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Effect of verapamil on urinary stone-forming risk factors

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Abstract Prevention of recurrent stone formation will only be possible with careful metabolic evaluation and appropriate management. In this present prospective study, a total of 95 patients with calcium oxalate (CaOx) stone disease were evaluated with respect to the effects of a calcium channel blocking agent (verapamil) therapy on stone-forming risk factors. A total of 95 patients with CaOx urolithiasis were well evaluated for the possible specific effects of verapamil administration on stone-forming risk factors during long-term follow-up. All patients had calcium-containing stones with normal renal morphology and function without any urinary tract infection. The follow-up period ranged from 12 to 36.6 months, with a mean value of 24.4 months. The age of the patients (54 male and 41 female; M/F: 1.31) ranged from 20 to 46 years (mean 34.3 years). On metabolic evaluation all patients had some kind of risk factors and patients were independently randomized into two groups, namely group 1 ($n = 49$): patients receiving calcium entry blocker, verapamil hydrochloride (isoptin 240 mg KKH tablets, oral t.i.d.); group 2 ($n = 46$): patients receiving no specific therapy (control patients) that were matched for sex and age. Follow-up results (at least 1 year) with respect to the changes in urinary stone-forming risk factors were recorded in both groups. During long-term follow-up patients undergoing no specific therapy did not show a significant change with respect to the urinary levels of stone-forming risk factors when compared with the others receiving verapamil on a regular basis. In the light of our results as well as the literature data, we believe that the pathophysiological mechanisms underlying the effect of verapamil on stone formation (as a result of enhanced crystal deposition) and on the excretion of the urinary stone-forming risk factors have to be well evaluated in further experimental as well as clinical studies. Although the exact mechanism of action is not clear; we may claim that the limitation of internal calcium shift by these agents may also well effect the tubular process related to oxalate handling which ultimately limits its excretion in urine.

Keywords Verapamil · Calcium oxalate urolithiasis · Risk factors

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Introduction

Prevention of recurrent stone formation in calcium stone formers is a difficult and sometimes controversial issue. Published clinical as well as research data have clearly pointed out that the progress gained in prevention was not as evident as that of stone removal. Although with the aid of minimally invasive procedures, the majority of the patients could be rendered stone free, a reasonable percentage of the untreated patients will show high recurrence rates owing to certain reasons. Keeping this fact in mind, it is clear that a subsequent appropriate medical therapy

will be beneficial, especially in high-risk patients, in an attempt to change the natural history of stone disease [1, 2].

In addition to deficient urinary excretion of crystallization inhibitors, another important factor causing stone formation is the increased excretion of stone-forming risk factors such as hyperoxaluria, hypercalcuria and hyperuricosuria [3]. Preventive measures aiming to limit the excretion of these risk factors have resulted in varying success rates, among which the effect of diet and various preventive agents were discussed in several publications [3, 4]. Although adequate fluid intake and a well-balanced diet are the mainstay of therapy and should be the first attempt to reduce the stone recurrence rate in the majority of cases, certain drugs have been used over the years to prevent the recurrence of calcium oxalate stones either by increasing the inhibitory potential of the urine or lowering the concentration of stone-forming risk factors [5]. Among these medications, a recently introduced effective agent, potassium citrate, and some other medications have been reported to have a modest degree of success and the results have been somewhat difficult to quantify due to the limited number of prospective, randomized, controlled medical trials [6–8].

Related to this subject, although the main target of an effective medical treatment protocol especially for calcium-containing stones is not to correct the urinary abnormalities but to reduce the stone recurrence, it would be logical and reasonable to apply selective treatment principles in order to correct urinary abnormalities, keeping in mind that there is no proof that a selective treatment is superior to a non-selective treatment.

Since their introduction more than 30 years ago, calcium antagonists have emerged as one of the most attractive and widely used classes of antihypertensive agent. In addition, recent investigations have focused on their possible protective effects on target organs, such as the heart and kidney, further enhancing their appeal. Although they differ in molecular structure, sites and modes of action and effects on various other cardiovascular functions, they effectively lower blood pressure mainly through vasodilatation and reduction of peripheral resistance. In this way, these agents can successfully increase in renal blood flow to maintain normal renal physiology [9, 12, 13]. Taking these specific protective effects on parenchymateous organs into account, studies dealing with the adverse effects of high energy shock waves (HESW) on renal tissue integrity have demonstrated well the protective effects of verapamil in terms of tissue alterations as well as crystal deposition and subsequent crystal formation or regrowth in traumatized tissue [14, 15]. In addition to these specific tissue-protective effects, these agents have also been found to decrease the urinary excretion of stone-forming risk factors such as oxalate [16–19].

In the light of some specific effects of these agents on stone-related events, the present study addresses the hypothesis that administration of calcium channel-blocking agents may limit the excretion of stone-forming risk factors.

Patients and methods

A total of 95 patients (54 male and 41 female, M/F: 1.31) with recurrent CaOx urolithiasis attack have been included in the study program and were well evaluated for the possible specific effects of verapamil administration on stone-forming risk factors during long-term follow-up. The initial study protocol was approved by the ethics committee of our hospital. Approval from the patients was obtained by written informed consent before performing any examination and/or treatment. All patients had calcium-containing stones located in the renal pelvis with normal renal morphology and function without any urinary tract infection. Patients were matched for age, stone size and location and the ones with anatomical abnormalities, previous stone surgery or urinary tract infection, renal tubular acidosis, renal functional abnormality, primary hyperoxaluria, hyperparathyroidism, etc.) were excluded from the study program. Patient characteristics are summarized in Table 1.

Patients included in the study program were on a free diet without any specific dietary or drinking advice. On metabolic evaluation the majority of the patients had some kind of risk factors and they were independently randomized into two different groups. Follow-up results (for at least 1 year) with respect to the changes in urinary stone-forming risk factors were recorded in both groups. Group 1 ($n = 49$) was composed of patients receiving calcium entry blocker verapamil hydrochloride (isoptin 240 mg. KKH tablets, oral t.i.d.). Although overall the follow-up period ranged from 12 to 36.6 months in both groups, with a mean value of 24.4 months, the mean duration of therapy with calcium antagonists was 10 months (6.4–18.2) in this group. Group 2 ($n = 46$) comprised patients receiving no specific therapy (control patients).

Following a detailed history and urological examination, plain film and sonography were performed to evaluate the characteristics of the stones and the urinary tract in stone-forming patients. Apart from urine

Table 1 Evaluation of patient characteristics along with the urinary risk factors in all groups

	n	Mean age	M/F	Mean stone size (mm)	Hypocitraturia (<320 mg/24 h)	Hyperoxaluria (>0.49 mmol/24 h)	Hypercalciuria (>4 mg/kg)	Hyperuricosuria (>1,000 mg/24 h)
Group 1	49	34.8 (20–46)	1.33	15.9 (11–25)	14 (28.5%)	21 (42.8%)	6 (12.2%)	3 (6.1%)
Group 2	46	33.8 (22–41)	1.30	16.1 (10–28)	14 (30.4%)	18 (39.1%)	5 (10.8%)	3 (6.5%)
Total	95	34.3 (20–46)	1.31	15.9 (10–28)	28 (29.4%)	39 (41%)	11 (11.5%)	6 (6.3%)

analysis and culture sensitivity tests, renal functional parameters (blood urea nitrogen and creatinine) and stone urinary risk factors were assessed in 24-h collected urine which were repeated at least two times (three 24-h urine specimens were collected in the majority of the patients—before, 6 and 12 months after medication—in specially prepared bottles provided by the laboratory). The analysis of the urine specimens included the assessment of the urinary risk factors, namely oxalate, calcium, uric acid and citrate. While urinary citrate was assessed by using the citrate lyase technique and urinary oxalate was determined with an enzymatic method using reagents, calcium and uric acid were assessed by previously described methods [10, 11].

The results obtained in each group were comparatively evaluated and the significance of the findings was tested using a Wilcoxon rank test.

Results

The age of the patients ranged from 20 to 46 years with an average value of 34.3 years. The follow-up period ranged from 12 to 36.6 months, with a mean value of 24.4 months. The mean age of the patients in each group with other patient characteristics and those of urinary risk factors are given in Table 1. Stone-forming patients had idiopathic calcium-containing stones located in the renal pelvis. Evaluation of our results demonstrated the following findings. There was no significant difference with respect to serum electrolytes (sodium, potassium, chloride), blood urea nitrogen, creatinine and the blood count in both groups. Likewise, evaluation of urinary pH did not demonstrate a significant difference, including the control group patients [mean urinary pH values in three groups were 6.4 (6.2–6.9), 6.6 (6.1–7.0), 6.7 (6.5–7.1), respectively]. Evaluation of the underlying causative risk factors in both groups did reveal that, while hyperoxaluria was detected as the primary risk factor (42.8 and 39.1%, respectively) in the majority of the patients, hypocitraturia was the second most common urinary risk factor (Table 1). Comparative evaluation of the patients after verapamil treatment with respect to the levels of urinary stone-forming risk factors showed that urinary oxalate excretion decreased significantly more than the other risk factors in patients receiving verapamil therapy when compared with the patients in the second group (Table 2). Thus verapamil therapy has been found to be significantly effective in decreasing the urinary oxalate levels when these patients were compared with the ones receiving no specific therapy ($P < 0.05$). Stone recurrence rate before and during the study period was calculated in both groups. At an average follow-up of 24.4 moths (12–36.6 months) the recurrence rate per patient-year decreased from 0.35 to 0.20 per patient-year in patients receiving the medication. These values were 0.33 and 0.29 for group 2 patients. Obtained data demonstrated a slight difference between two groups with respect to recurrence rates during the same period.

Hyperoxaluria was also a common urinary risk factor in the majority of the control patients when compared with patients in group 1. Although the excretion of oxalate was significantly limited in stone-bearing patients under verapamil therapy, this difference was not as significant as in the control patients (Table 2). Evaluation of the other risk factors demonstrated that although there was also a slight difference with respect to the excretion of calcium as well as citrate levels, this was not statistically significant. Again there was no significant difference with respect to the urine volume in the two groups (mean urine volume was 1,650

Table 2 Comparative evaluation of baseline urinary risk factors values within 12 months data in both groups

	Group 1		Group 2	
	Before therapy	After 12 months	Before therapy	After 12 months
Oxalate (mmol/24 h)	0.365 ± 0.10	0.324 ± 0.82*	0.407 ± 0.08	0.403 ± 0.10**
Citrate (mg/24 h)	432.12 ± 352.9	414.09 ± 336.4	365.24 ± 216.7	359.04 ± 211.9
Calcium (mg/kg)	241.4 ± 56.5	240.3 ± 55.9	268.8 ± 60.4	268.4 ± 59.8
Uric acid (mg/24 h)	336.8 ± 64.6	341.9 ± 66.2	296.8 ± 54.6	321.9 ± 63.2

* $P < 0.0001$

** $P = 0.085$

(1,200–2,150) in group 1 and 1,800 (1,350–2,400) ml in group 2). Although mean calcium excretion did decrease to some extent after treatment (Table 2), the medication had no effect on urinary uric acid levels.

Discussion

Recurrent urinary stone formation is a well-recognized clinical problem at least in a subset of stones and the significant expense along with patient morbidity associated with the disease necessitates an efficient medical prophylactic program. The aim should focus on urinary risk factors of stone formation and attempts to correct obvious abnormalities in order to reduce the risk of further stone formation. Dietary modification and drug therapies have long been advocated to reduce the likelihood of stone recurrence by altering the stone-forming risk factors in urine [2–4].

Concerning the preventive therapy, although some specific drugs have demonstrated reduced recurrence rates in calcium oxalate stone formers regardless of urinary biochemical background, medical therapy of stone prevention has been reported to have a modest degree of success where the results have been somewhat difficult to quantify due to certain factors [1, 2, 4]. Among these agents, as a pharmacological agent potassium citrate has been found to strongly inhibit calcium oxalate nucleation, aggregation as well as heterogenous nucleation with monosodium urate. In this way it has been used with acceptable success rates in recent years, especially in adults as well as in children [6–8].

Calcium antagonists (a heterogeneous group, which include three main classes, namely phenylalkylamines, benzothiazepines and dihydropyridines) have been found to be successful in limiting the ischemia-induced alterations in target organs such as the heart and kidney by lowering the blood pressure mainly through vasodilatation and reduction of peripheral resistance to increase renal blood flow for the maintenance of normal renal physiology [9–12, 20–23]. Related to this subject, studies dealing with the adverse effects of shock waves (SW) on renal tissue integrity have demonstrated well the reno-protective effects of verapamil in terms of tissue alterations as well as crystal deposition in traumatized tissue [15, 24]. We were able to demonstrate that, in addition to carefully controlled fluid intake, verapamil therapy has been found to be significantly effective in the medical prevention of stone recurrence as well stone regrowth after SWL [19]. This specific effect may be attributed to its regulatory role on blood distribution during possible transient ischemia induced by high energy shock waves and by taking its specific protective effects on renal morphology and function, and the close association of hypertension with stone-forming patients into account; verapamil has been found to be further effective in preserving renal integrity by lowering blood pressure, improving renal capacity and hemodynamics [13, 14].

In addition to specific renal tissue protection and its protective effects on crystal deposition, the effect of verapamil on urinary stone-forming risk factors, namely calcium and oxalate excretion, has also been evaluated. The calcium oxalate risk index of hypercalciuric and hyperoxaluric patients has been found to be significantly reduced after the administration of verapamil. In their original study Iguchi et al. focused on the effect of this agent on urinary calcium and oxalate excretion, and they were able to show that the calcium oxalate risk index of hypercalciuric and hyperoxaluric patients was significantly reduced after the administration of verapamil, which led them to conclude that verapamil is effective in reducing urinary oxalate excretion in hyperoxaluric patients [17]. Concerning the possible pathophysiological mechanisms underlying the effect of calcium antagonists on the excretion of the urine parameters, the authors stated that hypercalciuria may be the result of a reduced reabsorption of calcium in the tubulus, which could possibly be due to the lower calcium influx into the tubular cells [25–27]. However, hypo-oxaluric activity of calcium-antagonists may not be explained sufficiently by this effect and we believe that the renal tubular cell activity on calcium shift by verapamil may work well at the intestinal epithelial cell level, which could ultimately affect the uptake of oxalate at this level.

Our present study was performed to obtain further insight into the effects of verapamil on stone-forming risk factors in terms of urinary calcium, oxalate and citrate excretion. During an at least 1-year follow-up period, our results have clearly demonstrated that calcium antagonists may decrease the excretion of stone-forming risk factors in recurrent stone formers among which the excretion of oxalate has been significantly influenced by these agents.Taking the crucial role of hyperoxaluria in stone formation into account; our results indicated that calcium antagonists may have a preventive effect on new stone formation especially in recurrent stone formers. In addition to urinary oxalate levels, verapamil application did slightly affect the excretion of the other risk factors, although it was not statistically significant as it was for oxalate. The exact mechanism of action is not clear; depending on the literature data we may claim that the limitation of internal calcium shift by these agents may also well affect the tubular process related to oxalate handling which

ultimately limits its excretion in urine. However, hypooxaluric activity of calcium antagonists may not sufficiently be explained by this effect and taking the absorption process in the intestinal lumen (which is also a strong determinator of urinary oxalate levels) into account, we believe that the renal tubular cell activity on calcium shift by verapamil may work well at the intestinal epithelial cell level, which could ultimately affect the uptake of oxalate at this level.

However, we believe that the pathophysiological mechanisms underlying the effect of verapamil on stone formation (as a result of enhanced crystal deposition) as well as prevention (limitation of the excretion of urinary stone risk factors) have to be well evaluated in further experimental as well as clinical studies.

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