A Simple Method of Selecting Gout Patients for Treatment with Uricosuric Agents, Using Spot Urine and Blood Samples

TETSUYA YAMAMOTO, YUJI MORIWAKI, SUMIO TAKAHASHI, ZENTA TSUTSUMI, TUNEYOSHI KA, MINORU FUKUCHI, and TOSHIKAZU HADA

ABSTRACT. Objective. To develop a simple means of selecting gout patients for treatment with uricosuric agents.

Methods. In 124 gout patients, spot urine and blood were sampled before breakfast and after overnight fast (except water) on the day of 24 h urine collection. Spot urine uric acid/creatinine ratio (Ua/Cr mmol/mmol) and serum creatinine × Ua/Cr (Scr*Ua/Cr µmol/l) were calculated together with 24 h urinary uric acid excretion/body surface (24 Ua/S). The patients were then classified either below or above 2.84 mmol/m²/day for 24 Ua/S.

Results. Classifications based on spot urine Ua/Cr (cut off value set at 0.34), spot urine Scr*Ua/Cr (cut off value set at 28.1), and a combination of spot urine Ua/Cr and Scr*Ua/Cr were found to be not significantly different in diagnostic accuracy for the detection of patients with 24 Ua/S below 2.84 mmol/m² (77%, 81%, and 81%, respectively) and sensitivity (80%, 83%, and 76%, respectively). However, specificity by a combination of spot urine Ua/Cr, and spot urine Scr*Ua/Cr was higher than by spot urine Ua/Cr alone (91% vs 74%, P < 0.05), although the specificity was not significantly different between a combination and spot urine Scr*Ua/Cr alone (91% vs 78%) or between spot urine Ua/Cr and spot urine Scr*Ua/Cr (74% vs 78%).

Conclusion. A combination of spot urine Ua/Cr and spot urine Scr*Ua/Cr may be clinically useful in selecting gout patients with 24 Ua/S below 2.84 mmol/m² for treatment with uricosuric agents without adverse effects. (J Rheumatol 2002:29:1937–41)

Key Indexing Terms: URIC ACID CREATININE

URICOSURIC AGENTS GOUT

Gout is a disease manifested by an increase in serum urate concentration (hyperuricemia), recurrent attacks of acute arthritis, deposits of monosodium urate monohydrate in and around the joints of the extremities, renal disease involving interstitial tissues and blood vessels, and uric acid nephrolithiasis. Since hyperuricemia causes gout, it is treated with antihyperuricemic agents such as xanthine oxidase inhibitors and uricosuric agents. The latter can easily decrease the concentration of uric acid, though their main adverse effect has been suggested to be urolithiasis. Therefore, uricosuric agents are suitable for administration to gout patients who demonstrate a decreased urinary excretion of uric acid, whereas allopurinol, a xanthine oxidase inhibitor, is given to patients with increased urinary excretion of uric acid, although its main adverse effect is severe allopurinol reaction.

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drawn at least one month prior to study. Patients completed a questionnaire that was analyzed by a dietician for purine intake (155 ± 39 mg daily).

Twenty-four hour urine collections were performed for all patients who were on self-selected diets, all of whom abstained from alcoholic beverages. Spot urine was sampled before breakfast and after overnight fast (water allowed) on the day of the 24 h urine sample collection. Blood samples were drawn after taking spot urine. In 64 patients with gout, 24 h urine collections were performed twice in order to compare 24 h urinary uric acid and creatinine excretion in paired samples. The correlation coefficient of 24 h uric acid excretion was 0.80 and of 24 h creatinine excretion 0.90; thus 24 h urine collection was performed once in the other patients. In 64 patients with gout, uric acid and creatinine were determined using the first samples from 2 separate 24 h urine collections. Since 24 h urinary uric acid excretion was found to be 2.26 ± 0.29 mmol/m² body surface in 36 healthy male subjects (height, 168.7 ± 6.7 cm; body weight, 68.9 ± 10.9 kg; age, 49.0 ± 10.1 yrs) as described (Table 1)10, patients to whom uricosuric agents may be administered were defined as those with a uric acid excretion below 2.84 mmol/m² (mean + 2 SD) (24 h urinary uric acid excretion/body surface/day). In 64 patients, 2 patients with uric acid excretion below 2.84 mmol/m² in their first samples had results > 2.84 mmol/m² in their second samples, while 4 patients with uric acid excretion > 2.84 mmol/m² in their first samples had results below 2.84 mmol/m² in their second samples, suggesting that a single measurement of 24 h urinary uric acid excretion was not completely accurate.

The serum and urinary concentrations of both uric acid and creatinine were determined in triplicate by an enzymatic method, using commercially available kits (Uric Acid B Test Wako for uric acid measurement and L type Creatinine F for creatinine measurement, Wako Pure Chemical Industries, Osaka, Japan). The ratios of spot urine uric acid/creatinine concentration (spot urine Ua/Cr) and serum creatinine × spot urine uric acid/Cr (spot urine Scr×Ua/Cr) were then calculated. Sensitivity, specificity, and diagnostic accuracy for the detection of uricosuric agent-treatable gout patients by spot urine Ua/Cr and/or spot urine Scr×Ua/Cr findings were calculated by: true positive/(true positive + false negative), true negative/(true negative + false positive), and (true positive + true negative)/total results, respectively. Statistical analysis. Variables are shown as mean ± SD. The significance of difference between variables was determined by analysis of variance. The significance of sensitivity, specificity, and diagnostic accuracy was analyzed by chi-square test.

### RESULTS

Serum and 24 h urine laboratory data regarding uric acid metabolism in gout patients and healthy subjects. Serum and urinary data are shown in Table 1. Serum uric acid concentration was greater than 417 μmol/l in all of the gout patients. Further, there were 46 patients with 24 h urine uric acid excretion amounts greater than 2.84 mmol/m² (uric acid excretion/body surface) (24 Ua/S) and 78 with 24 h urine uric acid excretion below 2.84 mmol/m². In all patients, serum uric acid and creatinine levels were higher than in healthy control subjects. Twenty-four hour urine uric acid excretion, uric acid clearance, 24 Ua/S, 24 h urine Ua/Cr, and 24 h Scr×Ua/Cr values in total patients and patients with 24 Ua/S greater than 2.84 mmol/m² were each higher than in healthy control subjects (Table 1). Creatinine clearance was greater than 70 ml/min in all patients and controls, and was not significantly different among all groups, including healthy subjects.

Table 1. Serum and urine laboratory data regarding uric acid metabolism by subgroup: 1. gout patients with 24 h urine uric acid excretion amounts > 2.84 mmol/m² (uric acid excretion/body surface) (24 Ua/S); 2. gout patients with 24 h urine uric acid excretion < 2.84 mmol/m²; and 3. healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 124)</th>
<th>(1) (N = 46)</th>
<th>(2) (N = 78)</th>
<th>(3) (N = 36)</th>
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<tbody>
<tr>
<td>Sua, μmol/l</td>
<td>524 ± 77**</td>
<td>542 ± 101**</td>
<td>524 ± 71**</td>
<td>321 ± 48</td>
</tr>
<tr>
<td>Scr, μmol/l</td>
<td>84 ± 16**</td>
<td>88 ± 11**</td>
<td>82 ± 16**</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>24 h ua, mmol/day</td>
<td>4.82 ± 1.18**</td>
<td>5.98 ± 0.86**</td>
<td>4.14 ± 0.72</td>
<td>3.95 ± 0.63</td>
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<tr>
<td>24 h Cua, ml/min</td>
<td>5.3 ± 1.5**</td>
<td>6.5 ± 1.5**</td>
<td>4.6 ± 0.9**</td>
<td>7.5 ± 1.5</td>
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<td>24 h Ccr, ml/min</td>
<td>104.3 ± 17.1</td>
<td>108.5 ± 16.4</td>
<td>101.8 ± 17.2</td>
<td>109.1 ± 19.9</td>
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<tr>
<td>24 h Ua/S, mmol/m²</td>
<td>2.68 ± 0.60**</td>
<td>3.32 ± 0.38**</td>
<td>2.31 ± 0.35</td>
<td>2.26 ± 0.29</td>
</tr>
<tr>
<td>24 h Scr/S, mmol/m²</td>
<td>8.35 ± 1.21*</td>
<td>8.96 ± 1.09**</td>
<td>7.98 ± 1.12</td>
<td>7.80 ± 1.44</td>
</tr>
<tr>
<td>24 h urine Ua/Cr, mol/mol</td>
<td>0.32 ± 0.07*</td>
<td>0.37 ± 0.06**</td>
<td>0.30 ± 0.05</td>
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<td>24 h urine Scr×Ua/Cr, μmol/l</td>
<td>26.8 ± 6.6**</td>
<td>31.9 ± 6.0**</td>
<td>23.8 ± 4.8</td>
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<td>Spot urine Ua/Cr, mol/l</td>
<td>0.32 ± 0.09</td>
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<td>Spot urine Scr×Ua/Cr, μmol/l</td>
<td>26.2 ± 7.7</td>
<td>32.7 ± 6.5</td>
<td>22.6 ± 6.0</td>
<td>ND</td>
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</tbody>
</table>

Sua: serum concentration of uric acid; Scr: serum concentration of creatinine; 24 h Ua: 24 h urine uric acid excretion; 24 h Cua: uric acid clearance calculated using 24 h urine uric acid excretion; 24 h Ccr: creatinine clearance calculated using 24 h urine creatinine excretion; 24 Ua/S : 24 h urine uric acid excretion/body surface; 24 Cr/S: 24 h urine creatinine excretion/body surface; 24 Ua/Cr: 24 h urine uric acid/creatinine ratio; 24 h Scr×Ua/Cr: serum creatinine concentration × 24 h Uracr; spot urine Ua/Cr: spot urine uric acid/creatinine ratio; spot urine Scr×Ua/Cr: serum creatinine concentration × spot urine Ua/Cr; ND: not determined. *p < 0.05; **p < 0.01 vs healthy subjects.
N = 124) (Figure 1) and 24 h Ua/Cr (R = 0.79, P < 0.001, N = 124). Further, spot urine Ua/Cr was correlated with 24 h Ua/Cr (R = 0.79, P < 0.001, N = 124), and spot urine Ua/Cr was not different from 24 h urine Ua/Cr (Table 1). In the regression line obtained between 24 Ua/S and spot urine Ua/Cr using the least squares method (spot urine Ua/Cr = 0.035 + 0.106 × 24 Ua/S), the cut off value of spot urine Ua/Cr was calculated to be 0.34 (mol/mol) using the 24 Ua/S value (mean + 2 SD) (2.84 mmol/m²) from 36 healthy subjects.

**Relationship between 24 Ua/S and Scr*Ua/Cr.** Since body surface was also correlated with 24 h creatinine clearance without correction for body surface (R = 0.52, P < 0.01), 24 h urinary uric acid excretion and spot urine uric acid were corrected using body surface and spot urine creatinine clearance, respectively, and then those results were compared. Twenty-four Ua/S was correlated with spot urine Scr*Ua/Cr (R = 0.74, P < 0.001, N = 124) (Figure 2) and 24 h Scr*Ua/Cr (R = 0.76, P < 0.001, N = 124). Spot urine Scr*Ua/Cr was also correlated with 24 h urine Scr*Ua/Cr (R = 0.75, P < 0.001). In the regression line between 24 Ua/S and spot urine Scr*Ua/Cr (spot urine Scr*Ua/Cr = 0.168 + 9.84 × 24 Ua/S) the cut off value of spot urine Scr*Ua/Cr was calculated to be 28.1 (µmol/l) using the value of 24 Ua/S (mean + 2 SD) (2.84 mmol/m²).

**Selection of patients for uricosuric agents by spot urine Ua/Cr and spot urine Scr*Ua/Cr findings.** Patients with 24 Ua/S below 2.84 mmol/m² were estimated by spot urine Ua/Cr, with the cut off values of spot urine Ua/Cr set at 0.34 (Table 2, Figure 1). The diagnostic accuracy, sensitivity, and specificity for their estimation were 77%, 80%, and 74%, respectively. Patients with 24 Ua/S below 2.84 mmol/m² were also estimated by spot urine Scr*Ua/Cr, with the cut off values of spot urine Scr*Ua/Cr set at 28.1 (Table 3, Figure 2). Diagnostic accuracy, sensitivity, and specificity were 81%, 83%, and 78%, respectively. Further, patients with 24 Ua/S below 2.84 mmol/m² were estimated by a combination of spot urine Ua/Cr and Scr*Ua/Cr, with a diagnostic accuracy, sensitivity, and specificity of 81%, 76%, and 91%, respectively (Table 4, Figure 3). The diagnostic accuracy for the estimation of patients with 24 Ua/S below 2.84 mmol/m² (77% at 0.34 of Ua/Cr, 81% at 28.1 of Scr*Ua/Cr, and 81% in combination) as well as the sensi-

<table>
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<th>Spot Urine Ua/Cr</th>
<th>≥ 0.34</th>
<th>&lt; 0.34</th>
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<tr>
<td>Patients with 24 Ua/S ≥ 2.84 mmol/m²</td>
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<td>12</td>
</tr>
<tr>
<td>Patients with 24 Ua/S &lt; 2.84 mmol/m²</td>
<td>15</td>
<td>63</td>
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P < 0.01 by chi-square test. Spot urine Ua/Cr and 24 Ua/S are as in Table 1.

<table>
<thead>
<tr>
<th>Spot Urine Scr*Ua/Cr, µmol/l</th>
<th>≥ 28.1</th>
<th>&lt; 28.1</th>
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<tbody>
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<td>Patients with 24 Ua/S ≥ 2.84 mmol/m²</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>Patients with 24 Ua/S &lt; 2.84 mmol/m²</td>
<td>13</td>
<td>65</td>
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</table>

P < 0.01 by chi-square test. Spot urine Scr*Ua/Cr is as in Table 1.
activity (80% at 0.34 of Ua/Cr, 83% at 28.1 of Scr*Ua/Cr, and 76% in combination) were not significantly different. However, specificity by a combination of the 2 (91%) was higher than that by spot urine Ua/Cr (74% at 0.34) (P < 0.05), though it was not significantly different from that by spot urine Scr*Ua/Cr (78% at 28.1).

DISCUSSION
Our aim was to develop a simple means of selecting gout patients for treatment with uricosuric agents. Before determining an effective means of screening using spot urine results, we investigated the correlation coefficients of 24 h urinary uric acid excretion between 2 separate 24 h urine collections from patients with gout. In a recent study of 225 patients with renal stones who had 2 separate 24 h urine collections on self-selected diets, those coefficients were 0.80 and 0.90, respectively. The difference between the results of the 2 studies regarding the coefficient of urinary uric acid excretion seems to be ascribable to diet, as a positive relationship between 24 h urinary uric acid excretion/m² body surface and purine intake (R = 0.29, p < 0.01) was observed in our patients, who had received instruction regarding a proper diet regimen for hyperuricemia. Since the correlation coefficient of the two 24 h urinary uric acid excretion samples was high, a single measurement of 24 h urinary uric acid excretion was performed.

Anti-hyperuricemic agents are generally used for the treatment of hyperuricemia, to decrease the concentration of uric acid in serum and maintain it below 357 µmol/l without bringing on adverse effects of anti-hyperuricemic agents. They consist of several kinds of uricosuric agents (e.g., probenecid, benzbramone and sulfinpyrazone) as well as allopurinol (a xanthine oxidase inhibitor). The uricosuric agents have stronger hypouricemic effects than allopurinol, although they may cause uricosuria-induced urolithiasis. To prevent the onset of urate stones, the 24 h urinary excretion of uric acid is measured prior to treatment for hyperuricemia; the uricosuric agents are then administered to gout patients who under-excrete uric acid, while allopurinol is administered to those who over-excrete uric acid.

In a previous study, it was reported that more than 50% of the subjects with urinary excretion of uric acid greater than 6.55 mmol/day had urolithiasis. In another report, over-excretion of uric acid was defined as greater than 5.95 mmol/day with a regular diet. In addition, it has been shown that uricosuric agents are indicated for the treatment of hyperuricemia in gout patients who excrete less than 3.57 mmol of uric acid/day on a purine-free diet. From these findings, we estimated that about 4.76 mmol/day is an indicator for patients on a regular diet. In our previous study, the 24 h urinary excretion of uric acid was 2.26 ± 0.29 mmol/m² body surface (3.91 ± 0.51 mmol/1.73 m² body surface) in healthy subjects on a regular diet; thus, a 24 h urinary uric acid excretion of 4.76 mmol is nearly equal to the 24 h urinary uric acid excretion of the mean + 2 SD (4.92 mmol/1.73 m²) in those healthy subjects, assuming a mean body surface of 1.73 m². Further, we did not clinically detect the occurrence of urolithiasis in 50 gout patients who had received uricosuric agents for more than 10 years and with 24 h urinary excretion of uric acid levels below 2.84 mmol/m² (unpublished data). Therefore, a 24 h urinary excretion of uric acid below 2.84 (mean + 2 SD) mmol/m² (upper normal limits) was used as the indicator for uricosuric agents in our present study.

The selection of gout patients with increased urinary excretion of uric acid has been previously attempted using spot urine findings. However, since those results are controversial, the indication of anti-hyperuricemic agents by spot urine is not generally used to determine effective treat-
ment for patients with hyperuricemia. In many studies, 24 h urinary excretion of uric acid measurements were not corrected by body surface or body weight, although spot urine uric acid has been corrected by spot urine creatinine. We corrected the 24 h urinary excretion of uric acid by body surface, and observed a relationship between the ratio of uric acid/creatinine in spot urine and 24 Ua/S (R = 0.68, P < 0.01). Accordingly, using spot urine Ua/Cr, the diagnostic accuracy for patients with 24 Ua/S below 2.84 mmol/m² was calculated at 0.34 (the cut off value of spot urine Ua/Cr). Diagnostic accuracy, sensitivity, and specificity were 77%, 80%, and 74%, respectively; however, the specificity was not adequate to select gout patients for treatment with uricosuric agents.

A problem with Ua/Cr is that it is affected by the urinary excretion of creatinine that has escaped from muscle tissue. In our study, the urinary excretion of creatinine/body surface ratio was higher in patients with 24 Ua/S greater than 2.84 mmol/m² than in healthy subjects, i.e., in a range of 3.35 to 8.08 mmol/m²; thus, the urinary excretion of creatinine may have a significant effect on urine uric acid/creatinine values in spot urine specimens.

In addition to spot urine uric acid/creatinine, the urinary excretion of uric acid was estimated by spot urine Scr*Ua/Cr, which was calculated using the concentrations of uric acid and creatinine in serum and spot urine samples. Spot urine Scr*Ua/Cr was well correlated with 24 h urine Scr*Ua/Cr (R = 0.76); thus, using the regression line between spot urine Scr*Ua/Cr and 24 Ua/S, the cut off value of spot urine Scr*Ua/Cr (28.1 µmol/l) was also calculated based on 2.84 mmol/m² (24 Ua/S). At the cut off value of spot urine Scr*Ua/Cr (28.1 µmol/l), the diagnostic accuracy, sensitivity, and specificity for gout patients with 24 Ua/S below 2.84 mmol/m² were 81%, 83%, and 78%, respectively.

A problem with Scr*Ua/Cr is that it is affected by creatinine clearance. Since the creatinine clearance of gout patients in our study was in a range of 71 to 141 ml/min, creatinine clearance may have a considerable effect on spot urine Scr*Ua/Cr. To reduce the influence of urinary creatinine excretion on spot urine Ua/Cr, and of creatinine clearance on spot urine Scr*Ua/Cr, as well as to obtain a high specificity without a reduction of specificity, we used spot urine uric acid/creatinine and Scr*Ua/Cr in combination to differentiate gout patients who demonstrated a 24 h urinary excretion of uric acid below 2.84 mmol/m², because the relationship between 24 h urinary creatinine excretion/m² and creatinine clearance was weak, although significant (R = 0.24, P < 0.01). Combining the cut off value of spot urine Ua/Cr (0.34) and that of spot urine Scr*Ua/Cr (28.1) improved the specificity (91%) without a significant change in diagnostic accuracy (81%) or sensitivity (76%), as compared with that of spot urine Ua/Cr, even though the specificity was not significantly higher than that of spot urine Scr*Ua/Cr (Table 4). This specificity result suggests that it is possible to select gout patients with 24 Ua/S below 2.84 mmol/m² for the administration of uricosuric agents with a low risk of adverse effects of urolithiasis by a combination protocol of spot urine Ua/Cr and spot urine Scr*Ua/Cr.

In conclusion, estimation by a combination of spot urine Ua/Cr and spot urine Scr*Ua/Cr may be clinically useful to select gout patients for treatment with uricosuric agents as specificity as well as diagnostic accuracy are important to prevent the adverse effects of uricosuric agents (urolithiasis). However, the effect of urinary creatinine excretion or creatinine clearance on these values must also be considered.

REFERENCES