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Urological Research

Urinary Excretion of Urate in Patients with Calcium Oxalate Stone Disease

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Summary. The diurnal variation in excretion and concentration of urinary urate was studied in 31 patients with calcium oxalate stone disease. Urate excretion was highest during the day-time, decreased in the evening and was low during the night. Meal-related peaks were observed. The concentration of urate reached the highest levels during the morning hours and, attributable to a low pH in morning urine, most samples were at this time super-saturated with respect to uric acid. In addition, many urines appeared to be at high risk of exceeding the uric acid formation product. Concerning the ion-activity product of sodium urate, supersaturated samples were frequently found, but the risk of exceeding the formation product for sodium urate at a normal urate excretion was apparently low.

Key words: Crystallization risk, Sodium urate, Supersaturation, Uric acid, Urolithiasis.

Introduction

There is accumulating evidence that the reduction in urinary urate brought about by allopurinol might be effective in the prevention of recurrent renal calcium stone formation [1, 2, 6, 21, 30]. Some preliminary results from our own department also suggest a decreased rate of stone formation during administration of allopurinol to a group of calcium stone formers. However, in contrast to a number of reports on an increased urate excretion among calcium stone formers [3, 4, 14, 26, 28, 29], hyperuricosuria was found to be rare in Swedish stone formers [10, 33]. A possible effect of allopurinol on calcium oxalate stone formation, even in the absence of hyperuricosuria, is supported by the successful treatment of a number of evidently normouricosuric patients presented in the literature [1, 2, 6, 21].

Because no satisfactory explanation so far has been presented for the relationship between urinary urate and calcium oxalate stone formation, we found it of interest to study the diurnal variation of urate excretion in patients with calcium oxalate stone disease and to define risk periods for uric acid and sodium urate crystallization.

Materials and Methods

Patients

Twenty-four male and seven female patients with calcium oxalate stone disease were included in the study of urate excretion. Their mean (± SEM) urate excretion as obtained in a previous routine biochemical investigation, was 236 ± 11 mmol per mol of creatinine (2.92 ± 0.17 mmol per 24 h). During the study they were eating an ordinary hospital diet. The ingestion of fluids was not restricted, but the patients were asked to follow their normal drinking habits during the study. None of them were on any specific treatment for their stone disease or were taking any other drugs of importance for urate excretion.

Urate Analysis

Urine was collected every hour between 6.00 to 23.00 h in plastic bottles without any preservative. Between 23.00 and 6.00 h all urine was collected in one bottle. The samples were stored at +4 °C during the collection period and at −20 °C until analyzed, usually within a few days. Following thawing, heating to 37 °C, and careful mixing of the urine, urate concentration was determined by a uricase method [16].

pH Measurement

Analysis of pH was performed in urine collected every two or three hours from 11 male patients with calcium oxalate stone disease. The pH was measured with a glass electrode (Extech) in freshly voided urine, in order to avoid pH-changes attributable to storage of urine.

Definitions

The term *urate* will subsequently be used for the sum of urate ions and undissociated uric acid. The ion-activity products were calculated in the following way:

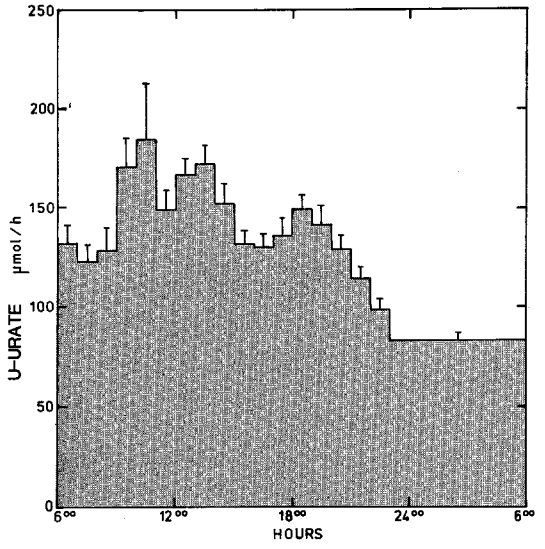

Fig. 1. Mean (± SEM) urinary urate (µmol/h) in 31 patients with calcium oxalate stone disease

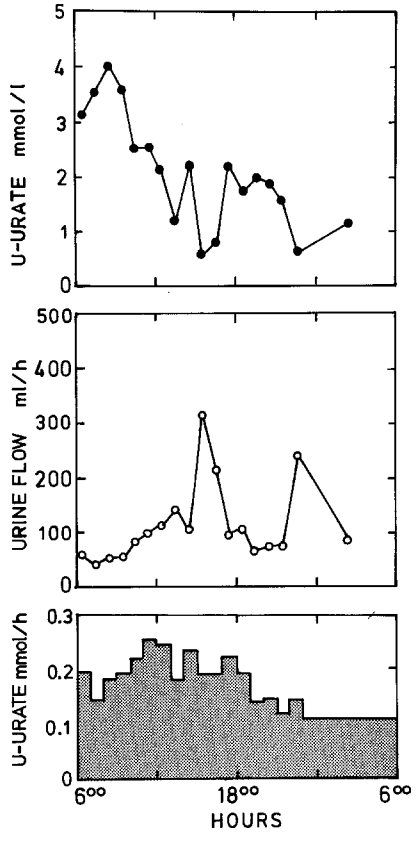

Fig. 2. Typical pattern of hourly urate concentration, urine flow and urate excretion in a male patient with calcium oxalate stone disease

$$\text{Uric acid} = C_{H_3O^+} \times C_{Ur^-} \times f_1^2$$

$$\text{Sodium urate} = C_{Na^+} \times C_{Ur^-} \times f_1^2$$

where f_1 is the activity coefficient of monovalent ions, $C_{H_3O^+}$ the hydrogen ion concentration, C_{Na^+} and C_{Ur^-} the concentrations of sodium and urate ions respectively (mol/l).

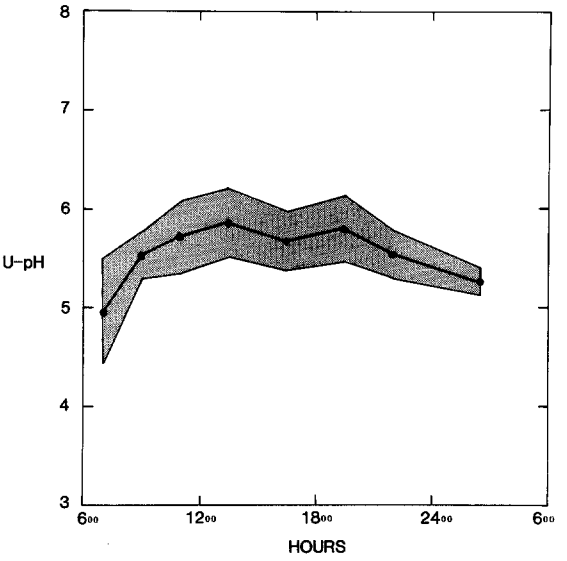

Fig. 3. Mean urinary pH and 95% confidence interval in 11 patients with calcium oxalate stone disease

Results

The mean (± SEM) hourly urate excretion in 31 calcium oxalate stone formers is shown in Fig. 1. Higher levels of urinary urate were observed during the day-time with suggested peaks in relation to meals. There was a decline in urate excretion during the evening hours and a rather low excretion during the night.

Because of a higher urine flow during the active part of the day, a quite different pattern was obtained for urinary urate concentration. A typical example, from a male patient, is shown in Fig. 2. The highest urate concentration was observed in the morning hours 6.00 to 10.00 h. This high concentration appears to be a result of a comparatively low urine flow rate at this time of the day.

When the whole group of patients was considered, the highest urate concentrations were recorded in samples collected between 6.00 to 7.00 and 7.00 to 8.00 h. The mean (± SEM) urine flow during these intervals averaged 71 ± 10 and 64 ± 8 ml/h.

Urine pH in 11 patients with calcium oxalate stone disease varied during the day as shown in Fig. 3. It is interesting to note the low pH level in the morning.

In Fig. 4 the mean and range of urate concentration values are shown together with calculated levels of total urate concentration required to reach a solubility product for uric acid of 2×10^{-9} M^2 and a formation product of 5×10^{-9} M^2 [18]. These values were obtained by means of the pH-values in Fig. 3. A pKs of 5.47 [11, 18] and an activity coefficient for monovalent ions of 0.7 [12] were used.

Evidently many urines are at risk of being supersaturated with respect to uric acid, and might in some patients occasionally exceed the formation product. This is further exemplified in Fig. 5 where urate concentration values in 52 urine samples during the first two morning hours (6.00–

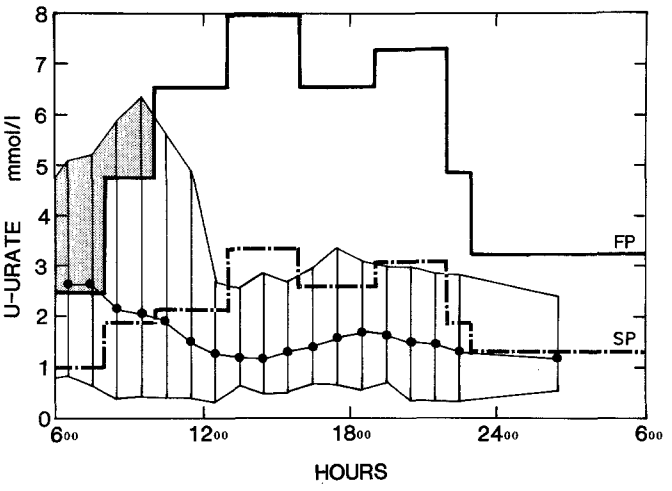

Fig. 4. Mean urinary urate concentration (•) and range recorded in 31 patients with calcium oxalate stone disease. The urate concentration corresponding to the solubility (*SP*) and formation products (*FP*) of uric acid at mean pH according to Fig. 3 are indicated. Concentration values within the shaded area represent a risk of spontaneous uric acid crystallization

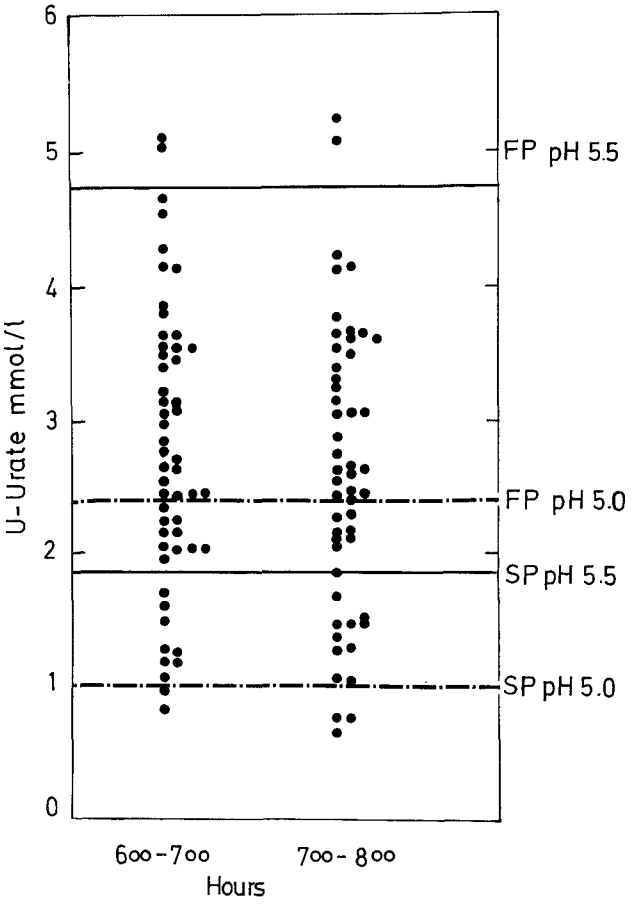

Fig. 5. Urate concentrations in 52 urine samples collected between 6.00–7.00 and 7.00–8.00 h. Urate concentrations corresponding to solubility (*SP*) and formation (*FP*) products at pH 5.0 (– · – · –) and 5.5 (——) are indicated

7.00 and 7.00–8.00) are demonstrated. The urate concentration values resulting in an ion-activity product at the level of the solubility product and the formation product at pH 5.0 and 5.5 respectively are indicated in the figure. It is evident that most urine samples would be metastably supersaturated at pH 5.5. At a pH of 5.0, 33 urine samples between 6.00 and 7.00 h and 30 samples between 7.00 and 8.00 h exceeded the formation product.

The ion-activity products of sodium urate were similarly calculated. Values for the solubility product and the formation product of 4.8×10^{-5} M^2 and 130×10^{-5} M^2 were used [18]. By means of a pH of 6.0 and a sodium concentration of 100 mmol/l, the ion-activity products of sodium urate obtained from the mean urate values in Fig. 4, exceeded the solubility product during long periods. However, the levels obtained were far below the formation product.

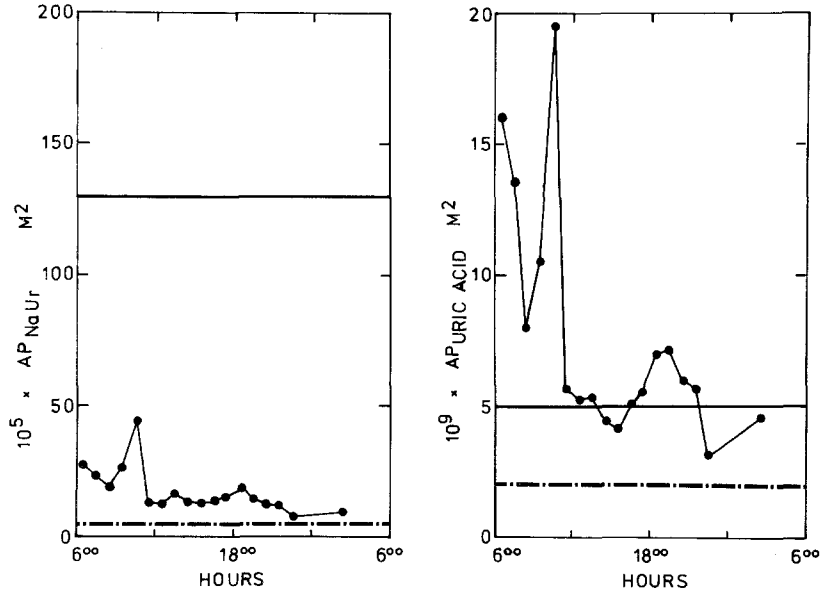

Fig. 6. Ion-activity products of sodium urate (*left*) calculated for a 24-h urine volume of 1,500 ml, a sodium concentration of 100 mmol/l and with the highest urate and pH values recorded at each hour, and ion-activity products of uric acid (*right*) calculated for a 24-h urine volume of 1,500 ml and with the highest urate and the lowest pH values recorded. The solubility product (– · – · –) and formation product (——) for the two crystal phases are indicated

In order to obtain some impression of the risk of reaching the formation product, the highest pH and the highest urate concentration during each hour were combined. The ion-activity product thus calculated at a sodium concentration of 100 mmol/l, was still far below the formation product.

To compensate for the rather high urine flow rate in the patients the ion-activity products of sodium urate and uric acid were also calculated for a total 24-h urine volume of 1,500 ml which is close to the mean 24-h volume found in stone formers and normal subjets [31]. The relative distribution of urine flow throughout the day, at low and high 24-h urine volumes, was shown to be comparable, and the hourly urine volumes were obtained by means of the average volume fraction during each hour in all patients studied. The ion-activity products of sodium urate were thus calculated for a 24 h urine volume of 1,500 ml by means of the maximal urate excretion and the highest pH recorded in each fraction, and the ion-activity products of uric acid by combining the highest urate and the lowest pH values (Fig. 6). Although the levels of supersaturation in this way were increased, the pattern was the same and the result did not alter the conclusions drawn with the higher average urine flow.

Discussion

The excretion of urate in each patient followed a fairly similar pattern with peaks occuring in relation to meals. This is evidently a result of ingested purine-containing food stoffs [7, 14, 15]. The pattern obtained was similar to that reported by Schneeberger et al. [27]. The urate excretion in the early morning hours was not remarkably high but, attributable to a relatively low urine flow, the urate concentration reached the highest level during this period. In most patients the morning urate concentration clearly exceeded that recorded during periods of high urate excretion.

Crystallization of uric acid is to a large extent determined by urinary pH. It is therefore of interest that the highest concentration of urate occurred when urine is supposed to be most acid and the solubility of uric acid poor. Thereby the calculated ion-activity product of uric acid reached the highest level. Because morning urine pH often is in the range of 5.0 to 5.5 it is evident that a large number of urines might be highly supersaturated with respect to uric acid. Several patients might obviously be at risk of producing urine with a uric acid ion-activity product above the level of metastability (Fig. 4).

The physico-chemical properties of urine have been considered to favour the formation of a sodium urate crystal phase [20, 22] before a phase of uric acid. Although this statement doubtless is true for most urines as far as the whole 24 h samples are considered, it is not necessarily valid for isolated urine fractions. In contrast the results in this study demonstrate the risk of forming a uric acid crystal phase. It has not been clarified whether uric acid plays any role in calcium oxalate stone formation, but it has been proposed that uric acid might act as a nucleus for heterogenous calcium oxalate crystallization [5, 7, 8, 17, 19]. Whereas some groups thus claim that sodium urate is more potent than uric acid in inducing calcium oxalate crystallization [11, 20, 25] recent observations suggest the opposite [17].

The ion-activity product of sodium urate, although often above the solubility product, was in all analyzed samples shown to be far below the level of spontaneous crystal formation. Unless a phase transformation to monosodium urate [23] occurs in urine, the risk of forming sodium urate crystals might be rather low and certainly less than the risk of forming crystals of uric acid. This statement is further supported by the results in Fig. 6, where maximally recorded urate and pH values were used for calculation of the sodium urate ion-activity product. This clearly exceeded the level of solubility but the distance to the formation product level was considerable.

The urine in this study was collected in one-hour fractions only between 6.00 to 23.00 h, whereas all the nighttime urine was analyzed in one fraction. Of course, it would be of interest to obtain information on the excretion patterns even during night hours, but the procedure of urine collection during the night is unphysiological.

In previous studies on urine biochemistry in stone formers larger urine volumes than in normal subjects were observed [31]. This is probably a result of universal recommendations to stone formers of the value of an increased urine flow in prevention of recurrences. The process of urine collection probably further increases the fluid intake despite intructions to follow normal drinking habits. This is certainly the explanation for the fact that urine volumes in some patients were larger than anticipated. This might lead to an underestimation of urate concentrations. Consequently the patients will be at an even higher risk of forming uric acid crystals in the morning under normal situations. The ion-activity products normally found in urine might thus be slightly higher than those reported in this study. But the conclusions drawn above are valid even in view of a lower urine volume as shown in Fig. 6.

In the absence of hyperuricosuria and with a reasonably normal urine flow the urine might be supersaturated with respect to sodium urate, but the risk of exceeding the formation product is apparently low. This is in contrast to uric acid supersaturation which will be high even at a relatively high urine flow and without significant hyperuricosuria. Occasionally this supersaturation might result in risk for spontaneous crystallization of uric acid.

Whereas the period required for uric acid to induce calcium oxalate crystallization according to some authors might be long [11, 20, 25] the start of stone formation could be explained by the fixed particle growth on aggregated uric acid crystals plugging the collecting tubule as suggested by Coe [7]. Uric acid crystals might also act by adsorbing urinary inhibitors of crystallization and thereby increase the risk of crystallization [9, 13, 24, 32, 33].

If future research confirms that uric acid is of importance for calcium oxalate stone formation, efforts aimed at reducing morning urate concentration and increasing the pH-level might be rewarding. This is of particular interest because the peak of uric acid supersaturation appears to coincide with a peak of calcium oxalate supersaturation (unpublished observation). However, further research concerning the urate-calcium oxalate connection is necessary.

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