The Role of Ureteral Relaxation in the Promotion of Stone Passage

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Abstract. In order to promote stone passage in renal colic, we must first understand normal ureteral activity and how this is affected by the presence of a stone. Measuring normal ureteral activity in humans is difficult without the use of invasive methods or techniques which in themselves may affect peristalsis. Monitoring the activity during confirmed renal colic is even more difficult and virtually impossible. Both animal and human studies have therefore been used in an attempt to understand the physiology of the ureter and how this is affected by the presence of a stone. Using this knowledge, drugs can be used to alter the behavior of the ureter in an attempt to promote stone passage. Peristalsis has always been thought to be essential to allow stone passage and therefore it has been necessary to determine whether stone passage occurs by promotion of ureteral activity or by smooth muscle relaxation. Research indicates that drugs which allow continued peristalsis whilst preventing the increased uncoordinated activity seen in renal colic would be the most advantageous. The alpha-1A-adrenoceptor antagonists are the most effective drugs to date.

Keywords: alpha antagonists, calcium channel antagonists, peristalsis, renal colic, ureter.
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INTRODUCTION

The use of pharmacological agents to promote stone passage in renal colic is not a new concept. An understanding of ureteral physiology and the pathological changes occurring in the presence of a ureteral stone is essential to determine those agents most likely to have a beneficial effect. Measuring normal ureteral activity in humans is difficult without the use of invasive methods or techniques which in themselves may affect peristalsis. Monitoring the activity during confirmed renal colic is even more difficult and virtually impossible. Both animal and human studies have therefore been performed. Those agents capable of causing ureteral smooth muscle relaxation have the most beneficial effect clinically; however the in vivo action on the human ureter remains unclear. Peristalsis has always been thought to be essential to allow stone passage and therefore it has been necessary to determine whether stone passage occurs by modulating ureteral activity or by causing smooth muscle relaxation. This chapter summarizes current research in this area.
URETERAL PHYSIOLOGY

Ureteral peristalsis may be triggered spontaneously via the pacemaker cells located at the pelvic-calyceal junctions, by external stimuli which may be electrical, mechanical (e.g. stretch) or chemical or conduction from an adjacent excited cell. In the resting state, the smooth muscle cell membrane potential is approximately -60mV and determined by the movement of potassium along its concentration gradient. If the stimulus is strong enough to decrease the transmembrane potential to the threshold potential, an action potential is generated. This is the primary event in the conduction of a peristaltic impulse and is capable of acting as the stimulus for excitation of adjacent quiescent cells to produce a coordinated ureteral contraction.

Excitation leads to an influx of calcium into the cell which results in the upstroke of the action potential. This is slow as compared to heart or skeletal muscle accounting for the slower conduction velocity seen in the ureter.

The action potential plateaus as a result of persistent calcium influx plus sodium influx via voltage dependent channels. The high intracellular calcium concentration triggers an outward movement of potassium via calcium dependent potassium channels causing repolarization.

In the pacemaker cells, the electrical activity arises spontaneously. The cell resting potential undergoes slow spontaneous depolarization until it reaches the threshold potential at which point an action potential is generated.

The contractile proteins, actin and myosin are located within the sarcoplasm of the ureteral cell. The contractile activity of each ureteral smooth muscle cell is dependent on the free sarcoplasmic calcium concentration in the region of the contractile proteins.

The release of calcium from the sarcoplasmic reticulum during excitation activates a cascade reaction resulting in cross-bridge formation between the myosin heads and the actin filaments producing a contraction. Relaxation occurs following reuptake of calcium into the sarcoplasmic reticulum.

Conduction between adjacent cells occurs via intermediate junctions at a conduction velocity of 2-6 cm/sec [1]. The volume and frequency of contractions can vary in relation to glomerular filtration; for example, both volume and frequency increase during diuresis.

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM

Ureteral peristalsis can occur without neuronal stimulation via the pacemaker cells. However the nervous system, predominantly the sympathetic nervous system, appears to play a modulating role. Adrenergic receptors are found along the length of the ureter [2,3] but mainly in the intramural segment. The alpha-adrenergic receptors are most prominent.

Alpha-adrenergic receptors are subdivided into alpha1 and alpha2 adrenoceptors [4]. Alpha1 adrenoceptors predominate in the human ureter and are further subdivided pharmacologically into alpha1A, alpha1B and alpha1D adrenoceptors [5]. The density of...
alpha_1 adrenoceptors is greatest in the distal ureter (52.5 ± 5.4 fmol/mg protein) as compared with the mid and proximal ureter (25.2 ± 1.7 fmol/mg protein and 23.4 ± 0.4 fmol/mg protein respectively). Alpha_1A and alpha_1D adrenoceptors predominate over alpha_1B at all levels. Activation leads to IP_3 and DAG production resulting in smooth muscle contraction.

THE EFFECT OF STONE ON URETERAL ACTIVITY

The presence of a stone within the ureter initially stimulates peristalsis in an attempt to move the stone. If the stone becomes lodged, then the surrounding smooth muscle goes into spasm, which is presumed to have a negative effect on the probability of stone passage. Accompanying edema and inflammation further narrow the ureter at the level of the stone. Proximal to the stone, ureteral peristalsis increases in an attempt to move the stone resulting in the characteristic pain of renal colic.

There is much debate as to whether peristalsis is necessary to promote stone passage or whether relaxation of ureteral smooth muscle would aid passage. It has been stipulated in the past that ureteral peristalsis is essential to allow spontaneous stone passage. However, irritation and stretch stimulation of the ureter by the stone may result in increased uncoordinated peristalsis [6], which may actually hinder stone passage. In a canine in vivo model of acute obstruction, the mean peristaltic rate, baseline pressure and peak pressures above the level of obstruction were all shown to increase significantly [7]. Conversely below the level of obstruction, the mean peristaltic rate remained unchanged but the baseline and peak pressures generated were both significantly reduced.

In an in vivo study yet to be published, we recorded human ureteral activity during an episode of pain similar to renal colic using a ureteral pressure transducer catheter [8]. The recording obtained demonstrated increased uncoordinated contractions of higher pressures than those usually recorded in the human ureter using the same catheter (see Figs. 1 and 2). Control of this increased, uncoordinated ureteral activity may promote normal peristalsis allowing stone passage.

FIGURE 1. 3-minute recording of proximal human ureteral activity obtained 24 hours post-ureteroscopy using the ureteral pressure transducer catheter.
FIGURE 2. 3-minute recording of human ureteral activity during pain typical of acute renal colic using the ureteral pressure transducer catheter.

METHODS FOR MONITORING URETERAL MUSCLE ACTIVITY

In Vitro Methods

Isolated animal and human tissue segments have proven to be useful in the investigation of ureteral physiology. However it is now known that the animal from which the ureter is obtained may affect the results. The most commonly used animal tissues are from pig, dog, guinea pig, rat, rabbit and sheep. Comparative studies have shown pig and sheep ureters to be more histologically similar to human ureter as compared with canine ureter [9]. In view of the differences seen between species, human tissue is now preferred.

Human ureteral tissue can be obtained at the time of open nephrectomy or cystectomy provided the ureter is patent, functional and disease free prior to removal. The tissue must be placed into a physiological buffered solution maintained at 4°C on removal until experimentation to maintain function. Ureteral specimens may be suspended as horizontal rings or longitudinal strips. They require continuous irrigation with a physiological buffered solution aerated with 95% oxygen/5% carbon dioxide mixture and maintained at 37°C. The ureteral strips are prepared, suspended within water baths and attached to a force transducer to allow changes in tension to be recorded. A resting tension is applied to the ureteral segment at the outset and the tissues are allowed to equilibrate within the buffer solution.

Spontaneous contractions are not seen in all human ureteral specimens. When present, the contraction frequency in vitro ranges from 1-10 contractions per minute, with the majority of studies reporting rates of 1-2 per minute [10-13].

Two general types of mechanical activity can be distinguished: phasic and tonic contractions. Phasic activity is characterized by regular rhythmic changes in tension,
which can be modified both in amplitude and frequency. In its purest form the baseline is always reached between two contractions, for example, spontaneous contractions. In contrast, tonic contractions reach a maximal tension, which is maintained over time under constant conditions.

Drug responses can be measured either by recording the effect on spontaneous contraction rates or by stimulating phasic or tonic contractions and recording the effect the drug has on tension generation. To test the drug response, the drug is added to the physiological solution at various concentrations. These solutions can then be applied to the ureter following equilibration to record the effect on spontaneous contraction frequency and amplitude. Alternatively, electrical field stimulation can be used to stimulate individual contractions.

Chemical stimulation can also be used, predominately carbachol (a muscarinic agonist) or potassium-enriched physiological solutions. The response to a pharmacological agent can then be determined by comparing the increase in tone generated by the stimulant with the response when the drug is used in addition to the stimulant. The drug response is expressed as the percentage change in tone as compared with resting levels.

Spontaneous contractions are preferred to prevent interference by artificial stimulation, however these are inconsistently seen.

**In Vivo Methods**

The physiology of the upper urinary tract has been studied in vivo in both animal and human models since the early 1900’s. Many extraluminal and intraluminal methods have been described combining ureteral catheters with strain gauges, strain gauge manometers or electromanometers [14-19], endoluminal ultrasound [20] and laparoscopic ultrasound [21-22]. Ureteral contraction frequency is relatively easy to measure, however contraction pressures are far more difficult as they require intraluminal methods which are far from ideal.

The limitations of the studies to date include:

- Antegrade or retrograde instrumentation of the ureter to site a catheter may disturb normal physiology.
- Extraluminal methods are invasive and require open or laparoscopic surgery to site the sensors; these methods are therefore rarely possible in human subjects.
- Animal studies may not always be representative of human ureteral activity [23].
- The preparation for general anesthesia (nil by mouth) and the anesthetic drugs themselves may affect excretory function [24] and ureteral peristalsis [25].
- Many recordings have been made over short periods of time leading to incorrect assumptions and preventing trends over time to be determined [17-19].

There is a need, therefore, for a method to allow monitoring over longer periods of time in human subjects and, if sited at cystoscopy under general anesthetic, could be left in situ for long enough to allow metabolism and excretion of the anesthetic agents and ureteral activity to recover following the instrumentation.
IN VITRO AND IN VIVO STUDIES TO DETERMINE THE ROLE OF SMOOTH MUSCLE RELAXANT DRUGS IN RENAL COLIC

By understanding ureteral physiology, pharmacological agents can be designed to reduce ureteral tone and control peristalsis. Previous research has suggested that there are many drugs in current use capable of influencing normal ureteral physiology and decreasing peristaltic frequency or tone generation in vitro. The most promising drugs for use in clinical practice to reduce ureteral activity, which are already in use, appear to be non-steroidal anti-inflammatory drugs, calcium channel antagonists and alpha-1-adrenoceptor antagonists.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by non-selective cyclo-oxygenase inhibition, preventing stimulation of smooth muscle contraction by prostanoids (prostaglandins, thromboxanes and prostacyclin). NSAIDs provide excellent analgesia in renal colic. In the laboratory, these drugs appear to reduce ureteral activity and in some cases, ablate all ureteral activity [10,26]. However, despite diclofenac and indomethacin being highly effective in reducing the number of new colic episodes and admissions to hospital, in clinical trials they do not affect the time to stone passage or the stone passage rate in renal colic [27-29].

Calcium Channel Antagonists

Calcium is necessary for the development of action potentials and therefore contraction of the ureter. Calcium channel blockers interfere with the inward displacement of calcium ions through the slow channels of active cell membranes and so would be expected to have an inhibitory effect on ureteral function.

There have been many studies investigating the use of nifedipine in renal colic [30-33]. Unfortunately all four studies have combined the use of nifedipine with a steroid. All four studies have indicated advantages to the use of nifedipine in renal colic. Since all have combined nifedipine with steroid, it is unclear as to the degree of benefit incurred with the use of nifedipine alone. Steroids not only have an anti-inflammatory effect on the ureter and so reduce edema at the level of the stone but they may also cause a degree of ureteral smooth muscle relaxation. All four studies have predominantly involved distal ureteral calculi and so it remains unclear as to whether the beneficial effects apply to stones at all levels or are limited to distal ureteral stones.

Alpha1A-adrenoceptor Antagonists

It may be that stone passage is hindered by the overactive ureter but that more controlled contractions, as opposed to complete ablation of all contractions, are necessary to aid stone passage. Within the sympathetic nervous system, alpha1 adrenergic fibers are excitatory; therefore, by blocking the alpha1-adrenergic receptors, smooth muscle relaxation and a reduction in contraction frequency should occur.
Since the sympathetic nervous system only has a modulating role, pacemaker driven peristalsis should continue.

Tamsulosin is an alpha<sub>1</sub>-adrenoceptor antagonist, which binds selectively and competitively to postsynaptic alpha<sub>1</sub>-receptors, in particular to the subtype alpha<sub>1A</sub>. There are no published studies in the literature demonstrating the effect of tamsulosin on the human ureter in vitro or in vivo. However there are many studies demonstrating the relaxant effects of non-selective alpha-adrenoceptor antagonists, namely phentolamine.

Tamsulosin has been used to promote stone passage in renal colic in many trials, but only in the treatment of distal ureteral calculi. All studies have shown a beneficial effect. These are summarized in a meta-analysis by Hollingsworth et al [34]. However many have been non-randomized, performed without blinding or placebo or in conjunction with other drugs making interpretation of results difficult.

**Direct Comparison between NSAIDs, Calcium Channel Antagonists and Alpha<sub>1A</sub>-adrenoceptor Antagonists**

We have published results from an in vitro study comparing the effects diclofenac, nifedipine and tamsulosin had on human ureteral activity to determine the promoting factor for stone passage [35]. Human ureter obtained at the time of open cystectomy or nephrectomy was used to determine the effect these drugs had on activity in vitro. Thirty-nine patients took part, providing 201 strips. Brading-Sibley tissue baths were used to perform this experiment. A tonic muscle contraction was first stimulated using potassium enriched physiological Kreb’s solution. Each of the three drugs was then applied in solution to each strip in increasing concentrations and the percentage reduction in contraction tone was calculated.

At all drug concentrations, the in vitro relaxant effect of nifedipine and 5-methylurapidil (5-MU, representing tamsulosin) was greater than diclofenac (see Fig. 3). At 10<sup>-5</sup>M concentration, the median reduction in tension generation for proximal and distal ureter seen in response to diclofenac, nifedipine and 5-MU was 18% vs. 5%, 47% vs. 57% and 33% vs. 65% respectively. Nifedipine and 5-MU predominantly affected the distal ureter [35].

In order to determine the effect these drugs had on human ureteral activity in vivo, we used a specially designed ureteral pressure transducer catheter. With REC approval and informed consent, the catheter was inserted into the normal contralateral ureter following ureteroscopy for stone and left in situ for 24 hours. The patient was randomized to receive oral diclofenac, tamsulosin or nifedipine. Ureteral activity was monitored using an ambulatory recorder for one hour prior to ingestion of the drug (Fig. 1) and continued to the time of maximal drug concentration within the body (Tmax). All in vivo studies were performed on the proximal ureter. An example of the results obtained is shown in Table 1 [8].
Diclofenac and nifedipine produced inconsistent ureteral pressure responses but had little effect on contraction frequency. Tamsulosin significantly reduced ureteral contraction pressure but had no effect on contraction frequency.

Nifedipine and 5-MU produced greater ureteral relaxation *in vitro* as compared with diclofenac. Nifedipine and 5-MU predominantly relaxed distal ureter. *In vivo*, varying results were seen for diclofenac and nifedipine; however, even in the proximal ureter, tamsulosin caused a significant reduction in ureteral contraction pressure. Most importantly, peristalsis was maintained despite the use of these drugs.

From this work, promotion of stone passage appears to be directly related to *in vitro* smooth muscle relaxation. *In vivo*, these results suggest that tamsulosin is clinically effective by maintaining ureteral contractions whilst preventing increases in ureteral contraction pressures in response to irritation by a stone. However, it remains extremely difficult to test this theory *in vivo*.
CONCLUSION

Research indicates that drugs which allow continued peristalsis whilst preventing the increased uncoordinated activity seen in renal colic would be the most effective for facilitating spontaneous stone passage. The alpha1A-adrenoceptor antagonists are the most effective drugs to date in both in vitro and in vivo human studies. In order to determine the true clinical effectiveness of alpha1A-adrenoceptor antagonists in renal colic, we have commenced a multicenter, randomized, double blind clinical trial using tamsulosin versus placebo for patients with confirmed ureteral stones. This study aims to recruit 250 patients and will determine the beneficial effect of tamsulosin for both proximal and distal ureteral stones.

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REFERENCES