Reviews in Endourology

Medical Therapy of Urolithiasis

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ABSTRACT

Nephrolithiasis treatment has become easier and less invasive with the development of extracorporeal shock-wave lithotripsy (SWL) and endourologic techniques. However, medical therapy represents a well-established and complementary approach that can improve the efficacy of SWL and endourology. During recent decades, pharmacologic intervention has become more effective in stone disease: drugs can control the pain of renal colic, interfere at various levels in lithogenesis, and contribute to the expulsion of stones. It is well known that lithogenesis is a multifactorial process influenced by environmental-nutritional factors (low urinary volume, diet rich in animal protein, etc) and metabolic alterations; i.e., hypercalciuria, hyperuricosuria, and deficiency of stone-inhibiting factors (citrate, magnesium, glycosaminoglycans [GAGs]). Specific drugs such as citrate, allopurinol, and thiazide represent highly effective treatments for the promoting factors. Furthermore, recent findings suggest an interesting role for a phytotherapeutic agent, *Phillantus niruri*, and its inhibitory action on calcium oxalate crystallization related to the higher incorporation of GAGs into the calculi. Another step forward in medical management of stone disease is expulsive therapy. Many studies have proven the efficacy of medical expulsive therapy with nifedipine and alpha-blockers: their specific action on ureteral smooth muscle in association with anti-edema drugs accounts for their efficacy in expelling ureteral stones. In this paper, we provide an update on the medical treatment of stone disease, focusing our attention on what is known and what is new in renal colic and litholithic and expulsive medical therapy.

INTRODUCTION

UROLITHIASIS represents a common and important problem in daily urologic practice, affecting 5% to 10% of the population of Europe and North America. During the last two decades, the management of this disease has changed radically: the advent of SWL and endourologic approaches; i.e., ureterorenoscopy (URS), percutaneous nephrolithotripsy (PCNL), and laparoscopy has made open surgery for urinary stones nearly obsolete. On the other hand, medical therapy has had an evolving role in stone treatment; it can represent a valid and complementary support for SWL and endourology owing to its effectiveness against the lithogenesis processes, induction of active expulsion of stones, and relief of renal colic.

Before considering specific drug treatments, the first step in the prevention of urolithiasis is conservative treatment. It is advisable to maintain a high fluid intake—at least 2 L of water per day—along with specific dietary measures, such as reduced animal protein and salt, normal intake of calcium, oxalate restriction, and increased citrus fruit intake.

One aspect of medical treatment is the management of acute renal colic, a condition that demands rapid and effective analgesia. Currently, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the best agents for acute renal colic, overshadowing other drugs such as antimuscarinics (i.e., hyoscine butylbromide) (Table 1). In addition to controlling the pain associated with obstructing calculi, drug therapy promotes the expulsion of stones. Expulsive treatment is an evolving aspect of medical therapy involving drugs that directly influence the contractile activity of the ureter. Calcium-channel blockers such nifedipine have an effective antispastic ureteral action without influencing the slower peristaltic activity, while alpha-1 blockers relax

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ureteral smooth muscle through alpha-1 receptors in the distal ureteral segment. These two classes of drugs, in association with corticosteroids (antiedema agents), are associated with a beneficial effect on ureteral stone passage with few side effects.7

Urine volume, solute concentration, and the presence of stone inhibitors (citrate, magnesium, glycosaminoglycans [GAGs], etc.) influence crystal formation.8 These factors can be modified, thereby interfering with the lithogenic process, comprising so called “litholytic therapy.” There are different classes of agents that inhibit crystal growth, promote stone dissolution, and also prevent stone recurrence. The use of litholytic therapy is especially supported by the use of alkali citrate for calcium and uric acid stones, which represent as many as 80% of all of urinary calculi9; furthermore, recent findings suggest new and evolving aspects in the inhibition of crystal growth related to specific pharmacologic actions such as enhanced incorporation of GAGs into calculi.10 In this paper, we review the principal pharmacologic approaches to nephrolithiasis, along with the mechanisms of actions, focusing on the modern treatment of acute renal colic and what is known and what is new about litholytic and expulsive therapy.

MEDICAL THERAPY FOR RENAL COLIC

Renoureteral colic is severe and debilitating pain associated with obstructing calculi, affecting 2% to 5% of the population.11 Typically, it consists of flank pain radiating to the ipsilateral groin that is associated with nausea, vomiting, hematuria, and irritative urinary symptoms if the stone is in the distal ureter. Renal colic occurs with migration of a stone along the ureter, causing smooth-muscle spasm, partial or complete obstruction of urinary flow, and subsequent urinary-tract distention.12 The higher intrarenal pressure promotes local synthesis and release of prostaglandins with subsequent vasodilatation; the latter promotes diuresis and a further rise in renal-pelvic pressure. In addition, ureteral smooth-muscle spasm is directly stimulated by prostaglandins.13

Observation with analgesia represents the initial approach to this acute pathological condition.14 However, in case of persistent ureteral obstruction or pain, other noninvasive or minimally invasive interventions are preferred (ureteral stenting, PCNL, SWL, URS).15 High fluid intake or use of diuretics represent cost-effective measures that potentially stimulate stone passage by increasing the hydrostatic pressure along the urinary tract. However, administration of intravenous fluids is advisable only at maintenance volumes in order to replace fluid loss from vomiting or reduced oral intake; high-volume fluid therapy or the use of diuretics during acute renoureteral colic is not recommended because of the risk of fornical rupture or renal impairment. Further studies are required to assess the role of fluid in promoting more rapid stone expulsion.16

The two principal classes of drugs used for analgesia in renal colic are NSAIDs and opioids. The NSAIDs have a direct action on the underlying cause of the pain by inhibiting prostaglandin synthesis and subsequently reducing vasodilation, intrarenal pressure, and urinary-tract inflammation. Side effects include gastrointestinal bleeding and renal impairment, particularly in the face of existing renal disease. Compared with NSAIDs, patients receiving morphine obtain better pain relief at 10 minutes; on the other hand, after 20 to 30 minutes, there is no significant difference between these two pharmacologic classes.17 Some studies have demonstrated an advantage of NSAIDs over opioids for the treatment of renal colic in reducing pain scores and decreasing the need for further analgesia in a short time.4 A variety of NSAIDs are available: intravenous

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Comment</th>
</tr>
</thead>
</table>
| NSAIDs (i.e., diclofenac, ketorolac) | Direct action on cause of pain by inhibiting prostaglandins synthesis | • Gastrointestinal bleeding  
• Renal impairment  
• Nausea  
• Vomiting  
• Constipation  
• Urinary retention  
• Respiratory depression  
• Hypotension  | First-choice analgesic               |
| Opioids (i.e., meperidine, tramadol) | Do not affect physiopathology of colic | • Constipation  
• Urinary retention  
• Accommodation disorders | Second-choice analgesic          |
| Antimuscarinic agents (i.e., hyoscine butylbromide) | Controversial: ureteral smooth-muscle relaxation? | • Risk of urinary tract rupture or renal impairment | Secondary and controversial role |
| High water intake and/or diuretics | Hypothetical stimulation of stone passage | • Hypertension  
• Headache  
• Asthenia | Not recommended               |
| Calcium-channel blockers and/or alpha-1 blockers | Relaxation of ureteral smooth muscle | • Hypotension  
• Headache  
• Asthenia | Alternative drugs with promising results |

*Fewer side effects.*
or intramuscular preparations of diclofenac or ketorolac are often used in clinical practice, although more studies are needed to demonstrate whether a specific NSAID has better analgesic effect or side effect profile. These drugs act more quickly if they are administered intravenously.\textsuperscript{18}

Opioids such as morphine and meperidine (pethidine) do not alter the physiopathology of renal colic, yet they are often used by the parenteral route as a second-choice analgesic.\textsuperscript{5,19} Adverse events include nausea, vomiting (especially with meperidine), constipation, urinary retention, and respiratory depression or hypotension with higher doses.\textsuperscript{4} In this class of drugs, fewer side effects are seen with tramadol, although it is less effective for severe acute pain.\textsuperscript{5,20}

Antimuscarinic agents such hyoscine butylbromide may play a theoretical role in the medical treatment of colic because of their action in relaxing ureteral smooth muscle. However, in an in-vitro ureteral model, Tomiak and colleagues\textsuperscript{21} demonstrated no contractions when the ureter was exposed to a muscarinic agonist, so these agents may be of limited benefit. Furthermore, a recent randomized trial\textsuperscript{6} showed no advantage to the addition of hyoscine butylbromide to NSAIDs and opioids for the management of renal colic.

Finally, medical treatment with NSAIDs, opioids, or both represents the preferred approach to renal colic. Nevertheless, because of the side effects associated with these agents, the development of alternative drugs for the treatment of renal colic is encouraged. A number of clinical trials have shown that calcium-channel blockers, particularly nifedipine, and alpha-1 blockers, owing to their relaxing action on ureteral smooth muscle, improve both analgesia and stone-passage rates.\textsuperscript{22–24}

### EXPULSIVE MEDICAL THERAPY

Spontaneous passage of urinary stones <5 mm in diameter may occur in as many as 98% of patients, although the stone may take 40 days or more to pass.\textsuperscript{14} Several mathematical models have been developed that predict the likelihood of spontaneous stone passage with high accuracy.\textsuperscript{25–27} However, prolonged partial obstruction (>6 weeks), the persistence of pain, or the suggestion of urinary infection mandate active intervention; i.e., ureteral stenting, percutaneous nephrostomy, SWL, or URS.\textsuperscript{15,28} Medical expulsive therapy has been recommended to promote stone passage and reduce the need for SWL or minimally invasive surgery. There are several classes of drugs with different mechanisms of action that promote expulsion of stones (Table 2). A few studies suggest the use of corticosteroids such as hydroxyprogesterone, along with NSAIDs to improve stone passage. The former can promote ureteral relaxation and dilation, and the latter can stimulate stone expulsion by reducing inflammation and edema, relaxing pelviureteral-wall smooth muscle and reducing intrapelvic pressure.\textsuperscript{29–32} However, the utility of these classes of drugs remains uncertain in expulsive stone therapy, and more studies are necessary to validate their effectiveness.\textsuperscript{7}

Calcium-channel blockers such nifedipine represent a valid and well-established pharmacologic treatment for urolithiasis.

### Table 2. Summary of Clinical Trials of Drugs Promoting Stone Expulsion

<table>
<thead>
<tr>
<th>Series</th>
<th>Therapy</th>
<th>No. patients</th>
<th>Mean stone size (mm)</th>
<th>Stone location</th>
<th>Stone passage rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikkelsen et al (1988)\textsuperscript{30}</td>
<td>IM hydroxyprogesterone (no control)</td>
<td>24</td>
<td>Not reported</td>
<td>Any</td>
<td>59</td>
</tr>
<tr>
<td>Ahmad et al (1991)\textsuperscript{31}</td>
<td>Diclofenac sodium (no control)</td>
<td>80</td>
<td>$\leq 5.0$</td>
<td>Any</td>
<td>57.5</td>
</tr>
<tr>
<td>Laerum et al (1995)\textsuperscript{32}</td>
<td>Diclofenac sodium v placebo</td>
<td>41</td>
<td>Not reported</td>
<td>Any</td>
<td>68 v 74</td>
</tr>
<tr>
<td>Borghi et al (1994)\textsuperscript{33}</td>
<td>Nifedipine + methylprednisolone v placebo + methylprednisolone</td>
<td>43 each</td>
<td>6.7 v 6.8</td>
<td>Any</td>
<td>87 v 65</td>
</tr>
<tr>
<td>Porpiglia et al (2000)\textsuperscript{34}</td>
<td>Nifedipine + deflazacort v watchful waiting</td>
<td>48 each</td>
<td>5.8 v $\leq 5.5$</td>
<td>Distal</td>
<td>79 v 35</td>
</tr>
<tr>
<td>Saita et al (2004)\textsuperscript{35}</td>
<td>Nifedipine + prednisolone v prednisolone</td>
<td>25 each</td>
<td>12.0 v 12.8</td>
<td>Any</td>
<td>81 v 68</td>
</tr>
<tr>
<td>Cervenakov et al (2002)\textsuperscript{36}</td>
<td>Tamsulosin v control</td>
<td>51 each</td>
<td>$&lt;10.0$</td>
<td>Distal</td>
<td>80 v 63</td>
</tr>
<tr>
<td>Dellabella et al (2003)\textsuperscript{37}</td>
<td>Tamsulosin + deflazacort v fluroglucone-trimetossibenzene + deflazacort</td>
<td>30 each</td>
<td>6.7 v 5.8</td>
<td>Distal</td>
<td>100 v 70</td>
</tr>
<tr>
<td>Porpiglia et al (2004)\textsuperscript{38}</td>
<td>Tamsulosin + deflazacort v nifedipine + deflazacort v control</td>
<td>28 v 30 v 28</td>
<td>4.7 v 5.4 v 5.4</td>
<td>Distal</td>
<td>85 v 80 v 43</td>
</tr>
<tr>
<td>Dellabella et al (2005)\textsuperscript{39}</td>
<td>Tamsulosin + deflazacort v nifedipine + deflazacort v control</td>
<td>70 each</td>
<td>7.2 v 6.2 v 6.2</td>
<td>Distal</td>
<td>97 v 77 v 64</td>
</tr>
<tr>
<td>Yilmaz et al (2005)\textsuperscript{40}</td>
<td>Tamsulosin + deflazacort v terazosin v doxazosin v control</td>
<td>28 v 28 v 29</td>
<td>6.0 v 6.0 v 5.9</td>
<td>Distal</td>
<td>79 v 79 v 76 v 74</td>
</tr>
<tr>
<td>Porpiglia et al (2006)\textsuperscript{41}</td>
<td>Tamsulosin v deflazacort v tamsulosin + deflazacort v control</td>
<td>33 v 24 v 33</td>
<td>6.0 v 5.8 v 5.9</td>
<td>Distal</td>
<td>60 v 37.5 v 85 v 33</td>
</tr>
</tbody>
</table>
owing to their spasmolytic action on the ureter. In both animal and human ureters, nifedipine eliminates the fast uncoordinated component of ureteral smooth-muscle contraction, leaving unmodified the slower peristaltic activity. Indeed, several authors have demonstrated enhanced stone passage in patients treated with nifedipine (30 mg/day slow release for 20–30 days) plus steroid as an antiedema agent (25 mg/day of methylprednisolone or 30 mg/day of deflazacort for 10 days). A higher stone-expulsion rate, shorter expulsion time, and reduced need for analgesia with an associated good tolerability and safety has been shown in several trials. Caution must be used when administering nifedipine to patients with cardiovascular disease because of the risk of serious side effects such as hypotension or palpitations. Minor side effects reported with nifedipine include headache and asthenia.

The presence of alpha- and beta-adrenergic receptors has been demonstrated in human ureters. Alpha-1 receptors, particularly subtype alpha-1d, are present in high density in the lower ureteral segment and may play an important role in lower-ureteral physiology through an effect on detrusor and ureteral smooth-muscle contraction. On the basis of these findings, the use of alpha-1 blockers for accelerating the expulsion of lower-ureteral stones was tested. Several investigators have shown the utility of alpha-1 blockers and their spasmolytic action in the active expulsion of stones from the distal ureter (juxtavesical or intramural tract) with a low incidence of side effects such as hypotension and asthenia. In two recent randomized controlled trials comparing tamsulosin and nifedipine combined with corticosteroids with placebo for lower-ureteral stones, a higher stone-expulsion rate and a reduced need for analgesia was demonstrated for both the drugs compared with placebo. However, tamsulosin (0.4 mg/day for 4 weeks) was associated with a shorter time to stone expulsion and less need for hospitalization.

In expulsive therapy, an important factor is edema of ureteral wall caused by stone irritation. It represents a cause of arrest of stone passage with consequent obstruction. Corticosteroids, especially deflazacort, are frequently used as an antiedema agent in association with calcium-channel blockers and alpha-blockers in order to promote stone expulsion. In general, corticosteroids are well tolerated if used for short periods of time.

Clinical trials have also supported expulsive medical therapy with calcium-channel blockers or alpha-1 blockers associated with steroids as adjunctive therapy after SWL of ureteral stones. An improvement in the success rate of a single SWL treatment and reduction in the need for secondary procedures, retreatment, and analgesia have been shown in clinical trials.

**LITHOLITHIC MEDICAL THERAPY**

Urinary stone formation is a complex and multifactorial process that is not completely understood in its pathophysiology and genetic basis. Nevertheless, there are three factors known to play a fundamental role in this disease: supersaturation of urinary solutes, the presence and concentration of urinary inhibitors of stone crystallization, and the presence of renal morphology that increases the residence time of urine in the kidney, thereby promoting crystal growth. A pharmacologic litholytic treatment can influence the first two factors, producing a beneficial effect in preventing stone formation (Fig. 1).

A common and well-established treatment for the prevention of calcium and uric acid stones is alkaline citrate therapy. For uric acid stones, the use of potassium citrate (30 to 60 mEq per day) promotes urinary alkalization to achieve pH values of 6 to 6.5 with a consequent dissolution of excreted uric acid and reduction of urinary uric-acid supersaturation. Oral alkalization also can be achieved by sodium bicarbonate (650 mg three times daily), a well-tolerated and inexpensive drug, but one that provides a sodium load, which is a disadvantage for patients with cardiovascular disease. The increased urinary sodium also stimulates excretion of calcium with a subsequent promotion of calcium-oxalate stone formation. Potassium citrate is considered first-line treatment for uric acid stone dissolution, with a reported success rate of nearly 80%, but it also has importance in the treatment of calcium and cystine stones. Urinary alkalization to achieve a pH between 6.5 to 7.5 with potassium citrate inhibits cystine stones formation by increasing the solubility of cystine.

For calcium stones, urinary citrate is an important inhibitor factor that forms a complex with calcium and slows stone formation. Hypocitraturia is a common condition, found in as many as 20% of stone formers, and it can be corrected by oral administration of potassium citrate or potassium magnesium citrate, as shown in randomized trials. Hypothetically, the addition of magnesium, which also is an inhibitor of calcium stones, might be more effective in calcium stone disease, but a direct comparison of potassium magnesium citrate with potassium citrate has not been reported. An increase in urinary citrate may be achieved by consuming citrus fruits or juices such as lemonade or orange juice and can be helpful especially in patients who cannot tolerate potassium citrate supplements. For uric acid stone formers, alkaline citrate therapy is often used con-

*See also article by Sarica et al in this issue.*
comitantly with allopurinol, a xanthine oxidase inhibitor, in order to correct hyperuricosuria, another important risk factor for uric acid and calcium urolithiasis. At a dosage of 100 to 300 mg per day, minor side effects are rare; they include skin rash, gastrointestinal irritation, and an allergic hypersensitivity characterized by hemorrhagic skin lesions and Stevens-Johnson syndrome preceded by pruritus. Dietary intervention in the form of a low-purine diet is advisable for the treatment of hyperuricosuria and may preclude the need for allopurinol.

An important metabolic factor that can be modified by medical therapy in calcium stone disease is hypercalciuria, which affects about 50% of patients with stones and may be corrected by thiazide diuretics. These drugs reduce hypercalciuria by augmenting tubular reabsorption of calcium in the nephron and decreasing intestinal calcium absorption. Many trials have confirmed the utility of these agents in treating calcium stones associated with hypercalciuria. However, long-term treatment with thiazides can lead to hypokalemia and hypochloridria; as such, it is advisable to add potassium citrate or potassium magnesium citrate in order to avert these side effects.

Other limitations to the long-term use of these diuretics include side effects such as hypotension, asthenia, and impotence.

In addition to the well-established treatments described above, new concepts are emerging in litholytic therapy, including the use if phytotherapy agents. The role of aqueous extract of Phyllantus niruri has recently been explored for the prevention and treatment of calcium oxalate urolithiasis. Phyllantus niruri is a plant used in Brazilian folk medicine for the treatment of urinary stones. Several investigators have demonstrated a beneficial effect on stone disease and the absence of toxicity of this drug.

Treatment with P. niruri was shown to have an inhibitory effect on calcium oxalate crystal growth as a result of incorporation of a greater amount of specific stone inhibitors (GAGs) into the calculi that causes them to become softer and smaller. With these properties, P. niruri appears to represent a nontoxic and low-cost alternative for the prevention and treatment of calcium oxalate stone disease. Micali and associates showed in a randomized trial that a regular intake of P. niruri is associated with a higher stone-free rate, a lower retreatment rate, and faster stone clearance, particularly for calculi in a lower calix. Furthermore, those investigators showed that treatment with P. niruri reduced the relative risk of SWL failure by 10.3% overall and by 33% for stones located in an inferior calix. Although the evidence is encouraging, the mechanism of action of P. niruri is not totally understood, and further study is necessary to validate these preliminary findings.

CONCLUSIONS

Medical therapy plays a fundamental role in the acute and chronic treatment of urolithiasis, as well as in the prevention of stone recurrence. Excluding complications related to stone disease such as severe hydronephrosis, renal insufficiency, intractable pain, or infection that mandate a more aggressive approach (ureteral stent, nephrostomy, URS, SWL), drug therapy is useful in the management of urolithiasis and represents an important adjunct to conservative therapy. With regard to cost, observation represents the most cost-effective approach to ureteral calculi, but it remains unsatisfactory for recurrent stone formers, in whom the high rate of recurrence precludes a conservative approach. For ureteral calculi, conservative therapy remains cost-effective if it is followed by stone expulsion; on the other hand, failure of this approach can produce higher costs than an invasive procedure such as URS when taking into account loss of work days and frequent physician visits. Therefore, the use of litholytic and expulsive therapy may be cost-effective, particularly for recurrent stone formers.

Medical therapy may also be of benefit as an adjunct to SWL. Several studies demonstrated an adjuvant role in stone clearance after SWL for potassium citrate, nifedipine, and tamsulosin in association with corticosteroids. Potassium citrate reduces aggregation of residual fragments and facilitates their discharge after SWL. Likewise, nifedipine and tamsulosin, in association with corticosteroids, influence ureteral smooth-muscle contractility and promote expulsion of stone fragments, thereby increasing the success rate of a single SWL session and reducing the need for analgesics drugs after the treatment.

In recent studies, tamsulosin has shown promise as an adjunct to SWL of renal stones and in the treatment of Steinstrasse after SWL. However, further studies are necessary to corroborate these findings and to understand the action of tamsulosin in promoting the passage of fragments from the kidney.

For acute renal colic, emergency SWL may be a valuable option, increasing the stone-free rate after 48 hours, especially for patients with proximal-ureteral stones. Further evaluation is needed to confirm the cost-effectiveness of emergency SWL and its role in addition to standard medical treatment in renal colic.

In summary, medical therapy for stone disease represents an important adjunct, not only to conservative therapy, but also to minimally invasive stone therapies such as SWL and for stone prevention. Its development at different levels as an expulsive, litholytic, and pain relief therapy offers better outcomes to patients affected by urinary stones. Future studies are likely to provide additional confirmation of the specifics of treatment in order to develop detailed guidelines for medical therapy for stone disease.

REFERENCES


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**ABBREVIATIONS USED**

GAGs = glycosaminoglycans; PCNL = percutaneous nephrolithotripsy; SWL = extracorporeal shockwave lithotripsy; URS = ureteroscopy.