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

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