Medical Expulsive Therapy

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Summary: Minimally invasive therapies for urolithiasis including extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrostolithotomy are highly efficacious, yet expensive. Medical expulsive therapy offers a cost-effective, nonsurgical approach for appropriate patients with ureteral stones. The use of hormones, nonsteroidal anti-inflammatories, calcium channel blockers, corticosteroids, and adrenergic alpha antagonists all have been proposed as a way to enhance stone passage. In view of the available clinical trials and meta-analysis, patients with distal ureteral stones measuring 1 cm who are candidates for observation deserve a trial of medical expulsive therapy. Nifedipine, a calcium channel blocker, and adrenergic alpha antagonists have been proven to be clinically efficacious, safe, and well tolerated as medical expulsive agents.
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The lifetime risk of urinary stone disease in the United States is 13%. In addition, 50% of these stone formers then will go on to have recurrence of renal colic within 5 years of their first episode.[1] The consequences of urinary stone disease are not only health related but economic as well. Total societal costs arising from urinary stone diagnosis, treatment, pain management, and lost wages total more than $2 billion annually.[2]

Many urinary stone patients can be managed conservatively. In the absence of infection, severe obstruction, and severe colic, a trial of conservative therapy is warranted because the majority of stones will pass spontaneously. Studies have shown spontaneous passage rates of 71% to 98% for small (<5 mm) distal ureteral stones,[3,4] with stone size and location being the two most important predictors of stone passage.[5] Alternatively, minimally invasive therapies such as extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrostolithotomy have emerged, altering surgical treatment dramatically for urolithiasis. Although efficacious, these techniques are not without morbidity and are quite costly.[3,6]

In light of these data, researchers recently have sought out pharmacologic means of increasing rates of stone passage and reducing both surgical intervention and financial costs. The use of hormones, nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, corticosteroids, and adrenergic alpha antagonists all have been proposed as a way to enhance stone passage. In this article, we discuss the agents available, review the clinical data, and present clinical recommendations.

HORMONES

Progesterone

Numerous laboratory, as well as clinical studies have shown that sex hormones have a dilatory effect on the urinary tract, suggesting a possible therapeutic role for hormones in facilitating stone passage. Progesterone has been one of the most studied hormones in this category. Progesterone has been proven to play an influential role in the renal pelvis and ureteral dilation seen in normal pregnancy. van Wagenen et al,[7] using rhesus monkeys, was the first to prove this effect by showing sustained or increased dilation of the ureter after removal of the fetus and thereby elimination of the mechanical obstruction while the placenta was left

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in situ.[7] Progesterone is believed to cause dilation of the ureter by acting on the beta adrenergic receptors.[8] It also has been shown to decrease the muscular activity of the ureter.[9] Finally, several investigators[10,11] have reported reversible hydronephrosis and ureteral dilation in women taking oral contraceptives.

Based on these findings, progesterone was studied as early as 1980 as a treatment option to facilitate the discharge of ureteral stones. In this early study, intramuscular injection of 250 mg of hydroxyprogesterone resulted in passage of ureteral stones within 24 hours in 2 patients.[12] Mikkelsen et al[13] further studied this drug in a nonrandomized study of 24 patients with ureteral calculi. All patients were given an intramuscular injection of 250 mg of hydroxyprogesterone and followed up until stone passage or surgical intervention. In all, 14 of 24 patients (59%) were able to pass their stone spontaneously, which is much higher than the previously reported rates for spontaneous stone discharge (18%-39%). No side effects of hydroxyprogesterone were observed in any patient. The investigators concluded that hydroxyprogesterone treatment is simple, inexpensive, and without side effects.[13]

Glucagon

Glucagon is a well-described smooth-muscle relaxant of the gastrointestinal system. The actions of glucagon on the urinary tract are not as well defined. In vitro and in vivo canine studies have shown that glucagon causes brief cessation of ureteral peristalsis.[14] In vivo animal and human studies have indicated that glucagon causes an increase in renal water and electrolyte excretion without significant change in the glomerular filtration rate.[15] Lowman et al[16] first published a preliminary report in 1977 describing 10 patients with ureteral calculi who were given 1 mg of intravenous glucagon. Three patients had spontaneous passage of their stone in 4 to 8 hours, however, no follow-up studies were ever published. Morishima and Ghaed[17] described a similar scenario with 5 patients given 1 mg of intravenous glucagon at the time of their intravenous pyelogram. Four patients spontaneously passed their stone within 2 hours and the fifth patient passed their stone within 8 hours. No side effects of the medication were reported. At this point in time, although glucagon has proven effects to the urinary tract, expulsive therapy for urolithiasis remains largely untested.

NSAIDS

Prostaglandins impede ureteral stone passage through several interrelated mechanisms. Prostaglandins are generated from arachidonic acid via cyclooxygenase (COX) activity. The 2 isoforms of COX are COX-1 and COX-2. These have been established and popularized by recent pathway-specific medications. In general, COX-1 is expressed constitutively whereas COX-2 is highly inducible by inflammatory and mechanical stimuli. Blockade of prostanoid synthesis via COX inhibition is the target of NSAIDs. Studies of ureteral contractility have shown that prostaglandin F2 alpha and prostaglandin E2 increase contractility in obstructive ureters and that indomethacin (a nonspecific inhibitor of COX) can inhibit generation of these contractions.[18–20] Besides alteration in contractility, NSAIDS also treat renal colic by blocking the local release of pain-mediating prostaglandins.[21]

Indomethacin

Al-Waili[22] first conducted an open study investigating the effect of indomethacin suppositories on both acute urinary colic and expulsion rates of stones resistant to conventional analgesics and antispasmodics. Patients were divided into 2 treatment groups based on the acuteness of their presentation. Of the 55 patients in the first group with resistant urinary colic and acute obstruction, 15 patients (27%) passed their stones (<10 mm) within 1 month of treatment. Of the 30 patients in the second group with subacute obstruction, 21 patients (70%) passed their stone within 1 month of treatment. No side effects were recorded and the investigators concluded that indomethacin suppositories have a beneficial effect on acute urinary colic and expulsion of urinary calculi.

Diclofenac Sodium

Diclofenac sodium has been studied in 2 clinical trials to date. The first, performed by Ahmad

et al,[23] described 80 patients with ureteral stones as large as 5 mm. All patients were given tablets of 100 mg of diclofenac sodium twice daily for 2 weeks, with follow-up evaluations at 2 and 4 weeks. Forty-six patients (57.5%) passed their stone over a period of 4 weeks, which is slightly higher than previous reports of spontaneous stone passage for similar size. In 17 of 30 patients (57%) with proximal ureteral stones who retained their stones despite treatment, the stones moved from the upper and middle ureter to the lower ureter. Complete pain relief was observed in 67 patients (84%), and no side effects were noted in any of the patients.

More recently, in a placebo-controlled, randomized clinical trial, 80 patients with acute unilateral urinary colic were randomized to receive either 50 mg of diclofenac sodium or matching placebo tablets 3 times a day for 7 days. After a 3-week observation period, no statistically significant difference in stone passage rate was detected in the 2 groups regardless of stone size. In addition, the mean time to stone expulsion was nearly identical. No intergroup differences were reported in side effects, which were minor and primarily gastrointestinal. The investigators concluded that although diclofenac sodium was successful in reducing the number and severity of new colic episodes and hospital readmission, it did not affect the stone passage rate.[24]

Although COX inhibitors have efficacy in urinary colic, studies examining their use in medical expulsion therapy have been limited and inconclusive. Future studies will elucidate further whether prostaglandin inhibitors can promote the passage of ureteral stones.

CALCIUM CHANNEL BLOCKERS

The primary anatomic unit of the ureter is the smooth-muscle cell, which functions in response to changes in calcium ion concentration. An increase in calcium concentration causes contraction. Conversely, a decrease in calcium concentration results in relaxation. Ureteral stones induce ureteral spasm, and this is thought to arrest stone passage.[25] Blocking calcium action on cells has been proposed to decrease ureteral contractions and subsequently decrease the pain of ureteral colic. Studies in both animal and human ureters have shown that nifedipine inhibits the quick phasic contractions of the ureter without affecting tonic activity.[26] For this reason, calcium channel blockers have been successful in treating a variety of medical conditions including hypertension, cerebral vasospasm, coronary vasospasm, and esophageal spasm.

Nifedipine

Six studies evaluating nifedipine as medical expulsive therapy have been reported to date (Table 1). Borghi et al[25] conducted the first randomized, double-blind, controlled trial using nifedipine. Eighty-six patients with a unilateral ureteral stone no larger than 15 mm were randomized to receive 16 mg of methylprednisolone plus either 40 mg of nifedipine or placebo daily (maximum, 45 d). Steroids have known anti-inflammatory effects, and have

Table 1. Nifedipine Trials

Study	Year	Country of Origin	Treatment Group (No. Passing Stone)	Control Group (No. Passing Stone)	Stone Size Studied	Statistical Significance Between Groups
Nifedipine + steroids vs steroids						
Borghi et al[25]	1994	Italy	87% (34/39)	65% (24/37)	<15 mm	Yes
Saita et al[28]	2004	Italy	80% (20/25)	68% (17/25)	<15 mm	Not performed
Dellabella et al[37]	2005	Italy	77% (54/70)	64% (45/70)	>4 mm	No
Nifedipine + steroids vs control						
Cooper et al[27]	2000	United States	86% (31/35)	54% (19/35)	2–6 mm	Not performed
Porpiglia et al[26]	2000	Italy	79% (38/48)	35% (17/48)	<10 mm	Yes
Porpiglia et al[33]	2006	Italy	80% (24/30)	43% (12/28)	<10 mm	Yes

been included in the majority of clinical trials for medical expulsion therapy. A statistically significant difference between the nifedipine and control groups was observed with regards to stone passage rate and the mean interval to stone passage. The nifedipine group had an 87% success rate and a mean interval of 11.2 days to passage, whereas the placebo group had a 65% success rate and a mean interval of 16.4 days to passage. For both treatment groups, side effects were minimal and affected only a few patients. Renal function was preserved in all patients. The investigators concluded that the combination of methylprednisolone and nifedipine is effective in improving spontaneous stone passage. Caution must be used in patients with comorbidities such as angina, carotid insufficiency, compromised myocardial contractility, or increased serum creatinine level. Moreover, prescribing physicians must consider steroid-associated complications. Generally, short courses of steroids are well tolerated in most patients.

Porpiglia et al[26] similarly showed that calcium channel blockers in combination with steroids increase the rate of stone passage. Ninety-six patients with distal ureteral stones were randomized into 2 equal groups. The first group received oral treatment with 30 mg of deflazacort daily (maximum, 10 d) plus 30 mg of slow-release nifedipine daily (maximum, 4 wk), whereas the control group received no medication. Deflazacort, a corticosteroid, has shown good efficacy with few side effects when used as an antiedemic agent. Porpiglia et al[26] found a statistically significant higher stone expulsion rate (79% vs 35%) and a decreased expulsion time (7 vs 20 d) in the treatment group. Minor side effects were reported in 10 of 48 treatment group patients (headache or asthenia). The investigators concluded that medical treatment with nifedipine and deflazacort was both safe and effective, as evidenced by increased stone expulsion rate, decreased expulsion time, and lessened need for analgesic therapy.

Cooper et al[27] confirmed these results in the United States by randomizing 70 consecutive patients to a control arm consisting of ketorolac, oxycodone, acetaminophen, and prochlorperazine and to a treatment arm consisting of these same medications and nifedipine, prednisone, and trimethoprim/sulfa combination tablets. The treatment arm showed higher stone passage rates (86% vs 56%) and fewer lost work days, emergency room visits, and surgical interventions. Both arms showed similar potential drug side effects.

Additional supporting evidence for nifedipine as a stone-expulsive agent comes from a study by Saita et al.[28] In this randomized trial, 50 patients were divided into 2 groups. The first group consisted of 25 patients who received prednisolone 25 mg a day (maximum, 10 d) and slow-release nifedipine 30 mg a day (maximum, 20 d). The second group consisted of 25 patients who received 25 mg/d of prednisolone. All patients had distal ureteral stones no larger than 15 mm. Spontaneous passage rates were 81% for the nifedipine group and 68% for the control group. Side effects in both groups were nearly equivalent. Six patients suspended therapy in the nifedipine group (erythema or stomach ache) and 7 patients suspended therapy in the control group (pain or stomach ache). No statistical analysis was performed in this study. Their conclusions were congruent to the first 2 studies.

ADRENERGIC ALPHA ANTAGONISTS

Studies have shown that both alpha and beta adrenergic receptors are located in the human ureter, although the alpha receptors predominate.[29] These alpha receptors are subclassified further into alpha 1 and alpha 2 receptors. In turn, alpha 1 receptors are classified further into subtypes based on their differential selectivity: alpha 1a (proximal urethra, prostate, and bladder outlet), alpha 1b (vessel smooth muscle), and alpha 1d (detrusor and lower ureter).[30] Alpha 1 receptors are believed to play an important role in lower ureteral physiology. Higher densities of alpha 1 receptors have been discovered in the lower ureters of animals and human beings.[31] Norepinephrine is the primary alpha agonist and exerts both a positive chronotropic effect of the ureter by increasing peristaltic frequency, and a positive inotropic effect by increasing muscle tone, stimulating obstruction. Of the known alpha 1 receptor subtypes, alpha 1d receptors have the most pronounced

effect on detrusor contraction and spasm of the lower ureter, particularly the intramural portion.[30] These receptors appear to be ideal targets for pharmacotherapy because they represent the greatest impediment to stone passage.

Alpha receptor antagonists have long been used to treat symptoms of benign prostatic hypertrophy and prostatitis. Their mechanism is via smooth-muscle relaxation of the prostate and bladder neck via inhibition of alpha 1a receptors, resulting in increased urinary flow. Tamulosin is uroselective for the alpha 1a and alpha 1d receptors, resulting in an overall lower side-effect profile compared with the nonselective agents. In the ureter, alpha 1 adrenergic receptor antagonists inhibit basal tone and also decrease peristaltic frequency and amplitude. Consequently, intraureteral pressure decreases and fluid transport increases. Given its receptor specificity and in vitro findings, it seems plausible that tamulosin would be useful in the treatment of obstructive ureteral calculi.

Tamulosin

Several clinical trials have shown that alpha 1 blockers not only are useful for stone expulsion, but for control of stone colic as well (Table 2). In 1999, Ukhal et al[32] was the first to report that alpha 1 blockers were effective in stone expulsion. These reports were confirmed by Cervenakov et al[30] in 2002 in a randomized, double-blinded study composed of 104 patients with stones less than 10 mm in the distal ureter. One group was randomized to receive the standard treatment (tramadol 50 mg and diazepam 5 mg) and the other group received the standard treatment supplemented with tamulosin 0.4 mg/d (maximum, 8-day course). The tamulosin group had a greater stone clearance rate (80% vs 63%). Furthermore, most stones in the tamulosin group were passed within the first 3 days of treatment and patients in this group also were less likely to experience recurrence of renal colic. The investigators concluded that tamulosin is effective in eliminating distal ureteral stones.[30]

Dellabella et al[29] subsequently evaluated the efficacy of tamulosin with corticosteroids as medical expulsive therapy. He enrolled 60 patients with distal ureteral stones and randomized them to receive standard treatment (floroglucine-trimetosiibenze, deflazacort, and cotrimoxazole) or standard treatment plus tamulosin 0.4 mg/d. Floroglucine-trimetosiibenze is an oral antispasmolytic. Tamulosin again proved to be beneficial with a statistically significant higher stone expulsion rate (100% vs 70%) with a shorter stone expulsion time (2.7 vs 4.6 d). No drug side effects were reported and hospital stays were reduced dramatically in the tamulosin group.[29]

In a groundbreaking study, Porpiglia et al[33] sought out to determine if the treatment success of tamulosin and corticosteroids was a result of a single drug or an association of the two. One hundred fourteen patients with distal ureteral stones greater than 5 mm were enrolled

Table 2. Tamulosin Trials

Study	Year	Country of Origin	Treatment Group (% Passing Stone)	Control Group (% Passing Stone)	Stone Size Studied	Statistical Significance Between Groups
Tamulosin vs control						
Porpiglia et al[33]	2006	Italy	60% (20/33)	33% (8/24)	>5 mm	No
Tamulosin + steroids vs control						
Porpiglia et al[36]	2004	Italy	86% (24/28)	43% (12/28)	<10 mm	Yes
Porpiglia et al[33]	2006	Italy	85% (28/33)	38% (9/24)	>5 mm	Yes
Tamulosin + steroids vs steroids						
Dellabella et al[29]	2003	Italy	100% (30/30)	70% (21/30)	No criteria	Yes
Dellabella et al[37]	2005	Italy	97% (68/70)	64% (45/70)	>4 mm	Yes
Tamulosin + diazepam vs diazepam						
Cervenakov et al[30]	2002	Bratislava	80% (41/51)	63% (32/51)	<10 mm	Not performed
Tamulosin + diclofenac vs diclofenac						
De Sio et al[34]	2006	Italy	90% (45/50)	59% (27/46)	<10 mm	Yes

Table 3. Tamulosin Versus Nifedipine Trials

Author	Year	Country of Origin	Tamulosin Group (% Passing Stone)	Nifedipine Group (% Passing Stone)	Stone Size Studied	Statistical Significance Between Groups
Porpiglia et al[36]	2004	Italy	85% (24/28)	80% (24/30)	<10 mm	No
Dellabella et al[37]	2005	Italy	97% (68/70)	77% (54/70)	>4 mm	Yes

into 4 groups. The first group received tamulosin 0.4 mg/d, the second group received deflazacort 30 mg/d, the third group received both medications, and the fourth group received only analgesics. Treatment duration was 10 days to limit the side effects of prolonged corticosteroid therapy. The rates of expulsion for the 4 groups were 60%, 38%, 85%, and 33%, respectively. There was a statistical difference between the combined tamulosin and deflazacort group and the other groups. Only 2 cases of drug side effects were reported with no drop-outs. The investigators concluded that the use of corticosteroids is efficient only when administered together with alpha 1 blockers (tamulosin). In addition, tamulosin used on its own as a medical expulsive therapy can be considered as an alternative treatment for those patients who are not suitable for steroid therapy.

De Sio et al,[34] in turn, studied the efficacy of tamulosin with a nonsteroidal anti-inflammatory. In a series of 96 patients with distal ureteral stones, 46 patients were randomized to receive diclofenac 100 mg/d plus aescin 80 mg/d. Fifty patients received the same treatment plus tamulosin 0.4 mg/d (maximum, 2 wk). Aescin, a saponin derived from the horse chestnut tree, inhibits edema formation by decreasing vascular fragility. The tamulosin group achieved statistically significantly higher rates of stone passage (90% vs 58.7%) over a shorter time period (4.4 vs 7.5 d). Lower analgesic use and fewer hospitalizations also were found in the tamulosin group without increased side effects.

Tamulosin Versus Nonselective Adrenergic Alpha Antagonists

In a comparative trial of nonselective versus selective alpha 1 adrenergic blockers, Yilmaz et al[35] enrolled 114 patients with distal ureteral stones. Patients were randomized into 4 groups. The first group acted as the control group, the second group received tamulosin 0.4 mg/d, the third group received terazosin 5 mg/d, and the fourth group received doxazosin 4 mg/d. These agents were given for up to 1 month and patients were encouraged to hydrate. The expulsion rate was highest in the tamulosin group (79%), followed by the terazosin group (79%), the doxazosin group (76%), and, finally, the control group (54%). In all treatment groups the number of pain episodes, expulsion time, and analgesic dose were found to be lower compared with those in the control group. The investigators concluded that all 3 agents tested were equally efficacious as medical expulsive treatment.

Tamulosin Versus Nifedipine

Porpiglia et al[36] was the first to conduct a randomized trial comparing the effectiveness of tamulosin versus nifedipine, both proven agents for medical expulsive therapy (Table 3). Eighty-six patients with stones less than 10 mm in the distal ureter were divided randomly into 3 groups. Groups 1 and 2 both received 30 mg/d of deflazacort (maximum, 28 d). Group 3 received no medication and served as controls. In addition, group 1 received 30 mg/d of nifedipine and group 2 received 0.4 mg/d of tamulosin. Expulsion was noted in 24 of 30 patients (80%) in group 1, in 24 of 28 patients (85%) in group 2, and in 12 of 28 patients (43%) in group 3. Statistical significance was achieved when comparing groups 1 and 2 with group 3. Statistical significance was not achieved when comparing the tamulosin group with the nifedipine group. On average, spontaneous stone passage occurred after 9.3 days in group 1, after 7.7 days in group 2, and after 12 days in group 3. Statistical significance was achieved only be-

tween groups 2 and 3. Two patients taking medical expulsive therapy developed side effects serious enough to necessitate its suspension (asthenia and hypotension) and 6 patients developed minor side effects.

In the largest comparison trial to date, Dellabella et al[37] was the first to prove the superiority of tamulosin over nifedipine as a stone-expulsion agent. A total of 210 patients with distal ureteral calculi greater than 4 mm were chosen randomly for home treatment with phloroglucinol, tamulosin, or nifedipine (groups 1-3, respectively). Each group also was given a corticosteroid drug, antibiotic prophylaxis, and injectable NSAID on demand. The expulsion rate was higher in the tamulosin group (97%) than in the nifedipine (77%) or phloroglucinol (64%) groups. The tamulosin group also achieved stone passage in a shorter time. No differences in side effects were observed among the groups. The investigators concluded that the use of tamulosin for distal ureterolithiasis produced stone expulsion in almost all cases in a short time, allowing complete home patient treatment.

Recently, Hollingsworth et al[38] provided further validation by reporting a meta-analysis assessing the efficacy of drug therapy in facilitating spontaneous passage of ureteral stones. Their study showed a benefit for calcium channel blockers and alpha adrenergic antagonists. They also concluded that the addition of corticosteroids might have a small advantage, but the benefit of drug therapy is not lost in those patients in whom corticosteroids might be contraindicated.

Multiple clinical trials have shown that tamulosin improves stone passage rates, decreases stone-expulsion times, and reduces the need for analgesic therapy, hospitalization, and surgery. Tamulosin appears to be most efficacious when used in combination with a corticosteroid, but it also is effective if used as single-drug therapy. The nonselective adrenergic alpha blockers also appear to be effective as well.

CONCLUSIONS

Medical expulsive therapy for ureteral stones provides another nonsurgical option for patients with ureteral stones. Multiple randomized clinical trials have shown that medical expulsive therapy is clinically efficacious, safe, and well tolerated.

In view of the earlier-described clinical trials and meta-analysis, patients with distal ureteral stones measuring less than 1 cm who are candidates for observation deserve a trial of medical expulsive therapy. Most likely, patients with stones throughout the ureter will benefit from medical expulsive therapy, and today alpha blockers are more commonplace than calcium channel blockers. Increased understanding of ureteral physiology will allow for future development of medical expulsive therapies.

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