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Understanding the Ureter: Challenges and Opportunities

Alyssa Park, MD, and Ramakrishna Venkatesh, MD

Abstract

The ureter is possibly the least studied and most poorly understood organ of the urinary tract. The pathophysiologic basis underlying the use of α -blockers to improve ureteral stone passage or to treat ureteral stent symptoms is poorly understood. This, in part, may explain why clinical studies of medical expulsive therapy for ureteral stone passage are fraught with conflicting data. Methods to study human ureter *in vivo* are few and challenging. The findings of many of the ureteral studies are from observational *in vitro* studies and were evaluated in other animal species that may not be applicable in human beings. There are few mechanistic studies evaluating the underlying molecular pathophysiologic mechanisms of human ureter. This is critical to our understanding and treatment of stent symptoms, including the development of a patient friendly ureteral stent and for the pharmacologic modulation of ureteral activity. The following is an overview of some of the observational and mechanistic ureteral studies evaluating the pharmacologic and stent effects, including potential areas for further research.

Introduction

UROLOGISTS HAVE BEEN using ureteral stents for more than four decades.¹ However, the exact mechanisms of ureteral stent pain, dilation of ureter with stenting, and treatment of ureteral stent symptoms are still elusive. Over the last decade, there has been wide use of α -blocker for ureteral stone passage and stent symptoms. There are many single-center studies confirming the benefit of α -blocker for stone passage, but a more recent well-designed, large, randomized prospective study showed no benefit of α -blocker in decreasing the treatment intervention rate compared with a placebo group.^{2,3} The earlier examples bring to question our understanding of the ureteral pathophysiologic mechanisms related to the use of ureteral stent and pharmacotherapy of ureteral stone passage.

The study of ureteral dynamics and smooth-muscle pharmacology has drawn significant conflicting findings, possibly because of the many differences in experimental techniques, animal models, and lack of sensitive instrumentation. Many authors have reported *in vitro* and *in vivo* ureteral studies related to ureteral instrumentation such as stenting and the effects of pharmacologic agents in many animal species that may not be transferable to human clinical application. The following overview of previous ureteral studies highlights some of the challenges in studying the ureter and potential opportunities for future research.

Ureteral Stent Studies

Animal studies

Ureteral stents help patients with stone colic by relieving renal obstruction. However, ureteral stents can cause partial obstruction to the upper urinary tract with rise in intrapelvic pressure that may contribute to the ureteral dilation. However, the intrapelvic pressure is known to decrease to normal levels in 3 weeks and hence the rise in intrapelvic pressure cannot fully explain ureteral dilation.⁴ Normal peristalsis is affected by the ureteral stent as demonstrated by *in vivo* animal ureteral studies. In a swine model, normal peristalsis was absent after 24 hours following ureteral stenting and peristalsis returned on day 5.⁵ In another porcine *in vivo* study, the peristaltic activity in response to stent placement increased immediately but decreased after 4–5 hours. Peristalsis was markedly reduced or abolished completely after 1 week.⁶ If stone pain is partly from ureteral spasm, ureteral aperistalsis induced by the presence of a stent may alleviate pain of ureteral colic.

The effects of calcitonin gene-related peptide (CGRP) on the ureter in another animal study provide another possible mechanism of action of ureteral stent pain. The CGRP peptide is a smooth-muscle relaxant and inhibits peristalsis.⁵ This could cause both dilation of the ureter and reduction of peristalsis. This peptide is released from unmyelinated sensory nerve endings in the ureter by pain stimulation such as a ureteral stent. It seems possible that both the initial increased upper tract pressure and CGRP may play a role in ureteral dilation/paralysis with

stenting. In an *in vivo* stented porcine ureter, we studied the effects of an alpha-blocker on the ureteral peristalsis and intrapelvic pressure.⁷ Alpha-blocker resulted in no significant effect on renal pelvic pressure, but a significant decrease in the number of ureteral peristalsis. Further investigation of the effects of alpha-blocker on ureteral dynamics is required to better understand its effects on stent-related symptoms.

Human studies

The *in vivo* ureteral studies related to ureteral instrumentation or stenting in humans are sparse. Miller and coworkers described the use of a ureteral catheter with pressure transducers that could measure ureteral peristaltic frequency and ureteral intraluminal pressure in an ambulatory situation.⁵ The authors used a single 4F ureteral catheter and reported their findings in six patients. Five subjects showed peristalsis on catheter insertion. Eighteen hours following ureteral catheter insertion, two had no peristalsis. One of these subjects had previously had a Double-J stent *in situ* for 10 weeks and the other patient had diclofenac for postoperative analgesia. One patient had diclofenac suppository before surgery and was found to have no peristalsis during the recording for over 24 hours. Excluding these three patients, the average baseline peristaltic rate was 2/min (range 2–4/min). Thus, in the earlier human study, the recently instrumented ureters displayed a variable peristaltic and pressure response that appeared to be related to previous physical or pharmacologic effects. The earlier study also showed *in vivo* evidence that diclofenac abolishes peristalsis in a human ureter.

In many patients, ureteral stents cause significant bothersome urinary symptoms (78%), stent pain (80%), sexual dysfunction (31%), and decreased work capacity (57%). However, there are few effective treatments for stent symptoms. A meta-analysis of several trials showed that alpha-blockers improve stent-related symptoms, including quality of life in patients with stents and recommend their use in clinical practice.⁸ In an interesting study, Gupta et al. evaluated in a randomized controlled study the effects of ipsilateral periureteral injection of botulinum toxin type A at a concentration of 10 U/mL at three sites around the ureteral orifice after ureteral stenting. They administered Ureteral Stent Symptoms Questionnaire (USSQ) 7 days after stent insertion and reported a significant decrease in postoperative pain and narcotic use, but no significant impact on any USSQ scores.⁹

Novel stents

Landman and his coworkers recently reported on custom-made ureteral stents where they printed ureteral stents using a three-dimensional printer. They evaluated the above in porcine and cadaver models.¹⁰ This is a fascinating area where surgical devices can potentially be printed in the operating room with implications on cost savings and the potential to create a specific sized and shaped device for each patient.

Common stent complications included encrustation, infection, pain, and discomfort. In recent years, progress has been made in the development of drug-eluting stents to improve the biocompatibility. Cadieux and colleagues reported on the use of triclosan-loaded ureteral stents to reduce stent-associated bacterial attachment, biofilm formation, and encrustation to potentially reduce infection. They performed a randomized study comparing the triclosan eluting stent with a noneluting stent.¹¹ No significant differences were observed for culture, biofilm, and encrustation between the two groups. However, the triclosan eluting stent led to significant reduc-

tions in several common ureteral stent-related symptoms, supporting its use in this patient population.

Effects of Medications on Ureteral Activity

α 1-Adrenoceptors (both 1A and 1D) have been detected both in animal and human ureters. Similar to muscarinic receptors, activation of α 1-adrenoceptors can activate the phospholipase C/inositol trisphosphate-diacylglycerol pathway and may cause ureteral contraction. The ureter has efferent and afferent innervation from cholinergic, adrenergic, nonadrenergic, and noncholinergic components. Innervation of the lower ureter is shown to be denser than the upper ureter in humans.

Animal studies

Nakada et al. evaluated doxazosin effects on the ureteral activity. This mechanistic *in vitro* porcine ureteral strips organ bath study showed that doxazosin reduces spontaneous and alpha(1)-agonist-induced ureteral contractility. No differential expression of alpha(1)-receptor subtypes was identified in the obstructed vs normal ureters. They hypothesized that alpha-receptor blockade might relax the ureter and induce stone passage by epinephrine activation of beta-receptors.¹²

Pick et al. studied urothelial permeability. By pretreating the intraluminal surface of the ureter with chitosan, which increases urothelial permeability, nifedipine blocks ureteral peristalsis at low concentrations.¹³ They found chitosan changes ureteral urothelial permeability without barrier disruption and had no observed effect on ureteral contraction.

Human studies

Davenport et al. used a ureteral pressure transducer catheter *in vivo* to evaluate the ureteral pressure response to tamsulosin, diclofenac, and nifedipine in 13 patients.¹⁴ Five French catheter was inserted into the contralateral ureter following ureteroscopy for stone disease. Patients were admitted to the hospital. Peristaltic frequency and ureteral pressure measurements were recorded at 24 hours. Each patient was randomly allocated to receive oral diclofenac, nifedipine, or tamsulosin. Measurements were taken following drug administration. Before drug administration, the mean number of contractions recorded was 0–4.1/min and the peak contraction pressure ranged from 11 to 35 mm Hg. Ureteral peristalsis persisted in all patients despite these drugs. Diclofenac and nifedipine produced inconsistent ureteral pressure responses but had little effect on contraction frequency. Tamsulosin significantly reduced ureteral pressure but had no effect on peristaltic frequency.

Adrenergic stimuli in the obstructed ureter produce increased contractility, which is blocked by adrenergic receptor blockers as first shown by Peters and Eckstein in canine ureters.¹⁵ They showed that use of a nonspecific alpha adrenergic blocker increased urinary flow while decreases the frequency of ureteral contractions in partially obstructed ureters. Specific alpha-1 blockade has received increased interest recently. Several randomized studies show shorter stone passage time and increased stone expulsion with alpha-blockers (tamsulosin) compared with placebo or nifedipine.¹⁶ In these studies, distal ureteral stones ranged in size from 4 to 6.7 mm and the stone expulsion rate with alpha-blockade was 97%–100% compared with 64%–70% in the placebo groups. All patients in these studies were given steroids and antibiotics while taking the study medications. With calcium channel blockers, the stone

passage rate was 97% in patients given tamsulosin vs 77% for those given nifedipine. Results to date seem to favor the use of alpha-blockade over calcium channel blockers. Calcium blocking action on cells has been proposed as a way to decrease ureteral contractions and subsequently decrease the pain and discomfort associated with ureteral stones. Nifedipine and verapamil decrease fast phasic contractions while leaving slow phasic contractions unaffected, suggesting preservation of peristalsis with decreased spasms. Relaxation of the ureter with calcium channel blockade might also facilitate stone passage. However, the exact ureteral dynamics related to this is not known. Calcium channel blockers have been evaluated to see their effect on pain from a ureteral stone. Caravati et al. compared nifedipine vs placebo in 30 patients.¹⁷ As measured on a visual analog scale, no significant difference in pain was noted. There is a growing body of literature demonstrating that calcium channel blockers may help with stone passage without significantly altering pain. A large randomized trial comparing placebo, tamsulosin, and nifedipine showed that tamsulosin 400 µg and nifedipine 30 mg are not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks for patients with expectantly managed ureteral colic. This shows that we do not fully understand the pathophysiology of the effects of drugs on the ureter. Randomized studies have demonstrated similar efficacy between selective (tamsulosin) and nonselective (terazosin and doxazosin) medications. Holdgate and Oh found no significant differences in initial or later opioid use when randomizing patients to anticholinergic therapy.¹⁸ The addition of anticholinergics did not seem to alter the pain level or facilitate stone passage in patients with ureteral stones in this study.

Conclusions

There is a need for better characterization of ureteral receptors and other neurogenic factors and also the understanding of cellular mechanisms underlying neurogenic and myogenic ureteral contractions. Also, the quest for better tools to study the human ureteral activity *in vivo* continues. Ureter is primarily a muscular organ transporting urine from the kidneys to bladder, but pharmacomodulation of its smooth muscle activity directly and indirectly through the autonomic and other modulators can be clinically useful to facilitate ureteral stone passage, ureteral instrumentation, such as ureteroscopy, and possibly to minimize stent symptoms. Basic science mechanistic studies understanding the molecular mechanisms of ureteral activity along with observational studies are essential for the development of optimal stents and for the sound use of pharmacologic agents to facilitate urinary stone passage.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviation Used

CGRP = calcitonin gene-related peptide