Does the Addition of Tamsulosin to Outpatient Analgesic Therapy Enhance Spontaneous Stone Passage in Patients With Uncomplicated Distal Ureteral Stones?

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From the Editor—Emergency physicians must often make decisions about patient management without clear-cut data of sufficient quality to support clinical guidelines or evidence-based reviews. Topics in the Best Available Evidence section must be relevant to emergency physicians, are formally peer reviewed, and must have a sufficient literature base to draw a reasonable conclusion but not such a large literature base that a traditional "evidence-based" review, meta-analysis, or systematic review can be performed.

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ABSTRACT

To determine whether the addition of an adrenergic α-antagonist to routine medical therapy enhances spontaneous passage of uncomplicated urolithiasis, we performed a MEDLINE search using the key words "urolithiasis AND adrenergic alpha-antagonists LIMIT humans" and "English." This search yielded 22 articles, 8 of which directly addressed this question. According to this review of the available evidence, adrenergic α-antagonists, such as tamsulosin, increase spontaneous stone expulsion rate and decrease time to stone expulsion, additional analgesic requirement, and hospitalization. Therefore, it would be within the standard of care to add a short course (2 to 4 weeks) of tamsulosin to standard analgesic therapy for patients discharged from the emergency department with appropriate urologic follow-up.

INTRODUCTION

Urolithiasis affects about 8% to 15% of the population in North America and Europe.[1] Pain control is the mainstay of emergency department (ED) treatment, and watchful waiting with analgesia is the common outpatient approach for uncomplicated distal ureteral stones. Minimally invasive procedures for stone removal such as shockwave lithotripsy and ureteroscopy are expensive and associated with some, although minimal, risk.[2] The addition of adrenergic α-1 antagonists to routine analgesia has been proposed to facilitate stone passage by inhibiting basal tone, peristaltic frequency, and ureteral contractions[3] through their action on the α-1 adrenergic receptors in ureteral smooth muscle.[4] The concentration of α-1 adrenergic receptors in ureteral smooth muscle is higher than that of other adrenergic receptors. We therefore searched the literature to determine whether the addition of an α-1 antagonist to routine medical therapy enhances spontaneous passage of ureteral stones. Because the α-1-D subtype is predominant in distal ureteral smooth muscle, the majority of studies that we identified used tamsulosin, a selective α-1-A/α-1-D adrenergic antagonist.

SEARCH STRATEGY

A MEDLINE search (mid-1960s to present) was performed using the key words "urolithiasis AND adrenergic alpha-antagonists LIMIT humans" and "English." This search yielded 22 articles. Bibliographic references in these articles were also examined to identify pertinent literature. We included only original, published articles that addressed the effect of an α-1 antagonist on the spontaneous passage of uncomplicated urolithiasis. We identified 8 studies that directly addressed this question (Table).

ARTICLE SUMMARIES

Hollingsworth et al[5]

This recent meta-analysis evaluated the efficacy of calcium channel blockers and adrenergic α-blockers in facilitating passage of ureteral stones, so we will briefly mention it in this review. The authors pooled data from 5 randomized control trials that used adrenergic α-antagonists in the treatment group. With regard to the likelihood of spontaneous stone passage, the pooled risk ratio of these studies was 1.54 (range 1.29 to 1.85), $P<.001$.

This study concluded that patients treated with tamsulosin have up to a 54% higher likelihood of spontaneous stone passage. Additional benefits were a decrease in the number of painful episodes and the need for additional analgesia.

Cervenakov et al[6]

This was a double-blind prospective Bratislavian study of 102 hospitalized patients with lower urinary tract stones (<10 mm), randomized to receive standard therapy

(saline+tramadol+diazepam+veral [medication name {classification} nonsteroidal anti-inflammatory]) or standard therapy plus tamsulosin. The addition of ureterorenoscopy or shock-wave lithotripsy was recommended for patients with unsuccessful stone expulsion.

There were 51 patients in each group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size in the less-than-6-mm group (4.0±1.8 versus 3.8±1.9 mm) and in the greater-than-6-mm group (7.6±1.6 versus 7.5±1.4 mm), a higher stone expulsion rate (80% versus 63%), and a similar mean stone expulsion time (3.1±1.5 versus 3.4±1.6 days). They did not report the need for additional analgesia. There were no adverse effects. The authors concluded that the addition of tamsulosin to their standard pharmacologic therapy improved the rate of stone passage.

Dellabella et al[1]

This was a prospective Italian study of 60 ED patients with uncomplicated juxtavesicular stones that were randomized to receive daily floroglucine-trimetossibenzene (medication name [classification] spasmolytic) (group 1) and tamsulosin (0.4 mg) (group 2). All patients were also treated with 10 days of deflazacort (medication name [classification] corticosteroid), 8 days of cotrimoxazole, and intramuscular diclofenac as needed. Patients were evaluated for stone passage rate and time, analgesia use, hospitalization, and need for uroscopic intervention. They were followed for 28 days or until stone expulsion.

There were 30 patients in each group. Compared with group 1, the tamsulosin group had a larger mean stone size (6.7±2.1 versus 5.8±1.3 mm; $P=.05$), a higher stone expulsion rate (100% versus 70%; $P=.001$), and a faster mean stone expulsion time (3±3 versus 5±3 days; $P=.02$) and required fewer diclofenac injections (0.1±0.4 versus 2.8±2.9 injections; $P<.001$). No patients in the tamsulosin group were hospitalized for pain control or unsuccessful expulsion after 4 weeks compared with 33% in group 1. No drug adverse effects were observed.

The authors concluded that the addition of tamsulosin to their standard pharmacologic therapy improved the rate of stone passage, decreased stone expulsion time, and decreased the need for additional analgesia and hospitalization.

Kupeli et al[7]

This was a prospective Turkish study of 78 patients with uncomplicated lower ureteral stones to determine the effect of tamsulosin on stone clearance in patients treated with conservative management or shock-wave lithotripsy. The patients were first separated by stone size (<6 mm [groups 1, 2] or >6 mm [groups 3, 4]) and then randomized to receive either standard medical therapy (groups 1, 3) or tamsulosin plus standard medical therapy (groups 2, 4). Standard therapy was oral hydration and oral diclofenac. Patients with stones greater than 6 mm were treated with shock-wave lithotripsy, in addition to the medical therapy. Patients were reevaluated 15 days after beginning treatment.

Of the 30 patients randomized to medical therapy without shock-wave lithotripsy, 15 patients were in the standard therapy group and 15 in the tamsulosin group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size (4.7 versus 4.9 mm; $P=.9$) and a higher, although not statistically significant, stone expulsion rate (53% versus 20%; $P=.13$). Expulsion time and need for additional analgesia were not reported.

In the 48 patients randomized to medical therapy with shock-wave lithotripsy, 24 patients were in the standard therapy group and 24 in the tamsulosin group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size (8.6 versus 8.2 mm; $P=.77$) but a higher stone expulsion rate (71% versus 33%; $P=.02$). One patient in the tamsulosin group reported mild dizziness.

This study concluded that tamsulosin appeared to facilitate stone expulsion in patients treated medically and with shock-wave lithotripsy. The observed difference in stone expulsion rate in the medical treatment groups was not statistically significant, because of the small sample size.

Resim et al[8]

This was a prospective Turkish study of 60 outpatient urology clinic patients with uncomplicated juxtavesicular ureteral calculi, randomized to receive standard therapy (hydration+tanoxicam [medication name {classification} nonsteroidal anti-inflammatory]) and tamsulosin plus standard therapy. Patients were followed for 6 weeks or until stone expulsion.

There were 30 patients in each group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size (7.8±2.3 versus 7.8±2.2 mm; $P=1.0$) and a higher, although not statistically significant, stone expulsion rate (87% versus 73%; $P=.2$). Stone expulsion time and need for additional analgesia were not reported. However, patients reported lower pain scores on a visual analog scale in the tamsulosin group (5.7±2.0 versus 8.3±1.2; $P<.0001$) and fewer episodes of ureteral colic (2.0±1.0 versus 2.6±1.1; $P=.04$). Several mild adverse effects associated with tamsulosin were reported, including headache, abnormal ejaculation, diarrhea, and dizziness. None required medical intervention or withdrawal from the study.

The authors concluded that tamsulosin decreased pain intensity and the frequency of ureteral colic. However, it did not increase the likelihood of stone passage and did produce some mild adverse effects.

Dellabella et al[9]

This was a prospective Italian study of 210 ED patients with uncomplicated juxtavesicular stones, who were randomized to receive daily phloroglucinol* (medication name [classification] antispasmodic) (group 1), tamsulosin (0.4 mg) (group 2), or nifedipine (group 3). All patients were also treated with 10 days

Table. Study summaries.

Studies by First Author	Study Size, Patients, No.	Treatment Groups	Stone Expulsion Rate, %	Stone Expulsion Time, days	Analgesia Use	Adverse Effects
Cervenakov, 2002[6]	102	Control: saline, tramadol, diazepam, veral	63%	3±2	N/A	None
		Group 2: tamsulosin plus control therapy	80%	3±2	N/A	None
Dellabella, 2003[1]	60	Group 1: floroglucine-trimetossibenzene	70%	5±3	3±3 Diclofenac injections	None
		Group 2: tamsulosin	100%	3±3	0.1±0.4 Diclofenac injections	None
		All received deflazacort, cotrimoxazole, diclofenac				
Kupeli, 2004[7]	30	Control: oral hydration and oral diclofenac	20%	N/A	N/A	None
		Group 2: tamsulosin plus control therapy	53%	N/A	N/A	Mild dizziness
Resim, 2005[8]	60	Control: oral hydration and tenoxicam	73%	N/A	VAS 8.3±1.2	None
		Group 2: tamsulosin plus control therapy	87%	N/A	VAS 5.7±2.0	Headache, abnormal ejaculation, diarrhea, dizziness
Dellabella, 2005[9]	60	Group 1: tamsulosin	64%	5	2 Vials	No serious adverse effects
		Group 2: tamsulosin plus deflazacort	97%	3	0 Vials	No serious adverse effects
Yilmaz, 2005[10]	57	Control: oral hydration and diclofenac	79%	11±2	182±20 mg Diclofenac	None
		Group 2: tamsulosin plus control therapy	54%	6±1	129±18 mg Diclofenac	None
Autorino, 2005[11]	64	Control: diclofenac and aescin	60%	7±2	31% Additional analgesia	Malaise, diarrhea
		Group 2: tamsulosin plus control therapy	88%	5±3	9% Additional analgesia	Transient hypotension, weakness, dizziness
		All received omeprazole and 7 days of levofloxacin.				
De Sio, 2006[12]	64	Control: diclofenac and aescin	59%	8±2	37% Additional analgesia	Malaise, diarrhea
		Group 2: tamsulosin plus control therapy	90%	4±2	10% Additional analgesia	Transient hypotension, weakness, dizziness
		All received omeprazole and 7 days of levofloxacin.				

of deflazacort, 8 days of cotrimoxazole, and intramuscular diclofenac as needed. Patients were evaluated for stone passage rate and time, analgesia use, hospitalization, and need for uroscopic intervention. They were followed for 28 days or until stone expulsion.

There were 30 patients in each group. Compared to group 1, the tamsulosin group had a higher mean stone size (7.2±2.4 versus 6.2±1.7 mm; P=.002), a higher stone expulsion rate (97% versus 64%; P<. 0001), and a faster mean stone expulsion time (3 versus 5 days; P<. 0001) and required fewer diclofenac injections (0 versus 2 vials; P<. 0001). No patients in the tamsulosin group were hospitalized for pain control compared with 16% in group 1. The authors reported no difference in the frequency of adverse effects between the groups, although the data were not shown in the article.

The authors concluded that the addition of tamsulosin to their standard pharmacologic therapy improved the rate of stone passage, decreased stone expulsion time, and decreased the need for additional analgesia and hospitalization.

Yilmaz et al[10]

This was a prospective Turkish study of 114 patients with uncomplicated distal ureteral stones, randomized to 4 treatment groups: no additional adrenergic α-antagonist (group 1), tamsulosin (group 2), terazosin (group 3), and doxazosin (group 4). All patients received standard therapy with oral hydration and intramuscular diclofenac. Patients were treated and followed for 1 month.

There were 28 patients in the standard therapy group and 29 patients in the tamsulosin group. Compared with the control group, the tamsulosin group had a similar mean stone size (6.0±1.3 versus 6.1±1.4 mm), a higher stone expulsion rate (79% versus 54%; P=.03), a faster mean stone expulsion time (6±1 versus 11±2 days; P=.04), and a smaller diclofenac requirement (129±18 versus 182±20 mg; P=.008). There was no difference in expulsion rate or time of expulsion among the 3 adrenergic α-antagonist groups. Six (21%) patients in the tamsulosin group required ureteroscopy or shock-wave lithotripsy compared with 13 (39%) patients in the control group. No drug adverse effects were observed that resulted in withdrawal from the study.

The authors concluded that adrenergic α-antagonists increased the rate of stone expulsion, decreased the time to stone expulsion, and improved pain intensity by decreasing additional analgesia requirement and the number of ureteral colic episodes.

Autorino et al[11]

This was a prospective Italian study of 64 urology clinic patients with uncomplicated distal ureteral calculi, randomized to receive standard therapy only (diclofenac+aescin; medication name [classification] an antiedema extract of the horse chestnut tree) and tamsulosin plus standard therapy. All patients received daily omeprazole during the treatment period and levofloxacin during the first week. Patients were followed for 2 weeks.

There were 32 patients in each group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size (6.5 versus 5.7 mm), a higher stone expulsion rate (88% versus 60%; P=.01), a faster mean stone expulsion time (4.8±2.7 versus 7.4±2.2 days; P=.005), and a lower analgesia requirement (9% versus 31%; P=.003). Three (9%) patients in the tamsulosin group were hospitalized for recurrent colic that did not require ureteral stenting compared with 7 (21%) patients in the control group that required ureteral stenting for uncontrollable pain, P=.01. Mild adverse effects were observed in both groups: malaise and diarrhea in the control group and transient hypotension, weakness, and dizziness in the tamsulosin group. None required cessation of therapy. After 4 weeks, 13 patients in the standard therapy group and 4 in the tamsulosin group required ureteroscopy or shock-wave lithotripsy for retained stones.

The authors concluded that tamsulosin increased stone expulsion rate and decreased stone expulsion time, hospitalization, and need for additional analgesia in patients with uncomplicated ureteral colic.

De Sio et al[12]

This was a prospective Italian study of 64 urology clinic patients with distal ureteral calculi randomized to receive standard therapy only (diclofenac+aescin) or tamsulosin plus standard therapy. All patients received daily omeprazole during the treatment period and levofloxacin during the first week. Patients were followed for 2 weeks.

There were 46 patients in the standard therapy group and 50 patients in the tamsulosin group. Compared with the standard therapy group, the tamsulosin group had a similar mean stone size (6.9±1.0 versus 6.4±1.3 mm), a higher stone expulsion rate (90% versus 59%; P=.01), a faster mean stone expulsion time (4.4±2.1 versus 7.5±1.8 days; P=.005), and a lower analgesia requirement (10% versus 37%; P=.003). Five (10%) patients in the tamsulosin group were hospitalized for recurrent colic that did not require ureteral stenting compared with 11 (28%) patients in the control group that required ureteral stenting for uncontrollable pain, P=.01. Mild adverse effects were observed in both groups: malaise and diarrhea in the control group and transient hypotension, weakness, and dizziness in the tamsulosin group. None required cessation of therapy.

The authors concluded that tamsulosin improved the rate of spontaneous stone expulsion, decreased the time to stone expulsion, and provided good pain control in patients with ureteral colic.

THE BOTTOM LINE

According to the available evidence, an adrenergic α-antagonist is an effective adjunct to analgesia in the outpatient pharmacological treatment of uncomplicated distal ureteral stones. Adrenergic α-antagonists, such as tamsulosin, increase spontaneous stone expulsion rate and decrease time to stone

expulsion, decrease additional analgesic requirement, and decrease hospitalization. Therefore, it would be within the standard of care to add a short course (2 to 4 weeks) of tamsulosin to standard analgesic therapy for patients discharged from the ED, with appropriate urologic follow-up. However, because the "standard" therapies in these studies used medications that are not typically used in the United States, a randomized controlled trial evaluating the addition of an adrenergic α-antagonist to routine analgesia might provide more evidence for its efficacy in the treatment of this common disease.

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CORRECTION

In the October 2007 issue, in the article by Fairbanks, et al ("Emergency Department Communication Links and Patterns"; pages 396-406), there was an error in the Discussion section on page 403. It should have said ". . . our data, which ranged from 1.8 for junior residents to 6.9 for attending physicians in the adult area." The authors regret this error.