, and insulin by 7.3-fold and 11.6-fold 30 minutes and 1 hour after the beginning of the infusion, respectively, but did not affect that of glucagon. On the other hand, the control infusion did not affect these values (Table 4).

Plasma Concentrations of Inorganic Phosphate, Sodium, and Chloride

Bucladesine sodium infusion decreased the plasma concentration of inorganic phosphate from 0.97 ± 0.12 to 0.71 ± 0.10 ($P < .01$) and 0.68 ± 0.08 ($P < .01$) mEq/L 30 minutes and 1 hour after the beginning of the infusion, respectively, whereas the control infusion did not affect the plasma concentrations of inorganic phosphate (1.00 ± 0.07 *v* 1.00 ± 0.07 and 0.97 ± 0.07 mEq/L). Neither bucladesine infusion nor control infusion affected plasma concentrations of sodium and chloride (data not shown).

Urinary Excretion of Sodium, Chloride, and Inorganic Phosphate

Bucladesine sodium infusion increased the 1-hour urinary excretion of inorganic phosphate from 0.81 ± 0.19 to 1.05 ± 0.22 mmol/h ($P < .01$), that of sodium from 6.7 ± 2.6 to 10.30 ± 4.25 mmol/h ($P < .01$), and that of chloride from 8.20 ± 2.73 to 11.38 ± 4.19 mmol/h ($P < .01$), whereas the control infusion did not affect the urinary excretion of inorganic phosphate (0.66 ± 0.27 *v* 0.72 ± 0.17 mmol/h), sodium (7.8 ± 2.5 *v* 7.7 ± 2.6 mmol/h), and chloride (8.9 ± 2.6 *v* 8.5 ± 2.4 mmol/h).

DISCUSSION

In the present study, bucladesine sodium decreased the plasma concentrations of hypoxanthine, xanthine, uridine, and inorganic phosphate (Table 1), and increased the urinary excretion of hypoxanthine, uric acid (Table 2), inorganic phosphate, sodium, and chloride, as well as the plasma concentrations of glucose and insulin (Table 4). However, it did not affect the plasma concentration of uric acid (Table 1) or the urinary excretion of xanthine (Table 2). These results indicate that a decrease in the plasma concentration of hypoxanthine is ascribable to bucladesine sodium-induced increase in the urinary excretion of hypoxanthine and the decrease in the plasma concentration of hypoxanthine may result in a decrease in the plasma concentration of xanthine, which is produced from hypoxanthine by xanthine dehydrogenase. Furthermore, it was indicated that the effect of bucladesine sodium (6 mg/kg weight) on the urinary excretion of oxypurines in the present study is different from that of glucagon (1 mg) on the urinary excretion of oxypurines in a previous study,[7] although the effect of bucladesine sodium is similar to that of glucagon on the plasma concentration and urinary excretion of inorganic phosphate and the urinary excretion of uric acid,[7] sodium, and chloride.[10-12] The effect of bucladesine sodium on the urinary excretion of oxypurines in the present study is noteworthy, since no previous study has encountered such a drug as bucladesine sodium, which enhances the urinary excretion of hypoxanthine, but does not enhance that of xanthine. Many previous studies[13-16] have suggested that the renal transport pathway(s) of oxypurines comprises the process of reabsorption and secretion, as does the renal transport of uric acid. In addition, it has been suggested that hypoxanthine, xanthine, and uric acid partly share one renal transport pathway.[13-16] The present study demonstrated that bucladesine sodium increased the fractional clearance of hypoxanthine by greater than 100% (Table 3), indicating that this drug affects the secretory process of the renal transport of hypoxanthine in addition to an increase in glomerular filtration rate. Furthermore, it was also suggested that hypoxanthine may share the same renal transport pathway partly with uric acid, since bucladesine sodium increased the fractional clearance of uric acid.

Table 4. Concentration of Glucose, Insulin, and Glucagon in Plasma (N = 8)

Infusion	30 Minutes Before Infusion	30 Minutes After Beginning Infusion	1 Hour After Beginning Infusion
Bucladesine sodium			
Glucose (mmol/L)	5.49 ± 0.27	9.93 ± 0.44**	10.73 ± 1.73**
Insulin (μU/mL)	5.0 ± 2.1	41.4 ± 13.8**	62.9 ± 23.6**
Glucagon (pg/mL)	73.9 ± 36.1	76.0 ± 48.0	71.1 ± 37.0
Control (physiological saline)			
Glucose (mmol/L)	5.52 ± 0.16	5.46 ± 0.17	5.48 ± 0.20
Insulin (μU/mL)	5.0 ± 1.7	5.1 ± 1.6	5.2 ± 1.6
Glucagon (pg/mL)	71.6 ± 15.6	74.3 ± 20.5	71.8 ± 21.0

*$P < .05$.
†$P < .01$.

Bucladesine sodium passes into cells and then is converted to cyclic AMP. Therefore, most of the action of bucladesine sodium is ascribable to that of cyclic AMP in the cells. A previous study[4] suggested that in hepatocytes, an increase in cyclic AMP enhances glycogenolysis, resulting in an increase in the plasma concentration of glucose, and in islet cells, an increase in cyclic AMP enhances the secretion of insulin. These effects were demonstrated in the present study. Previous studies[19-24] have demonstrated that ischemia, muscular exercise, ethanol ingestion, fructose infusion, and xylitol infusion increased the plasma concentration of uridine, as well as that of purine bases (hypoxanthine, xanthine, and uric acid), suggesting that adenosine triphosphate (ATP) consumption causes pyrimidine degradation, as well as purine degradation. Although bucladesine sodium decreased the plasma concentration of oxypurines, its decrease seems to be ascribable to bucladesine-induced increase in the urinary excretion of hypoxanthine. Therefore, bucladesine sodium does not seem to affect the production or consumption of ATP. A recent study[17] demonstrated that bucladesine sodium, glucagon, and insulin enhanced uridine uptake into hepatocytes via the Na-dependent nucleoside transport pathway in vitro, suggesting that bucladesine sodium may affect the plasma concentration of uridine via the Na-dependent nucleoside transport pathway in vivo. The present study showed that bucladesine sodium decreased the plasma concentration of uridine in humans without the increased urinary excretion of uridine, suggesting that bucladesine sodium may enhance uridine uptake into cells, including hepatocytes, in vivo. Although the mechanism of the uridine uptake into cells by bucladesine sodium is undetermined, it seems possible that bucladesine sodium directly enhances uridine uptake into cells via the Na-dependent nucleoside

transport pathway in vivo. Moreover, an effect of insulin on Na-dependent nucleoside transport[17] is also possible, because bucladesine sodium stimulates the secretion of insulin, as shown in the present study. However, oral glucose loading (75 g) did not decrease the plasma concentration of uridine in healthy subjects, although it increased the plasma concentrations of glucose and insulin to the same degree as bucladesine sodium did (unpublished data, August 1997). Therefore, insulin does not seem to play a significant role in a decrease in the plasma concentration of uridine by the administration of bucladesine sodium.

It has been suggested that the physiologic role of the Na-dependent nucleoside transport pathway is to preserve extracellular nucleoside for the endogenous synthesis of nucleic acid.[25,26] In fact, this nucleoside transport is enhanced in response to a mitogenic stimulus like a partial hepatectomy.[26] Therefore, the administration of bucladesine sodium may play a beneficial role in nucleic acid biosynthesis in physiological situations that lead to hypertrophia and hyperplasia, such as partial hepatectomy. However, since this remains undetermined, further investigation including the effect of bucladesine sodium on nucleic acid biosynthesis in these situations is needed.

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