Urol Res (1990) 18:13–16

Urological Research

Effects of different doses of alkaline citrate on urine composition and crystallization of calcium oxalate

C. Berg[1], L. Larsson[2], and H.-G. Tiselius[1]

Departments of [1]Urology and [2]Clinical Chemistry, University Hospital, Linköping, Sweden

Accepted: May 10, 1989

Summary. Prophylactic treatment with alkaline citrate in patients with recurrent calcium oxalate (CaOx) stone disease results in reduced CaOx supersaturation and increased urinary citrate. The effects of a single evening dose were compared with those of two and three daily doses in six recurrent CaOx stone formers with hypercalciuria, hypocitraturia or raised calcium/citrate quotients. While on a standardized hospital diet the patients were given 7.5 g (28 mmol) of sodium potassium citrate (URALYT-U) in one, two, and three doses. Fractional urine collections during 24 hours were analyzed for pH, composition, and crystallization risk (CR). All dosage regimens had favourable effects on urinary calcium, citrate, calcium/citrate quotients, and CaOx-CR. The most sustained effect was recorded with three divided doses. Single evening doses resulted in the most pronounced effects between 22.00–06.00 h, thereby counteracting the increased risk of CaOx crystallization during that period. In terms of 24 h urine composition the best effect was recorded with alkaline citrate administered three times daily, but because of the favourable response by a single evening dose between 22.00–06.00 h the assumption was made that this dosage regimen might be sufficient to reduce the risk of CaOx crystallization and stone formation. However, the validity of such an assumption can only be established by long-term clinical studies.

Key words: Alkali – Calcium oxalate – Calcium phosphate – Citrate – Crystallization – Kidney calculi – pH – Urine – Urolithiasis

Recurrent calcium oxalate (CaOx) stone formation often is the result of increased excretion of urinary calcium and oxalate, decreased excretion of urinary citrate and an abnormal urinary pH. Correction of these abnormalities will reduce the risk of forming CaOx crystals and thereby hopefully prevent CaOx stone formation. Medical treatment for this purpose must continue for a considerable period of time, necessitating a drug without disturbing side effects and possible to administer in a convenient way [18].

According to several recent reports alkaline citrate has appeared to be useful in CaOx stone prevention [6, 7, 12, 16, 17]. There are several possible explanations for such an effect inasmuch as alkaline citrate can raise urinary pH and reduce the CaOx crystallization risk (CaOx-CR) [3], increase urinary citrate and thereby complex calcium, inhibit growth of CaOx as well as of calcium phosphate (CaP) crystals [4, 5, 26] and inhibit CaOx crystal agglomeration [13]. In addition alkaline citrate is easy to administer and apparently free from significant side effects [17]. This treatment thereby satisfies many of the requirements of an ideal therapy for prevention of CaOx stone formation.

There is no information available on the most appropriate dosage regimen of alkaline citrate, although most authors have given three daily doses [6, 7, 12, 16]. In a previous study [1] analysis of urine composition suggested a risk period for CaOx precipitation during late night and morning hours. This tempted us to administer alkaline citrate in a single evening dose to a group of patients with recurrent CaOx stone disease.

The aim of the present study was to get information on the effects on urine composition and risk of CaOx and CaP crystallization with different dosage regimens of alkaline citrate.

Material and methods

Six patients, 4 men (40, 52, 56 and 57 years of age) and 2 women (54 and 56 years of age) with recurrent CaOx stone disease but without stone prophylactic treatment were included in the study. They had hypercalciuria, hypocitraturia, or a high calcium/citrate quotient as measured in a 24 h urine collection. Four patients had previously been operated on because of their stone disease and four had residual stones. All patients had normal serum levels of calcium, phosphate, urate, magnesium, sodium, potassium, chloride, bicarbonate, and creatinine. They also had negative urine cultures. During the evaluation period ordinary drinking habits were recommended together with the standardized hospital diet which had a daily energy content of 6.7 MJ. This diet contained in average 78 g of protein, 50 g of fat, 196 g of carbohydrate, 35 mmol of calcium, and 1 mmol of oxalate.

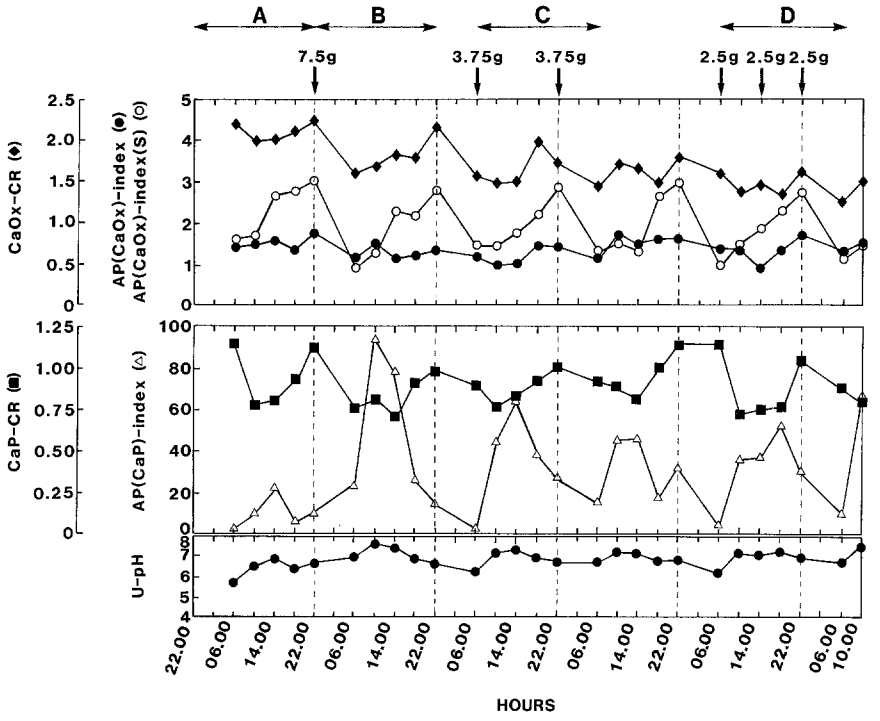

Fig. 1. Variations in median CaOx-CR (♦), CaP-CR (■), AP(CaOx)-index (●), AP(CaOx)-index(s) (○), and AP(CaP)-index (△) during intake of sodium potassium citrate as indicated by arrows. The median of each variable during the particular collection period is indicated at the end of the period. A, B C, and D indicate periods without treatment, and with one, two, and three daily doses of alkaline citrate respectively

A total dose of 7.5 g (28 mmol) of sodium potassium citrate (URALYT-U, Madaus GmbH & Co) was given in one (regimen B), two (regimen C), and three (regimen D) divided doses on days 2 (22.00 h), 4 (06.00 h, 22.00 h), and 6 (06.00 h, 14.00 h, 22.00 h) respectively. A 24 h pre-treatment period constituted regimen A. Urine was collected in four 4-hour portions between 06.00–22.00 h, and one 8-hour portion between 22.00–06.00 h, starting at 22.00 h on day 1 and completing the collection at 10.00 h on day 7. In each sample pH was measured immediately in the fresh urine, after which the sample was acidified and kept frozen until analyzed for its content of calcium [28], oxalate [14], citrate [10], magnesium [11], phosphate [15], and creatinine [9]. By means of the total 4 h and 8 h excretions of calcium (Ca), oxalate (Ox), magnesium (Mg), citrate (Cit), and phosphate (P) expressed in mmol and the urine volume (V) expressed in litres the following calculations were made:

AP(CaOx)-index [21]:
$k_1 * Ca^{0.71} * Ox * Mg^{-0.14} * Cit^{-0.10} * V^{-1.2}$

AP(CaOx)-index(s) [25]:
$k_1 * Ca^{0.71} * Ox * Mg^{-0.14} * Cit^{-0.10} * 0{,}25^{-1.2}$

AP(CaP)-index [22]:
$k_2 * 10^{-3} * Ca^{1.07} * P^{0.70} * (pH\text{-}4.5)^{6.8} * Cit^{-0.20} * V^{-1.31}$

In these expressions the values of the factors k_1 and k_2 were 6.17 and 4.30 respectively for 4 h urine samples. The value of the standardized volume in AP(CaOx)-index(s) was 1.5 litres for a 24 h sample and consequently 250 ml for a 4 h sample.

The risk of crystallization was measured as CaOx-CR [23] at pH 5.8 and as CaP-CR [24] starting from a pH of 5.8 in aliquots containing 90 per cent of urine.

Statistical evaluation was performed by means of Wilcoxon's rank sum test on paired samples.

Results

As evident from Fig. 1 administration of alkaline citrate resulted in a lower CaOx-CR with all dosage regimens, and the most sustained effect was recorded with regimen D. As a result of the increased pH levels during administration of alkaline citrate. AP(CaP)-index was markedly increased. The highest AP(CaP)-index peaks were recorded with regimen B. There were no negative effects on the risk of CaP crystallization in terms of CaP-CR as determined from a starting pH of 5.8, neither were there any significant changes in AP(CaOx)-index. In contrast, peaks of AP(CaOx)-index(s) were recorded around 22.00 h, irrespective of therapeutic regimen.

As evident from Fig. 2 the most pronounced reduction of the calcium/citrate quotients was observed with regimen D during the period 22.00–06.00 h ($P<0.05$). This was the result of a reduced calcium and an increased citrate ($P<0.05$) excretion. Between 06.00 and 10.00 h the citrate excretion was increased by all three regimens, although most efficiently by regimens C ($P<0.05$) and D ($P<0.05$). The calcium/citrate quotients during this period were also favourably affected by all three regimens ($P<0.05$). The excretion of calcium between 06.00 and 10.00 h most efficiently was reduced by regimens B and D and with a similar tendency recorded also for regimen C, but a statistically significant difference was not obtained for any of these regimens. It is noteworthy that regimen B increased urinary citrate during the whole period 22.00 h to 14.00 h, and that this effect decreased later during the day.

During the whole 24 h period (Fig. 3) alkaline citrate administered according to regimen D had the most pronounced effects by decreasing urinary calcium ($P<0.05$), increasing urinary citrate ($P<0.05$), and thereby reducing the calcium/citrate quotient ($P<0.05$). However, citrate excretion as well as the calcium/citrate quotient were favourably affected also by regimens B ($P<0.05$) and C ($P<0.05$).

As regards 24 h urinary magnesium, oxalate, and phosphate as well as the urine volumes there were no significant differences between the different dosage regimens.

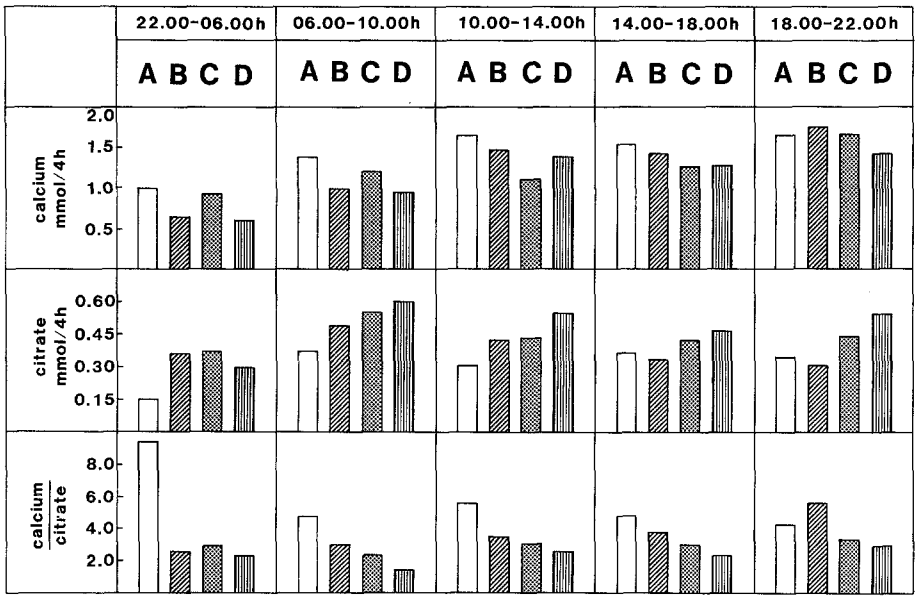

Fig. 2. Median urinary excretion of calcium and citrate, and calcium/citrate quotients per 4 h during periods without (A) and with administration of alkaline citrate in one (B), two (C), and three (D) daily doses

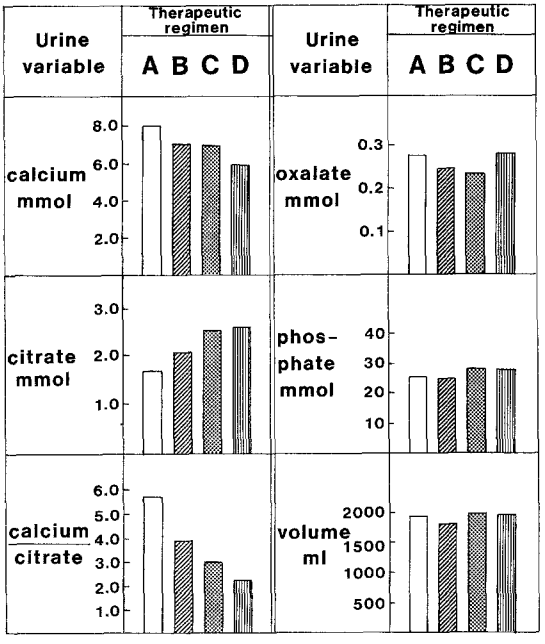

Fig. 3. Median 24 h urinary calcium, oxalate, citrate, phosphate, calcium/citrate quotient, and urine volume during periods without (A) and with administration of alkaline citrate in one (B), two (C), and three (D) daily doses

Discussion

Most authors who have reported on the beneficial effect of alkaline citrate in CaOx stone prevention have administered the drug in three daily doses [6, 7, 12, 16]. Because of earlier observations of increased CaOx supersaturation during late night and morning hours [1] and the lowest diurnal urinary pH during this period [27] we found it logical to give alkaline citrate as a single evening dose. Furthermore, single dose administration undoubtedly is a most practical form of therapy and intake in the evening probably will be associated with a good patient's compliance. This is of utmost importance in stone prophylactic treatment because such treatment must continue for a considerable period of time, certainly in many cases for the rest of life.

Alkaline citrate in the form of URALYT-U is a granulate that needs to be dissolved in a glass of water before ingestion. This extra load of water in the evening associated with all dosage regimens should be beneficial in terms of CaOx supersaturation, but in this study no increase in urine volumes during the night was observed. This probably can be explained by already good drinking habits as a result of earlier information to these recurrent stone formers. This also might be the reason why no increment in CaOx supersaturation, calculated as AP-(CaOx)-index, was recorded, in contrast to the raised AP(CaOx)-index(s) calculated for a standardized volume of 250 ml per 4 h.

The CaOx-CR determined at pH 5.8 was reduced by all dosage regimens with the most sustained effect recorded with three divided doses (regimen D). In addition, alkalinization of urine has been shown to result in reduced CaOx-CR values for a pH above 5.8 [3] and inasmuch as higher pH levels were found during this treatment with alkaline citrate, the real risk of CaOx crystallization might be even lower. However, at pH above 5.8 there is an increased formation of CaP crystals [2, 3] and as could be expected the treatment with alkaline citrate resulted in AP(CaP)-index peaks at increased pH levels. The highest AP(CaP)-index peaks were observed with single dose administration (regimen B), but the clinical importance of this is difficult to establish. The higher citrate concentration did not counteract the pronounced effects of pH on CaP-supersaturation. Neither was CaP-CR as measured in a urine with an initial pH of 5.8 reduced. However, according to some previous observations CaP crystals initially appear to be small [3], at least in the presence of physiological concentrations of citrate [4]. Previous clinical studies with alkaline citrate [8, 12, 17] have not disclosed an increased risk of CaP stone formation,

but long-term studies in carefully evaluated patients are necessary before such a risk can be completely disregarded.

The effects on CaOx-CR, urinary calcium, citrate, and calcium/citrate quotients during the risk period 22.00–06.00 h were similar for treatment with a single dose in the evening as for treatment with two or three daily doses. Furthermore the single evening dose was the only dosage regimen that raised urinary pH during this period. Therefore these results give support to the usefulness of a one dosage regimen in CaOx stone prophylactic treatment.

One interesting observation when the pre-treatment day number 2 was compared with the treatment-free day number 5, was a reduced calcium excretion, an increased citrate excretion and consequently a decreased calcium/citrate quotient during the latter period. This to some extent could be due to the short period of adaptation to the standardized diet in the beginning, but most probably to a residual effect from the preceding days of citrate administration. The elimination of such possible sources of errors would require a longer period of adaptation on standardized diet and longer wash-out periods between periods with different dosage regimens. However, it was not possible for our patients to follow such a programme. For a most appropriate risk evaluation the study also should have been performed with the patients in their usual environment maintaining ordinary dietary and drinking habits. The need for immediate pH measurement, and preparation of each urine sample made such an outpatient evaluation impossible.

In conclusion, a total daily dose of 7.5 g of sodium potassium citrate, administered in one, two and three divided doses, had a beneficial effect on urine composition and CaOx-CR. In view of 24 h urine composition it should best be administered three times daily. Because of favourable effects on urine composition and CaOx-CR between 22.00 and 06.00 h by a single evening dose, such a regimen might be sufficient to prevent CaOx crystal formation and hopefully arrest CaOx stone formation. However, such effects can only be concluded from long-term clinical experience.

Acknowledgement. This study was supported by generous grants from Södermanlands läns landsting and Dr. Madaus GmbH & Co. The technical assistance by Mrs. Anne-Marie Fornander and Mrs. Mari-Anne Nilsson is highly appreciated.

References

1. Ahlstrand C, Larsson L, Tiselius HG (1984) Variations in urine composition during the day in patients with calcium oxalate stone disease. J Urol 131:77
2. Ahlstrand C, Tiselius HG, Larsson L (1984) Studies on crystalluria in calcium oxalate stone formers. Urol Res 12:103
3. Berg C, Tiselius HG (1986) The effect of pH on the risk of calcium oxalate crystallization in urine. Eur Urol 12:59
4. Berg C, Tiselius HG (1989) The effects of citrate on hydroxyapatite induced calcium oxalate crystallization and on the formation of calcium phosphate crystals. Urol Res 17:167
5. Bisaz S, Felix R, Neuman WF, Fleisch H (1978) Quantitative determination of inhibitors of calcium phosphate crystal formation in whole urine. Miner Electrolyte Metab 1:74
6. Butz M (1986) First long-term results of oxalate stone prevention by alkaline citrate. Urol Res 14:95
7. Butz M (1986) Rational prevention of calcium urolithiasis. Urol Int 41:387
8. Butz M, Knispel HH, Dulce HJ (1988) Seven years experience with citrate therapy in recurrent oxalate stone formers. In: Martelli A, Buli P, Marchesini B (eds) Inhibitors of crystallization in renal lithiasis and their clinical application. Acta Medica, Bologna, p 159
9. Chasson AL, Grady HJ, Stanley MA (1961) Determination of creatinine by means of automatic chemical analysis. Am J Clin Pathol 35:83
10. Grunbaum BW, Pace N (1970) Determination of citric acid in microliter quantities of urine. Microchem J 15:673
11. Hansen JL, Freier EF (1967) The measurement of serum magnesium by atomic absorption spectrophotometry. Am J Med Technol 33:158
12. Hauser W, Kunit G, Frick J (1987) Long-term treatment with "Oxalyt C" in recurrent Ca-Ox stone formers. In: Martelli A, Buli P, Marchesini B (eds) Inhibitors of crystallization in renal lithiasis and their clinical application. Acta Medica, Bologna, p 291
13. Kok DJ, Papapoulos SE, Bijvoet OLM (1986) Excessive crystal agglomeration with low citrate excretion in recurrent stone formers. Lancet I:1056
14. Larsson L, Libert B, Asperud M (1982) Determination of urinary oxalate by reversed-phase ion-pair "high performance" liquid chromatography. Clin Chem 28:2272
15. Lawrence R (1974) Assay of serum inorganic phosphate without deproteinisation: automated and manual micromethods. Ann Clin Biochem 11:234
16. Pak CYC, Fuller C, Sakhaee K, Preminger GM, Britton F (1985) Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol 134:11
17. Pak CYC (1987) Citrate and renal calculi. Miner Electrolyte Metab 13:257
18. Thomas WC (1974) Medical aspects of renal calculous disease. Urol Clin North Am 1:261
19. Tiselius HG (1981) The effect of pH on the urinary inhibition of calcium oxalate crystal growth. Br J Urol 53:470
20. Tiselius HG (1981) Inhibition of calcium oxalate crystal growth in patients with urolithiasis. In: Smith LH, Robertson WG, Finlayson B (eds) Urolithiasis: clinical and basic research. Plenum Press, New York, p 623
21. Tiselius HG (1982) An improved method for the routine biochemical evaluation of patients with recurrent calcium oxalate stone disease. Clin Chim Acta 122:409
22. Tiselius HG (1984) A simplified estimate of the ion-activity product of calcium phosphate in urine. Eur Urol 10:191
23. Tiselius HG (1985) Measurement of the risk of calcium oxalate crystallization in urine. Urol Res 13:297
24. Tiselius HG (1987) Measurement of the risk of calcium phosphate crystallization in urine. Urol Res 15:79
25. Tiselius HG (1989) Standardized estimate of the ion activity product of calcium oxalate in urine from renal stone formers. Eur Urol 16:48
26. Tiselius HG, Fornander AM (1981) Evaluation of a routine method for determination of calcium oxalate crystal growth inhibition in diluted urine samples. Clin Chem 27:565
27. Tiselius HG, Larsson L (1983) Urinary excretion of urate in patients with calcium oxalate stone disease. Urol Res 11:279
28. Trudeau DL, Freier EF (1967) Determination of calcium in urine and serum by atomic absorption spectrophotometry. Clin Chem 13:101

Hans-Göran Tiselius, MD
Department of Urology
University Hospital
S-58185 Linköping
Sweden