

## Medical expulsive therapy

Kyle D. Wood, Ilya Gorbachinsky, Jorge Gutierrez

Department of Urology, Wake Forest Baptist Health, Winston-Salem, NC, USA

### ABSTRACT

The objective of this review article is to present the current literature on medical expulsive therapy (MET) and help guide practitioners in the appropriate use of MET for treatment of stone disease. Kidney stones can be treated with multiple modalities including medical therapy, ureteroscopy, shock wave lithotripsy (SWL), percutaneous nephrostolithotomy, open/laparoscopic stone removal, and/or combinations of these modalities. The choice of intervention depends on patient factors, anatomical considerations, surgeon preference, and stone location and characteristics. MET is an excellent treatment modality in the appropriately selected patient. The AUA/EAU guidelines suggest MET as a reasonable treatment choice in select patients. A review of the data suggests the use of alpha antagonist and calcium channel blockers can improve stone expulsion rates. Most data suggests alpha antagonists as superior to calcium channel blockers. There are numerous available alpha antagonists, all of which have supporting data for their use in MET. Evidence suggests that MET can decrease colic events, narcotic use, and hospital visits. MET may also reduce medical costs and prevent unnecessary surgeries and the associated risks. Further, there is a role for alpha antagonists and calcium channel blockers in improving stone passage and decreasing pain in those subjects treated with other modalities (i.e. SWL and ureteroscopy). Despite this evidence, MET remains underutilized as a treatment modality.

**Key words:** Kidney, stones, urolithiasis

### INTRODUCTION

The lifetime risk of kidney stones is estimated to be between 5% and 10% with the recurrence rate as high as 50%.<sup>[1]</sup> Further, the prevalence of nephrolithiasis is increasing, resulting in an ever increasing economic burden.<sup>[2,3]</sup> The estimated prevalence in National Health and Nutrition Examination Survey (NHANES) data from 1994 was 5.2% overall, men at 6.3%, and women at 4.1%.<sup>[2]</sup> Scales and colleagues reviewed the NHANES data from 2007 to 2010 and demonstrated the prevalence of kidney stones to be 8.8%, significantly higher. Among men, the prevalence of kidney stones was 10.6% and 7.1% in women. Hispanics and

African Americans had lower prevalence at 6.4% and 4.3%, respectively.<sup>[3]</sup> A similar rise in the prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome has been documented. Not surprisingly, the risk of kidney stones has been associated with these medical conditions.<sup>[4,5]</sup>

Kidney stones can be treated with multiple modalities including medical therapy, ureteroscopy, shock wave lithotripsy (SWL), percutaneous nephrostolithotomy, open/laparoscopic stone removal, and/or combinations of these modalities. The choice of intervention depends on patient factors, anatomical considerations, surgeon preference, and stone location and characteristics. Medical expulsive therapy (MET) is an excellent treatment modality in the appropriately selected patient.<sup>[6]</sup> This article reviews medical expulsive therapy in facilitating the spontaneous passage of ureteral stones and its use as an adjunct to other treatment modalities.

### METHODS

A nonsystematic review of the literature was performed using the National Library of Medicine database (PubMed) and the Cochrane Library. The Medline search was performed using the term: Medical expulsive therapy. Only papers written in English were incorporated. A special focus on recent review articles and articles from 1995 to present date was performed. A few older articles were cited for historical

**For correspondence:** Dr. Kyle D. Wood, Urology Resident, Wake Forest Baptist Health, Department of Urology, Medical Center, Boulevard, Winston-Salem, NC 27157, NC, USA.  
E-mail: kwood@wakehealth.edu

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purposes. It was felt that recent articles served as a better representation of current practice patterns and guidelines.

## URETERAL STONES

### *Spontaneous passage*

Spontaneous passage of ureteral stones is dependent on stone size and location among other factors. Coll *et al.* demonstrated with unenhanced computed tomography that ureteral stones < 5 mm had a greater than 75% chance of spontaneous passage regardless of location.<sup>[7]</sup> Larger stones were less likely to pass (for stones 5-7 mm, 60%; for stones 7-9 mm, 48%; and for stones larger than 9 mm, 25%). Stone location regardless of size was also a significant factor; spontaneous passage rates were 48% for stones in the proximal ureter, 60% for mid ureteral stones, 75% for distal stones, and 79% for ureterovesical junction stones. Miller *et al.* demonstrated that time to stone passage can take greater than a month but can be as high as 95% in stones < 5 mm in size.<sup>[8]</sup>

A meta-analysis performed by the AUA/EAU guidelines panel demonstrated that for stones  $\leq$  5 mm, 68% of stones would pass spontaneously. For stones > 5 mm and  $\leq$  10 mm, 47% would pass spontaneously.<sup>[6]</sup> In those patients with no infectious parameters, adequately controlled symptoms, and smaller ureteral stones, spontaneous passage is an excellent option. Attempts at spontaneous passage of stones can save a patient invasive surgical intervention as well as significant cost.<sup>[9]</sup> Observation is not indicated in those patients with unremitting or recurrent disabling pain, persistent urinary obstruction, infection, solitary kidney, or electrolyte abnormalities with or without renal insufficiency.

### *Medical expulsion therapy*

Prior to the use of calcium channel blockers and alpha antagonist, spontaneous passage was aided with increased fluid intake along with antiemetics and analgesics. Characterization of adrenergic receptors in the human ureter<sup>[10]</sup> and smooth muscle physiology<sup>[11]</sup> led to the development of targeted medical treatment. As with most medical developments, the benefits of antagonists to adrenergic receptors and blockers of calcium channels were demonstrated first in animal models.<sup>[12-14]</sup> In current practice, two treatments have been studied in randomized controlled trials: Nifedipine and alpha antagonists (i.e., tamsulosin, doxazosin, alfuzosin, or terazosin).

Hollingsworth *et al.* published a meta-analysis in 2006 of medical treatment and its use to facilitate stone passage.<sup>[15]</sup> The group analyzed a total of nine randomized controlled trials combining the results of those using calcium channel blockers and alpha antagonists to treat ureteral stones. The article demonstrated those patients given calcium channel blockers or alpha antagonists had a 65% greater likelihood of stone passage ( $P < 0.0001$ ), with a number needed to treat of four patients.

More recently, the AUA/EAU guidelines panel has further analyzed all available data on the use of calcium channel blockers and alpha antagonists. The panel demonstrated that nifedipine had an absolute increase of 9% in stone-passage rates compared to alpha antagonists that had a 29% when compared to control; nifedipine results were not statistically significant whereas alpha antagonists results were statistically significant.<sup>[6]</sup> In head to head comparisons of these two classes of medication, alpha antagonists appeared superior to calcium channel blockers.

Other authors have reviewed and corroborated the evidence that medical treatment with either class of agent facilitates stone passage.<sup>[16,17]</sup> Singh *et al.* analyzed 16 studies using an alpha antagonist and 9 studies using a calcium channel blocker. Their analysis suggested that the addition of these agents compared to standard therapy significantly improved spontaneous stone expulsion. Alpha-antagonist had a relative risk (RR) of 1.59 and a number needed to treat of 3.3 patients. As for calcium channel blockers, the RR was 1.50 and the number needed to treat was 3.9. Subgroup analysis of trials using low-dose steroids, antibiotics, and anticholinergic agent (in addition to calcium channel blockers and alpha antagonist) did not yield further benefit.<sup>[16]</sup> Adverse effects such as transient hypotension, dizziness, headaches, and nausea/vomiting were 4% in those treated with alpha antagonist and 15.2% in those receiving calcium channel blockers.

Other investigators have demonstrated a benefit with the addition of corticosteroids. Porpiglia *et al.* performed a prospective study of 114 patients divided into four groups (controls, tamsulosin alone, deflazacort alone, or a combination of tamsulosin and deflazacort). The group receiving combination therapy had an 84.4% expulsion rate compared to 60% for the tamsulosin group ( $P < 0.05$ ). Combined therapy with tamsulosin and deflazacort may improve stone passage rates.<sup>[18]</sup>

Hermanns and colleagues randomized 100 patients with < or = 7 mm distal ureteral stones to either placebo or tamsulosin treatment.<sup>[19]</sup> Median stone size was 4.1 mm for tamsulosin group and 3.8 mm for placebo group ( $P = 0.3$ ). Stone expulsion rates were similar between the two groups, 86.7% and 88.9%, respectively. However, the tamsulosin group required significantly less analgesics. This suggests that alpha antagonists may not increase stone passage in all cases, but may still be beneficial given its association with decreased analgesic use.

Not all alpha antagonists work the same. Most research and results were studied with tamsulosin, making it the most commonly prescribed alpha antagonist in the United States. Pedro and colleagues studied the use of alfuzosin as the agent of choice for medical expulsive therapy.<sup>[20]</sup> They randomized 76 patients to placebo or alfuzosin treatment with mean

stone size comparable between the two groups (4.08 vs 3.83 mm). Stone passage rates were similar between the two groups, 77.1% for placebo and 73.5% for alfuzosin group. However, the alfuzosin group had less discomfort as evidenced by pain scores and also had decreased times to passage.

Alpha adrenergic receptors are present in high density within the distal ureter. There are three types of receptors in the distal ureter:  $\alpha$ 1A,  $\alpha$ 1B, and  $\alpha$ 1D. The receptor with the highest density is the  $\alpha$ 1D and therefore it is not surprising that specific antagonists to this receptor have been developed.<sup>[21]</sup> Sun and colleagues randomized 60 patients to watchful weighting versus 50 mg of naftopidil (specific  $\alpha$ 1D-adrenergic receptor antagonist).<sup>[22]</sup> The stone expulsion rate was significantly higher in the naftopidil group (90.0% vs 26.7%) and the patients had no side effects. Zhou *et al.* randomized 131 patients to 10 mg naftopidil daily, tamsulosin 0.4 mg daily, or watchful waiting. Both naftopidil and tamsulosin had similar stone expulsion rates (72.1% and 82.2%, respectively).<sup>[23]</sup> Naftopidil remains a drug choice in MET.

The efficacy of MET does not appear to be limited to adults. Limited information has been published in children. However, MET is attractive in this population as it can prevent unnecessary anesthetic and surgical risk. Van Savage *et al.* published recommendations for children; they suggested stones < 3 mm would pass spontaneously but that calculi > 4 mm would require surgical management.<sup>[24]</sup> Recently, Erturhan and colleagues randomized 45 children ages 3-15 with a single ureteral stone to ibuprofen versus ibuprofen and nightly doxazosin. The rate of stone passage was 28.5% in the former group and 70.8% in the latter group ( $P = 0.001$ ). Numbers of pain attacks and time to stone passage were also significantly lower in the doxazosin plus ibuprofen cohort. In the doxazosin treatment group, stones < 5 mm were expelled at a significantly greater rate than stones 5-10 mm (100% vs 53.3%;  $P < 0.007$ ). With respect to the age range, children < 7 years old passed the stones with significantly greater rates than children aged > 7 years (65.2% vs 36.3%, respectively;  $P < 0.009$ ).<sup>[25]</sup> These results suggest that children are capable of passing larger stones and a trial of MET is reasonable in the correct clinical setting.

#### **Predictors of medical expulsive therapy success**

In addition to the aforementioned studies on stone size and location for predicting stone passage rates, other studies have suggested imaging findings and laboratory values can be predictive of stone passage. Recently, Lee and colleagues retrospectively investigated stone passage with tamsulosin-based MET along with parameters on CT imaging including transverse stone diameter, longitudinal stone diameter, ureteral diameter (proximal to stone), and ureter-to-stone diameter ratio. They noted that each of these

factors were inversely associated with successful stone passage, regardless of stone position within the ureter ( $P < 0.001$ ). Interestingly, only longitudinal stone diameter (maximal stone diameter on coronal reconstruction) was significantly associated with stone passage on logistic regression analysis. Stone expulsion rates appeared to drastically decrease at the 5 mm mark measured longitudinally with 70% and 84.3% passage of 4-5 mm upper and lower ureteral stones, respectively and 42.9% and 44.8% passage of 5-6 mm upper and lower ureteral stones, respectively.<sup>[26]</sup>

Aldaquadossi studied 235 patients receiving MET. Stone expulsion within 4 weeks was recorded in 129 patients (54.9 %), while 106 patients (45.1 %) underwent ureteroscopy for stone extraction. C-reactive protein (CRP) was significantly different in the two groups; stone expulsion had significantly lower serum CRP levels (16.45 + 2.58) compared to those who failed (39.67 + 6.30). He suggested a cut-off point of 21.9 mg/L for CRP with those below benefiting from MET and those above being offered immediate, minimally invasive ureteroscopy.<sup>[27]</sup> The use of laboratory values to predict stone expulsion rates is an interesting concept but needs to be further studied prior to widespread implementation.

#### **Medical expulsive therapy with other treatment modalities**

The use of medical expulsive therapy is appealing in SWL as there will be residual stone fragments following treatment. Seitz *et al.* evaluated the efficacy and safety of MET with alpha-blockers and calcium channel blockers for upper urinary tract stones in a review of 47 randomized controlled trials. Out of the 47 studies, 13 studies (1007 patients) were analyzed for MET with SWL; most of the studies (10 out of 13) used tamsulosin as a drug choice. Treatment was given after SWL and compared to placebo. Overall benefit for stone expulsion was RR of 1.29. Two studies looked at calcium channel therapy and overall treatment benefit for stone expulsion was RR of 1.57. Those treated with MET had lower analgesic requirements, fewer colic episodes, and fewer hospitalizations.<sup>[17]</sup>

Zhu *et al.* reviewed seven trials with a total of 484 patients that were treated with tamsulosin following SWL. The pooled absolute risk difference of clearance rate was 16% in favor of the tamsulosin group, with a number needed to treat estimated at six patients to achieve clearance benefit. The expulsion time was analyzed in three studies and the mean difference was 8 days in favor of the tamsulosin group. Pain and analgesic use was reported to be lower with tamsulosin as well.<sup>[28]</sup>

Gravina and colleagues randomized 130 patients who underwent a single SWL session to tamsulosin or control for a maximum of 12 weeks. When stratified to stones size greater than 10 mm, the tamsulosin group had higher success rates than the control group (81% vs 55%, respectively).

However, when stone size was between 4 and 10 mm, similar success rates were seen between the two groups (75% vs 68%).<sup>[29]</sup>

Zheng *et al.* evaluated the efficacy of tamsulosin in the treatment of the renal and ureteral stones after SWL. This group analyzed 15 studies with 1326 subjects and determined that those treated with tamsulosin had a 24% improvement in stone clearance.<sup>[30]</sup>

The use of MET is not limited to SWL. John and colleagues prospectively evaluated 78 patients with large renal or ureteral calculi who underwent ureteroscopic laser lithotripsy by a single urologist. After treatment, the patients were randomized to treatment with tamsulosin or control. Overall stone free rates were 86.5% and 69.4%, respectively ( $P < 0.01$ ). In addition, the ureteric colic rate was 5.4% and 22.2%, respectively.<sup>[31]</sup>

### Current trends in medical expulsive therapy

Despite AUA/EAU guidelines suggesting MET as a reasonable treatment in patients who are medically stable with symptom control and with ureteral stones less than < 10 mm, MET continues to be underutilized. The reasons for underutilization have been studied by a number of investigators.

Hollingsworth *et al.* studied claims data and compared ureteroscopy to MET in men between 2002 and 2006.<sup>[32]</sup> They demonstrated that MET was much more likely to be chosen as a treatment choice when patients presented to the emergency room on weekends. Men treated with MET were more often salaried, had full time employment, and lived in urban areas. Further, they demonstrated only 25% of men treated with MET required subsequent surgical intervention. The authors demonstrated a significant cost saving in the MET group. In a separate article, Hollingsworth *et al.* reviewed roughly 80,000 patients seen for acute stone episodes. Patients prescribed MET were more likely to be older, more likely to be male, and have full time employment. In addition, the odds of receiving MET were fivefold higher if seen by a urologist.<sup>[33]</sup> These studies demonstrated the underutilization of MET as a treatment choice.

Recognizing the underutilization in certain demographic groups and implementing education and changes in the hospital setting will ultimately lead to more appropriate use of MET. Brede *et al.* performed an educational intervention on ED physicians and analyzed emergency department practices before and after intervention. Following education on the use of MET, the group noticed a fourfold increase in alpha antagonist prescriptions in the emergency room (comparing pre and post intervention) as well as an overall decrease in cost per patient and a decrease in adverse events.<sup>[34]</sup>

## CONCLUSION

The AUA/EAU guidelines suggest MET as a reasonable treatment choice in select patients. Previous studies have demonstrated a significant benefit in stone expulsion rates with the use of MET. A review of the data suggests greater success rates occur with the use of alpha antagonist compared to calcium channel blockers. The use of MET is not limited to just those patients attempting passage of calculi without other interventions; there is also an advantage to MET in those subjects treated with other modalities (i.e. SWL and ureteroscopy).

Even with multiple studies demonstrating the benefits of MET, it still is underutilized as a treatment modality. Education in the hospital setting appears to be beneficial in changing practice behaviors. MET may reduce medical costs and prevent unnecessary surgeries and the associated risks.

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