Renal Handling of Urate in Two Patients with Hyperuricemia and Primary Hyperparathyroidism

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Two patients with primary hyperparathyroidism had hyperuricemia due to the decrease in urate clearance. In analysis by 4-component model system, the tubular secretion of urate commonly decreased without changes in either filtered urate or presecretory reabsorption of urate. Both patients had a reduction of urea clearance, and both parathyroidectomy in the former case and intravenous infusion of saline in the latter case could reduce the serum urate level associated with the increase in the ratio of urate clearance to creatinine clearance. It is of interest that the former case with a higher serum urate level had a relatively higher postsecretory reabsorption, even with the decrease in tubular secretion of urate. However, the latter patient with a lower serum urate level had a decrease in postsecretory reabsorption of urate in proportion to the decrease in tubular secretion. These results suggest that in hyperuricemia patients with primary hyperparathyroidism, the reduction of tubular urate secretion via hypoperfusion of the capillary network is typically present, however, the severity of the hyperuricemia might be dependent on the dysfunction of the postsecretory reabsorption of urate. (Internal Medicine 31: 807–811, 1992)

Key words: volume contraction, tubular secretion of urate, postsecretory reabsorption of urate

Introduction

It is well known that hyperuricemia is often associated with primary hyperparathyroidism (1–5). However, the mechanism of hyperuricemia associated with primary hyperparathyroidism remains unclear. A recent report (6) suggested that hyperuricemia in primary hyperparathyroidism patients is the result of decreased urinary excretion of urate. In their patients, urate clearance returned to normal after the removal of parathyroid adenomas, suggesting that the renal urate handling in hyperparathyroidism might be impaired. In contrast, other reports (7) have shown that the serum urate in patients with primary hyperparathyroidism does not correlate with urate clearance. Therefore, to elucidate the mechanisms of hyperuricemia in primary hyperparathyroidism patients, it is necessary to study the renal handling of urate in these patients according to the 4-component model (8). However, few reports discuss the precise renal handling of urate in hyperuricemic patients with primary hyperparathyroidism. Therefore, in order to study the mechanism of hyperuricemia in primary hyperparathyroidism from the viewpoint of the renal handling of urate, we examined the urate metabolism of two hyperuricemic patients with hyperparathyroidism based on the pharmacological estimation using pyrazinamide, a urate secretion inhibitor (9), and probenecid, a urate postreabsorption inhibitor (10, 11).

Report of Cases

Case 1

A 69-year-old male was admitted on February 12, 1990 for investigation of both hypercalcemia and hypophosphatemia. Physical examination revealed a normal man. On admission, he was found to have hyperuricemia (10.6 mg/dl) as measured by a uricase assay. Urinalysis revealed neither proteinuria nor aminoaciduria. Other
findings of blood chemistry were as follows: sodium 137 mEq/l, potassium 5.1 mEq/l, chloride 105 mEq/l, calcium 13.2 mg/dl, inorganic phosphate 1.8 mg/dl, urea nitrogen 34 mg/dl, creatinine 1.6 mg/dl, triglycerides 91 mg/dl, cholesterol 233 mg/dl and fasting blood sugar 100 mg/dl. Serum protein was 6.7 g/dl with a normal electrophoretic and immunoelectrophoretic pattern. He had a renal stone. A liver function test, and roentgenogram of the chest, spine, and long bones were normal. Morning urinary pH remained less than 6.0. Blood pH was 7.43 and PaCO₂ was 36.6 mmHg. Creatinine clearance was 57.4 ± 5.4 ml/min/1.73 m² body surface area (n = 4). C-terminal-HSPTH was 2.5 μg/ml and HS-middle molecule PTH was 4092.7 pg/ml as measured by PTH Kit-Yamasa (Yamasa, Chiba, Japan). Tubular reabsorption of inorganic phosphate was 65.5%. Urea clearance was 16.1 ml/min/1.73 m² body surface area (normal subjects, n = 5: 60.5 ± 7.3 ml/min/1.73 m² body surface area). There was no evidence for renal tubular acidosis or any other tubular abnormalities. Careful examination did not reveal any sign of malignancy or bone pathology. We diagnosed this patient as hyperuricemia associated with primary hyperparathyroidism.

Case 2

A 72-year-old female was admitted on April 24, 1990 for investigation of both hypercalcemia and hypophosphatemia. Physical examination revealed a normal woman. On admission, she was found to have hyperuricemia (8.2 mg/dl) as measured by a uricase assay. Urinalysis revealed neither proteinuria nor aminoaciduria. Other findings of blood chemistry were as follows: sodium 141 mEq/l, potassium 5.2 mEq/l, chloride 103 mEq/l, calcium 12.3 mg/dl, inorganic phosphate 2.5 mg/dl, urea nitrogen 31 mg/dl, creatinine 1.1 mg/dl, triglycerides 200 mg/dl and cholesterol 260 mg/dl. Serum protein was 6.8 g/dl with a normal electrophoretic and immunoelectrophoretic pattern. A liver function test, and roentgenogram of the chest, spine, and long bones were all normal. She had no history of a renal stone. Morning urinary pH remained less than 6.0. Blood pH was 7.39 and PaCO₂ was 43.9 mmHg. Creatinine clearance was 78.8 ± 1.97 ml/min/1.73 m² body surface area (n = 4). C-terminal-HSPTH was 3.6 ng/ml and HS-middle molecule PTH was 2.5 jg/ml and HS-middle molecule PTH was 4092.7 pg/ml as measured by PTH Kit-Yamasa (Yamasa, Chiba, Japan). Tubular reabsorption of inorganic phosphate was 65.5%. Urea clearance was 16.1 ml/min/1.73 m² body surface area (normal subjects, n = 5: 60.5 ± 7.3 ml/min/1.73 m² body surface area). There was no evidence for renal tubular acidosis or any other tubular abnormalities. Careful examination did not reveal any sign of malignancy or bone pathology. We diagnosed this patient as hyperuricemia associated with primary hyperparathyroidism.

Methods

Throughout the study, the patients were maintained on a regular diet. Serum urate (Sur) and urinary urate concentrations were determined by a uricase assay (12) and serum and urinary creatinine levels were determined by an enzymatic method. A 7-day period was allowed between tests to avoid pharmacological interference. The study started in the morning after an overnight fast; breakfast was omitted. Bladder catheterization was avoided by oral hydration with 500 ml of water before and during each study. All urine specimens exceeded 200 ml in volume. Pyrazinamide and probenecid tests were performed according to the methods of Steele and Rieselbach (13) and Barrientos et al (14), respectively. Each test consisted of two phases: one before and one after drug administration (pyrazinamide 3 g orally in a single dose; probenecid 2 g orally in a single dose). In each study, both phases consisted of at least three 30-min clearance periods. A venous blood sample was drawn in the middle of each clearance period.

The first clearance period started after 60 min of drug administration. Endogenous creatinine clearance (Ccr) was used throughout the studies to estimate the glomerular filtration rate (GFR). It is well known that it takes 1 hour to show the effect of pyrazinamide and probenecid and 1.5 hour to achieve the maximum effect after administration of these drugs (15). Actually, the majority of subjects (10, 11, 15) exhibit minimum uricosuria following pyrazinamide and maximum uricosuria following probenecid in the second clearance period after drug administration. Presecretory reabsorption of urate was calculated as filtered urate (GFR x Sur) minus the minimum amount of urate excreted after pyrazinamide administration; this was expressed as the percentage of filtered urate. Tubular secretion of urate was calculated as the maximum urate excretion after probenecid administration and was expressed in terms of percentage of filtered urate. Postsecretory reabsorption of urate was calculated as the difference between tubular secretion of urate and the amount of urate excreted in the basal periods; this was expressed in terms of percentage of secreted urate. In aged-matched control subjects (n = 5), presecretory reabsorption was 99.3 ± 0.3%, tubular secretion was 40.4 ± 4.5%, and postsecretory reabsorption was 76.8 ± 5.6%. These levels are similar to those reported by Puig et al (16).

Results

1) Urate metabolism

In case 1, the serum urate value was 9.3 ± 1.2 mg/dl (n = 4), urinary urate excretion was 321 mg/day, urate clearance (Cur) was 2.80 ± 0.57 ml/min/1.73 m² body surface area (n = 4) and the ratio of urate clearance to creatinine clearance (Cur/Ccr) was 4.86 ± 0.56% (n = 4). In case 2, the serum urate value was 7.6 ± 0.4 mg/dl (n = 4), urinary urate excretion was 394 mg/day, urate clearance was 3.77 ± 1.27 ml/min/1.73 m² body surface area (n = 4) and Cur/Ccr was 7.70 ± 0.26% (n = 4)
Table 1. Effect of Pyrazinamide and Probenecid on Urate Metabolism

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Vu (ml/min)</th>
<th>Pur (mg/dl)</th>
<th>Per (mg/dl)</th>
<th>Uur (mg/dl)</th>
<th>Ucr (mg/dl)</th>
<th>Cur (ml/min)</th>
<th>Cer (ml/min)</th>
<th>Cur/Cer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.8</td>
<td>9.6</td>
<td>1.6</td>
<td>27.7</td>
<td>103.2</td>
<td>2.69</td>
<td>60.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Minimum urate excretion</td>
<td>3.4</td>
<td>9.7</td>
<td>1.6</td>
<td>0.5</td>
<td>23.9</td>
<td>0.2</td>
<td>51.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Maximum urate excretion</td>
<td>4.1</td>
<td>7.0</td>
<td>1.3</td>
<td>33.8</td>
<td>20.6</td>
<td>19.9</td>
<td>65.4</td>
<td>30.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 2</th>
<th>Vu (ml/min)</th>
<th>Pur (mg/dl)</th>
<th>Per (mg/dl)</th>
<th>Uur (mg/dl)</th>
<th>Ucr (mg/dl)</th>
<th>Cur (ml/min)</th>
<th>Cer (ml/min)</th>
<th>Cur/Cer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.3</td>
<td>7.3</td>
<td>0.9</td>
<td>24.6</td>
<td>39.8</td>
<td>4.5</td>
<td>59.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Minimum urate excretion</td>
<td>2.8</td>
<td>7.7</td>
<td>0.9</td>
<td>0.5</td>
<td>12.0</td>
<td>0.2</td>
<td>37.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Maximum urate excretion</td>
<td>2.5</td>
<td>6.8</td>
<td>0.9</td>
<td>23.1</td>
<td>17.0</td>
<td>8.5</td>
<td>47.2</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Vu: urine volume, Pur: serum urate level, Per: serum creatinine level, Uur: urinary urate level, Ucr: urinary creatinine level, Cur/Cer: ratio of urate clearance to creatinine clearance

Table 2. Tubular Phases of Urate Excretion

<table>
<thead>
<tr>
<th></th>
<th>Presecretory reabsorption (%)</th>
<th>Tubular secretion (%)</th>
<th>Postsecretory reabsorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>99.5</td>
<td>24.2</td>
<td>81.5</td>
</tr>
<tr>
<td>Case 2</td>
<td>99.7</td>
<td>13.4</td>
<td>52.0</td>
</tr>
<tr>
<td>Normal values</td>
<td>99.3 ± 0.3</td>
<td>40.4 ± 4.5</td>
<td>76.8 ± 5.6</td>
</tr>
</tbody>
</table>

Normal values of parameters (mean ± SD) taken from 5 normal adults

2) Tubular phases of urate excretion

Table 1 shows the levels of serum and urinary creatinine and urate, urine volume, Cur, Cer, and Cur/Cer in control phase and in both the minimum and maximum urate excretion phases following either pyrazinamide or probenecid administration. Filtered urate was 5779.2 µg/min in case 1 and 4307.0 µg/min in case 2 (normal subjects: 4743.1 ± 900 µg/min; n = 5). Based on the pyrazinamide and probenecid tests, the minimum urate excretion was 29.97 µg/min in case 1 and 14 µg/min in case 2, and the maximum urate excretion was 1395.94 µg/min in case 1 and 577.5 µg/min in case 2. The tubular phase of urate excretion in both cases is summarized in Table 2. Both patients had a normal presecretory reabsorption, however, their tubular secretion was decreased. Case 1 had a normal postsecretory reabsorption but case 2 had a decreased postsecretory reabsorption.

3) Effects of adenomectomy and hydration on urate excretion

In case 1, after serum C terminal-HSPTH level returned to the normal level at 0.9 ng/ml by parathyroidectomy, the serum urate decreased to 7.0 mg/dl and Cur/Cer increased to 11.3%. In case 2, after intravenous infusion of saline at 500 ml/30 min, Sur was reduced from 7.4 mg/dl to 7.1 mg/dl and Cur/Cer was increased from 7.8% to 11.1%.

Discussion

In the present study, we analyzed the urate metabolism of two patients with hyperuricemia and primary hyperparathyroidism based on the pharmacological evaluation. There are three mechanisms which may lead to an increase in serum urate: endogenous overproduction, decreased urinary excretion, or a combination of both (8). The normal urate excretion in the present cases could negate the possibility of endogenous urate overproduction. On the other hand, the decrease in Cur and Cur/Cer suggests that the hyperuricemia in these patients might have been caused by impaired renal urate handling.

The present concept of renal tubular urate handling proposes a four-component mode: glomerular filtration, presecretory reabsorption, tubular secretion, and postsecretory reabsorption (8). Theoretically, the decreased
fractional excretion of urate could be due to 1) reduced filtration of urate, 2) enhanced reabsorption, or 3) decreased secretion (8). Attempts to localize the site of the defect of urate transport in the nephron have been thwarted by the limitation of available techniques. The only technique used to differentiate these possibilities has been the pyrazinamide or probenecid test. Although the assumption that pyrazinamide selectively inhibits urate secretion, and that probenecid selectively inhibits postsecretory urate reabsorption may not be entirely valid. These tests presently are the most available for studying renal urate handling in human. As there is no direct evidence of localization of the nephron site of altered urate handling in hyperuricemia of hyperparathyroidism by the use of pharmacologic inhibitors, we tried to apply the pharmacological evaluation to the present cases by using pyrazinamide and probenecid. The results of both cases showed that the tubular secretion of urate was commonly reduced without changes in either the filtration of urate or presecretory reabsorption of urate.

The possible causes which could affect the urate tubular secretion in the hyperparathyroidism patients are as follows: 1) a direct action of parathyroid hormone on the tubular transport of urate, 2) volume contraction, because the other causes for the decrease in tubular secretion of urate, such as hypertension, drugs, and ketosis could be denied. It is difficult to identify which mechanism is responsible for the hyperuricemia in hyperparathyroidism patients. Indeed, a direct action of PTH on the tubular transport of urate might also be advocated since PTH is known to modulate the tubular reabsorption of several molecules and to stimulate c-AMP production in the proximal tubule, but plasma urate does not change in normal subjects after PTH injection (17) and no correlations were found between plasma urate and PTH in a hyperparathyroidism group (6). In the present cases, while PTH activity was higher in case 2 than that in case 1, the serum urate level was higher in case 1 than that in case 2, thereby, the overactivity of PTH was unlikely the main cause of hyperuricemia in the present cases. Volume contraction secondary to dehydration, which may result from hypercalcemia, is well known to decrease urate clearance and to raise serum urate, probably by decreasing the urate secretion (18). It is important to check whether the present cases had volume contraction or not. The urea clearance is a good index of volume depletion (19). In both of the present cases, the urea clearance decreased in comparison with control subjects, which might suggest that volume contraction secondary to dehydration from hypercalcemia might exist in the present cases. In case 2, intravenous infusion of saline reduced the serum urate level associated with the increase in Cur/Ccr, which finding might directly support the above possibility. In addition, in case 1, adenomectomy reduced the serum urate level with an increase in Cur/Ccr; this phenomenon was similar to the effect of intravenous hydration. Therefore, the hypothesis that hypoperfusion of the peritubular capillary network due to volume contraction could decrease the tubular secretion of urate was in favor of the hyperuricemia in our data and this finding might be the reverse pathophysiology of the diabetic renal hypouricemia described by Shichiri et al (10). These cases of hyperuricemia with hyperparathyroidism have been reversible by means of either adenomectomy or intravenous hydration.

It has been previously reported that the mean serum urate level tends to be greater and the mean fractional excretion lesser with a history of urolithiasis (6, 20). Case 1 with urolithiasis had the higher serum urate and the lesser urate excretion, compared to case 2 without urolithiasis, which is well compatible with the above reports. The severity of the hyperuricemia in the present cases might be related to the difference of function of the postsecretory reabsorption of urate among cases. The function of postsecretory reabsorption of urate is dependent on the amount of urate tubular secretion. In the case of hyperuricemia caused by hypersecretion (10, 21), probenecid or benz bromarone-induced block on postsecretory reabsorption could markedly increase Cur compared to control, which indicates that postsecretory reabsorption could be dependent on tubular secretion. In contrast, it is reasonable to assume that the decrease in postsecretory reabsorption in case 2 was accompanied by a decrease in tubular secretion of urate, as the postsecretory reabsorption of urate might be attenuated due to the reduction of urate secretion. However, the postsecretory reabsorption of urate in case 1 was not altered even when the tubular urate secretion was reduced; this may have elevated the serum urate in case 1 via dysfunction of postsecretory reabsorption which was larger than in case 2. These results suggest that the common pathophysiology to reveal hyperuricemia in the present cases in mainly a result of the reduction of tubular urate secretion mediated by volume depletion-induced hypoperfusion of the capillary network, but the severity of hyperuricemia might be related to the existence of urolithiasis and the dysfunction of postsecretory reabsorption of urate.

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References
Hyperuricemia and Primary Hyperparathyroidism


