

# Use of drugs for nephrolithiasis

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## Summary

Renal stone disease often begins by renal colic. In order to manage this event adequately, several goals should be pursued: first, attenuate pain; second, favour progression and spontaneous expulsion of stones; third, prevent from obstructive and infectious complications. All of the aforementioned points pertain to medical management of this disease.

Concerning prevention, it is widely agreed that pathogenesis of kidney stones is a consequence of abnormalities in urine environment, leading to a disequilibrium between promoters and inhibitors of crystallization. Therefore, the rationale for therapy is to make urine less conductive to stone formation, by both decreasing state of saturation and increasing inhibitory potential.

In only some types of stone-forming salts it is possible to obtain undersaturation with the solid phase. Indeed, uric acid stones can be chemically dissolved by using alkali and allopurinol. To a lesser extent, this also applies to cystine stones, with the use of thiols and alkali. In these subsets, the aforementioned tools are also effective to prevent new stone formation.

Much more challenging appears the treatment of calcium containing stones. About 10% of such stones is caused by systemic disorders and, in these cases, the prevention of new stones is successfully accomplished by curing the underlying disease. For instance, parathyroidectomy cures calcium nephrolithiasis in case of hyperparathyroidism.

However, the majority of patients with calcium stones are idiopathic stone-formers, in whom metabolic abnormalities often occur, namely, hypercalciuria, hyperoxaluria, hypocitraturia. The correction of these abnormalities by using thiazide diuretics, alkaline citrates, potassium phosphate and bisphosphonates is based on the prevailing metabolic defect. Among the most recent available tools, *Oxalobacter Formigenes* and probiotics have been proposed to treat primary or secondary hyperoxalurias.

In general, the treatment of stone disease reduces its recurrence rate, but only seldom results in stable remission. Anyway, less stones mean reduction of the need for urological

procedures and the associated infective or obstructive complications.

Of course, medical prevention implies financial efforts, but a careful cost to benefit analysis demonstrates that these are well justified.

*KEY WORDS:* renal colic, nephrolithiasis, thiazides, alkali citrate, bisphosphonates, *oxalobacter formigenes*.

## Introduction

The very first manifestation of renal stone disease is often represented by renal colic. This event requires patients be managed adequately pursuing several goals: first, attenuate pain; second, favour progression and spontaneous expulsion of stones; third, prevent from obstructive and infectious complications.

Subsequently, after resolution of the acute episode, patients should be considered for prevention of new stones or, in particular cases, for dissolution of existing stones.

All of the aforementioned points pertain to medical management of this disease, and will be the object of the present review.

## Medical management of renal colic

### Pain relief

Patients with renal colic are more frequently seen in emergency units, where physicians are asked to attenuate flank pain which is often much troublesome. Therapeutic options in this respect include spasmolytic, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs). Efficacy of either drugs is mainly dependent on individual response, though NSAID such as ketorolac, alone or in association with morphine, have given better results to reduce pain (1). It is now agreed that fluid infusion should be limited to restore the fluids lost with sweating and vomiting, which often accompany renal colic, in order to both reduce hydronephrosis and avoid to untowardly increase flank pain. Conversely, anti-diuresis has been carried out using desmopressin spray, usually in combination with other analgesic drugs, to obtain pain relief with favourable results (2).

### Stone expulsion

Many papers have recently been published supporting the efficacy of medical expulsion therapy with alpha-adrenoceptor antagonists or calcium channel antagonists. Among the former, tamsulosin was shown to increase the rate of spontaneous stone passage by approximately 50% for small distal stones. In a randomized perspective study in patients with distal ureteral stones, tamsulosin gave an expulsion rate of 97.1% vs 77.1% of nifedipine ( $p < 0.0001$ ). These patients achieved stone passage in a shorter time and showed a significantly decreased number of hospitalizations and endoscopic procedures. Alone

or in association with NSAIDs, tamsulosin also appeared to decrease the severity of renal colic (3).

This issue was addressed in a recent review of papers reporting expulsion facilitation of moderately sized, distal, ureteral stones. Treatments with alpha-antagonists or calcium-channel blockers were compared to a standard therapy group in studies that reported stone expulsion rates. A pooled analysis of 16 studies using an alpha-antagonist and 9 studies using a calcium-channel blocker suggested that the addition of each of these agents, compared to standard therapy, significantly improved spontaneous stone expulsion (relative risk 1.59 vs 1.50 and number needed to treat 3.3 vs 3.9, for alpha-antagonists and calcium channel blockers, respectively). Subgroup analysis of trials using concomitant medications such as low-dose steroids yielded a similar improvement in stone expulsion rate. Adverse effects were only minor and rare. It was concluded that expulsive therapy, using either alpha-antagonists or calcium channel blockers increased the stone expulsion rate (4).

#### *Prevention of obstructive and infectious complications*

In a previous paper we reported that obstruction and infection, connected to invasive urological procedures, were the major causative factors of renal insufficiency in patients with recurrent stone disease (5). The occurrence of renal insufficiency has been likely abated with the use of modern non-invasive procedures, but attention should still be paid to the association between obstruction and infection, which represents a threat for the development of urosepsis. When a patient with renal colic is suspected to progress to this dangerous complication, he should urgently be referred to a urologist in order to remove the obstruction, either temporarily (ureteral stenting) or ultimately (ureteroscopic ESWL, ureterolitholapaxy). Any way, timely and aggressive antibiotic therapy, moderate hydration and close follow-up of patient's chemistries and imaging are mandatory.

#### **Medical management of the kidney stone disease**

Renal stones are thought to be caused by abnormalities in urine environment, namely, an imbalance between promoters and inhibitors of stone formation. This in turn depends on abnormalities of the most relevant urine constituents. Therefore, the medical management is aimed at normalizing these derangements, to reduce the risk of forming new stone. This is accomplished by either reducing urine state of saturation with respect to a given salt or increasing urine inhibitor activity, or both. A brief review of the current medical therapies of renal stone disease is reported below.

#### *Uric acid and cystine stones*

In only some types of stones it is possible to obtain undersaturation with the solid phase. Indeed, uric acid stones can be chemically dissolved by using alkali and allopurinol. To a lesser extent, this also applies to cystine stones, with the use of thiols and alkali. In these subsets the aforementioned tools are also effective to prevent new stone formation.

In a recent review of Guidelines of Renal Stones by the AURO (Associazione Urologi Ospedalieri), the medical treatment of uric acid and cystine stones was set as follows (6):

Uric acid stones:

- bring urine pH at  $> 6.0$  by using sodium bicarbonate (30-40 mg/kg body weight daily) or potassium citrate (1-2 mEq/kg b.w./day) or sodium citrate (same dosages);

- reduce urinary concentration of uric acid by diluting with high fluid intake, or with allopurinol (150 mg/day), only in hyperuricemic patients.

Cystine stones:

- maintain urine pH between 7.0 and 7.5, by using sodium bicarbonate, potassium or sodium citrate;
- reduce cystine concentration at  $< 1$  mmol/L (300 mg/L) by using any type of thiols, such as thiopronine (20 mg/kg/day) or D-penicillamine (12-15 mg/kg/day);
- the disappearance of spontaneous crystalluria can be taken as an index of efficacy of medical treatment (7).

In patients with good compliance to the above advice it is possible to obtain stable remission of the stone disease. Surprisingly, despite clear cut physicochemical evidence of the efficacy of medical therapy, for both types of stones there are no prospective evidence-based studies on this issue.

#### *Calcium nephrolithiasis*

Much more challenging appears the treatment of calcium containing stones. About 10% of such stones is caused by systemic disorders and, in these cases, the prevention of new stones is successfully accomplished by curing the underlying disease. For instance, parathyroidectomy cures or greatly improves calcium nephrolithiasis in the course of hyperparathyroidism (8).

However, in case of the so-called idiopathic calcium nephrolithiasis, remission of the disease is not a rule. In addition to problems arising from a poor patients' compliance to therapy, the fact that defined cause(s) of the disease is not straightforward explains the unsatisfying outcomes or failures in medical management.

To partly overcome these difficulties, many Centres adopt diagnostic protocols designed to ascertain metabolic abnormalities, which may guide the choice of prescribed therapy (9, 10). Table I lists the drugs currently used in patients with calcium nephrolithiasis, and the recognized rationale for their use.

Apart from the pathophysiological evidence suggesting beneficial effects to counteract the stone disease, whether drugs be actually effective to reduce recurrence rate is not definitely established. In fact, due to the nature of the disease, characterized by unpredictable periods of active disease and prolonged relapses, it is very difficult to obtain evidence based data on the effects of a given drug on the natural history of nephrolithiasis. Indeed, very few placebo-controlled randomized studies are so far available. An incomplete list of randomized trials, performed by using thiazide diuretics is given in Table II. It can be seen that the follow-up were relatively short, the number of patients enrolled low, the baseline stone recurrence not much high. Anyway, quite all the quoted studies reported significant reduction of the severity of stone disease, but complete remissions were obtained only in a part of the patients, with a significant advantage with treatment in some but not all studies (11). The same applies to trials which used alkali citrate (Table II).

A more recent meta-analysis on trials concerning the efficacy of alkali citrate to prevent calcium oxalate nephrolithiasis considered 43 papers, written in English or German, and enrolling up to 1000 patients. Overall, citrate reduced recurrence rate by 47% to 100%; in 4 randomized studies conducted on 227 patients, 53.5% vs 35% remained stone-free over 1 year, with citrate and placebo, respectively (12). Of interest was also the finding the alkali citrate favoured dissolution or clearances of residual fragments after ESWL (66% vs 27.5%,  $p < 0.0001$ ). However, if not for other reasons, validation to the use of alka-

Table I - Drugs currently used for the prevention of calcium nephrolithiasis and their rationale.

Drug	Indications	Actions
Thiazide diuretics	Hypercalciuria	Decrease in urine calcium Improved bone turnover Slight decrease of urine citrate
Alkali citrate salts	Hypocitraturia Acidic urine pH	Increase in urine citrate Increase in urine pH Mild decrease in urine calcium
Allopurinol	Hyperuricosuria	Decrease in urate excretion
Bisphosphonates	Dietary independent hypercalciuria associated with high bone turnover	Decrease fasting calciuria Less marked decrease in 24-hr calciuria
Potassium phosphate	Phosphate leak hypercalciuria	Increase serum phosphate Increase urine phosphate Possible increase in urine pyrophosphate
<i>Oxalobacter Formigenes</i> and other probiotics	Primary or enteric hyperoxaluria	Decrease oxalate excretion

Table II - Randomized trials on the efficacy of thiazide diuretics on the prevention of calcium stone disease.

Author	Follow-up	Nr. of patients		Stone/pt/year		% Remissions		P
		Therapy	Placebo	Therapy	Placebo	Therapy	Placebo	
Ohkawa, 1992	2	82	93	0.13	0.31	86.5	55.9	<0.05
Brocks, 1981	4	33	29	0.09	0.11	84.8	82.8	n.s.
Scholz, 1982	1	25	26	0.2	0.2	76	76.9	n.s.
Ettinger, 1988	4	23	31	0.05	0.22	87	54.8	<0.05
Lerum Larsen, 1984	3	23	25	0.07	0.18	78.3	52.0	0.05
Wilson, 1984	3	23	21	0.15	0.31	–	–	0.05
Robertson, 1985	3	13	9	0.22	0.58	–	–	sign
Borghini, 1993	3	19	21	0.06	0.28	84.2	57.1	<0.05

Table III - Randomized trials on the efficacy of alkali citrate for the prevention of calcium oxalate nephrolithiasis.

Author	Follow-up	Nr. of patients		Stone/pt/year		% Remissions		P
		Therapy	Placebo	Therapy	Placebo	Therapy	Placebo	
Barcelo, 1993	3	18	20	0.1	1.1	72.2	20.0	<0.05
Hofbauer, 1994	3	16	22	0.9	0.7	31.3	27.3	n.s.
Ettinger, 1997	3	16	25	–	–	87.1	36.4	RR=0.16

line citrate salts comes from findings supporting favourable effects on bone mineralization (13).

Quite recently, the presence of *Oxalobacter Formigenes* was shown to be associated with a 70% reduction of the risk of being a calcium stone former (14). The mechanism of these anaerobic bacteria is to promote oxalate catabolism in the intestine, thereby preventing intestinal absorption and urinary excretion. This is likely to apply to patients in which nephrolithiasis is associated with inflammatory bowel disease and cystic fibrosis. The hypothesis that patients with idiopathic stone disease have an increased oxalate excretion due to a decreased intestinal colonization by these bacteria deserves further investigations.

## Conclusions

Medical management of patients with urolithiasis is crucially important for their outcome. The principal goals of medical efforts are manifold as listed below:

1. relief pain during renal colic;
2. favour spontaneous expulsion of ureteral stones;
3. prevent formation or growth of renal stones;
4. reduce the need of urologic procedures;
5. reduce the occurrence of complicating events, such as infection and/or obstruction;

6. prevent renal tissue injury;
7. avoid onset and progression of renal insufficiency.

That therapy may significantly improve the natural course of stone disease has been definitely stated for some but not all the aforementioned issues. The nature of this disease, especially the idiopathic calcium nephrolithiasis, requires that related studies be designed so as to enrol a large number of patients to be treated over a long term follow-up.

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