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Review Article

Tamsulosin Versus Silodosin for The Treatment of Distal Ureteric Stones: A Review

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ABSTRACT

Stones refer to solid mineral and crystalline deposits that form within the urinary system, including the kidneys, ureters, bladder, and urethra. These stones are composed of various minerals and can range in size from small particles to larger, more obstructive structures. These guidelines serve as a valuable resource for healthcare professionals in understanding the epidemiology and recommended management strategies for distal ureteric stones. The main etiological factors are Urinary tract infections, Certain medical conditions, Anatomical factors. Signs and symptoms are Flank pain , Hematuria Dysuria,Urinary urgency, frequency, Nausea and vomiting. Diagnostic tests like Non-contrast Computed Tomography (CT), Intravenous Pyelogram (IVP), Ultrasonography (US), Retrograde Ureterography, Management like Extracorporeal Shock Wave Lithotripsy (ESWL), Ureteroscopy, Percutaneous Nephrolithotomy (PCNL), Alpha-blockers, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Analgesics. Pharmacodynamics of tamsulosin is the relaxation of smooth muscle in the ureter, which is achieved through the blockade of alpha-1 adrenergic receptors. Tamsulosin is well absorbed, protein binding of approximately 99%, eliminated mainly via hepatic metabolism, with less than 1% of the dose excreted unchanged in the urine. Adverse effects of tamsulosin Intraoperative floppy iris syndrome (IFIS) , Abnormal ejaculation and retrograde ejaculation, Dizziness and postural hypotension. Pharmacodynamics of silodosin in ureteric stones is believed to involve the relaxation of smooth muscle in the ureter, which promotes stone passage. Silodosin is wellabsorbed, moderate volume of distribution eliminated mainly via hepatic metabolism, with less than 1% of the dose excreted unchanged in the urine.

INTRODUCTION

Stones refer to solid mineral and crystalline deposits that form within the urinary system, including the kidneys, ureters, bladder, and urethra. These stones are also known as urinary

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stones, uroliths, or calculi. They can vary in size, ranging from tiny grains to larger, more obstructive structures. Ureteric stones are solid masses that form in the ureter, the muscular tube connecting the kidneys to the bladder. These stones are composed of various minerals and can range in size from small particles to larger, more obstructive structures (Türk C, 2021). Urinary stones are typically composed of various minerals, with the most common types being calcium oxalate, calcium phosphate, uric acid, and struvite stones. The composition of the stone depends on factors such as urine pH, concentration of minerals, and underlying metabolic abnormalities (Türk C, 2021). The formation of urinary stones occurs when there is an imbalance in the urine composition, leading to the precipitation and aggregation of minerals. Factors that contribute to stone formation include inadequate fluid intake, high dietary intake of certain substances (e.g., oxalate-rich foods), urinary tract infections, urinary stasis, and genetic predisposition (Pearle MS, 2014).

DEFINITION: Distal ureteric stones are solid mineral and crystalline deposits that form in the distal portion of the ureter, which is the lower part of the ureter closer to the bladder. These stones can obstruct the flow of urine from the kidney to the bladder, leading to symptoms and potential complications (Preminger GM T. H., 2007).

EPIDEMIOLOGY

The prevalence of distal ureteric stones varies depending on the population studied. In a study conducted in the United States, the overall prevalence of kidney stones was reported to be around 8.8%, with distal ureteric stones accounting for a significant portion of these cases (Scales CD Jr, 2012).

The European Association of Urology (EAU) guidelines on urolithiasis provide comprehensive information on the diagnosis and management of kidney stones, including distal ureteric stones These guidelines serve as a valuable resource for healthcare professionals in understanding the epidemiology and recommended management strategies for distal ureteric stones (Türk C, 2020.). The EAU guidelines on diagnosis and conservative management of urolithiasis emphasize the importance of accurate diagnosis and appropriate conservative management options for patients with distal ureteric stones. These guidelines provide evidence-based recommendations that can assist healthcare professionals in optimizing patient care (Türk C N. A., 2021;). Distal ureteric stones in pregnant women are a specific concern, and their epidemiology and management have been reviewed in the literature. Understanding the unique considerations and challenges associated with distal ureteric stones in pregnant women is crucial for providing appropriate care during pregnancy (Yan H, 2018). There have been notable changes in the epidemiological features of urolithiasis, including distal ureteric stones, over the past few decades in the United States. These changes may be attributed to various factors, such as dietary and lifestyle changes, as well as advancements in diagnostic techniques (J, 2011;).

ETIOLOGY

1. Urinary tract infections (UTIs) can play a role in the development of distal ureteric stones. The presence of UTIs can lead to inflammation and changes in urinary composition, increasing the risk of stone formation (Türk C P. A., 2016).
2. Certain medical conditions, such as gout or inflammatory bowel disease, have been associated with an increased risk of distal ureteric stone formation.These underlying conditions can contribute to metabolic abnormalities and promote stone development.
3. Anatomical factors, including ureteral strictures or abnormal ureteral anatomy, can

predispose individuals to the formation of distal ureteric stones.These structural abnormalities can impede the normal flow of urine and increase the likelihood of stone formation. Genetic factors may also contribute to the development of distal ureteric stones. Certain genetic disorders, such as cystinuria, primary hyperoxaluria, and Dent disease, are known to increase the risk of stone formation. (Türk C N. A., EAU guidelines on diagnosis and conservative management of urolithiasis., 2021).

SIGNS AND SYMPTOMS

Flank pain: Severe, colicky pain in the flank region is a common symptom. The pain may radiate to the lower abdomen or groin.

Hematuria: Blood in the urine is another frequent symptom of ureteric stones. The urine may appear pink, red, or brown.

Dysuria: Pain or discomfort during urination may be present. This can manifest as a burning sensation or a feeling of urgency.

Urinary urgency and frequency: Increased urgency to urinate and more frequent urination may occur.

Nausea and vomiting: Some individuals with ureteric stones may experience nausea and vomiting, particularly if the stone causes significant pain or obstruction (Stamatelou KK, 2003;.), (Tanaka ST, 2021;).

PATHOPHYSIOLOGY

The pathophysiology of ureteric stones involves multiple processes that contribute to their formation and subsequent clinical manifestations. Stone formation occurs due to the precipitation and crystallization of substances, such as calcium, oxalate, uric acid, or cystine, within the urinary tract. Factors that influence stone formation include urine composition, pH, and the presence of inhibitors or promoters of stone formation (Romero V, 2010;).

DIAGNOSTIC TESTS

Diagnostic tests play a crucial role in the evaluation of ureteric stones. Here are some commonly used diagnostic tests for ureteric stones.

Non-contrast Computed Tomography (CT): Non-contrast CT is considered the gold standard imaging modality for diagnosing ureteric stones due to its high sensitivity and specificity. It allows for accurate identification of stone location, size, and obstruction. Additionally, it can provide information on stone composition and the presence of associated complications.

Intravenous Pyelogram (IVP): IVP involves injecting a contrast agent intravenously and taking X-ray images at specific time intervals to visualize the urinary tract. It can provide information on the presence of obstruction, stone size, and location. However, due to its invasiveness and the availability of more advanced imaging techniques, IVP is less commonly used nowadays (Moore CL, 2019;).

Ultrasonography (US): Ultrasonography is a widely available, non-invasive imaging technique that can be used as an initial diagnostic tool for suspected ureteric stones, especially in pregnant women or individuals with contraindications to CT. It is less sensitive than CT but can detect hydronephrosis and provide information on stone size and location (Smith-Bindman R, 2014;).

Retrograde Ureterography: Retrograde ureterography involves the injection of a contrast agent directly into the ureter, typically performed during cystoscopy. It allows for direct visualization of the ureter and identification of the stone's location and size. Retrograde ureterography is commonly used when other imaging modalities are inconclusive or when additional information is needed for surgical planning (Fwu CW, 2013;).

MANAGEMENT:

Observation and Supportive Care: Observation and supportive care may be appropriate for small

distal ureteric stones (<5 mm) that are asymptomatic or causing mild symptoms. This approach involves pain management, hydration, and the use of alpha-blockers to facilitate stone passage.

Extracorporeal Shock Wave Lithotripsy (ESWL): ESWL is a non-invasive procedure that uses shock waves to break up the stone into smaller fragments, facilitating their passage. It is generally suitable for stones less than 2 cm in diameter and is commonly used for distal ureteric stones.

Ureteroscopy: Ureteroscopy involves the use of a thin, flexible instrument (ureteroscope) to directly visualize and access the ureter and stone. It allows for the fragmentation and removal of the stone or placement of a stent to relieve obstruction. Ureteroscopy is commonly used for distal ureteric stones, particularly larger stones (>1 cm) or stones that are causing significant symptoms

Percutaneous Nephrolithotomy (PCNL): PCNL is a minimally invasive surgical procedure used for larger or complex distal ureteric stones that cannot be effectively treated with other methods. It involves accessing the urinary tract through a small incision in the back and removing or fragmenting the stone using specialized instruments (Türk C S. A., 2021).

Alpha-blockers: Alpha-blockers, such as tamsulosin and terazosin, are medications that help relax the smooth muscle in the ureter, facilitating the passage of distal ureteric stones. They can help improve stone clearance rates and reduce the time to stone expulsion (Furyk JS, 2016;).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs, such as ibuprofen or diclofenac, are commonly used to provide pain relief in patients with distal ureteric stones. They work by reducing inflammation and relieving associated symptoms (Holdgate A, 2015;).

Analgesics: Analgesics, such as opioids (e.g., morphine, oxycodone) or non-opioid pain relievers (e.g., acetaminophen), may be prescribed to manage severe pain associated with distal ureteric stones. These medications help alleviate pain and discomfort during stone passage (Goldfarb DS, 2014;).

PHARMACODYNAMICS OF TAMSULOSIN:

The proposed mechanism is the relaxation of smooth muscle in the ureter, which is achieved through the blockade of alpha-1 adrenergic receptors. This relaxation can help facilitate stone passage by reducing ureteric spasm and promoting the dilation of the ureter (Hollingsworth JM, 2016;).

PHARMACOKINETICS OF TAMSULOSIN:

Absorption: Tamsulosin is well absorbed from the gastrointestinal tract after oral administration. The absorption is relatively rapid, with peak plasma concentrations reached within about 4 to 6 hours after oral dosing.

Distribution: Tamsulosin has a high protein binding of approximately 99%, primarily to alpha-1 acid glycoprotein. It has a large volume of distribution, indicating extensive tissue distribution.

Metabolism: Tamsulosin undergoes extensive hepatic metabolism through the cytochrome P450 enzyme system, primarily CYP3A4. The major metabolites formed are the pharmacologically inactive N-dealkylated metabolites.

Elimination: Tamsulosin and its metabolites are primarily eliminated via hepatic metabolism and subsequent biliary excretion. Only a small portion of the drug is excreted unchanged in the urine. The elimination half-life of tamsulosin is approximately 9 to 13 hours, which may be prolonged in patients with hepatic impairment (Salem EA, 1999;).

ADVERSE EFFECTS OF TAMSULOSIN:

1. **Intraoperative floppy iris syndrome (IFIS):** Tamsulosin has been associated with the development of intraoperative floppy iris syndrome (IFIS) during cataract surgery. The

use of tamsulosin has been identified as a risk factor for IFIS (Chang DF, 2005;).

2. **Abnormal ejaculation and retrograde ejaculation:** Tamsulosin can cause adverse effects related to ejaculation. These may include abnormal ejaculation, such as decreased semen volume or absence of semen, as well as retrograde ejaculation where semen is redirected into the bladder instead of being expelled through the penis (Lepor H, 1997;).
3. **Dizziness and postural hypotension:** Tamsulosin, like other alpha-1 adrenergic receptor antagonists, can cause dizziness and postural hypotension. These adverse effects may lead to lightheadedness or a sudden drop in blood pressure upon standing up, which can result in fainting or falls (Roehrborn CG, 2003).

PHARMACODYNAMICS OF SILODOSIN:

The mechanism of action (MOA) of silodosin in ureteric stones, are : Silodosin, although primarily indicated for the treatment of benign prostatic hyperplasia (BPH), has been studied for its potential use in facilitating the passage of ureteric stones. While its use in this context is off-label, the MOA of silodosin in ureteric stones is believed to involve the relaxation of smooth muscle in the ureter, which promotes stone passage. Silodosin is a selective alpha-1A adrenoceptor antagonist. By blocking alpha-1A adrenergic receptors in the smooth muscle of the ureter, silodosin inhibits the action of norepinephrine, a neurotransmitter that normally binds to these receptors. This blockade leads to smooth muscle relaxation in the ureter (MC., 2009 Apr;).

Some studies are evaluated the efficacy of silodosin in facilitating the passage of distal ureteral stones. The authors found that silodosin treatment resulted in a higher stone expulsion rate compared to placebo, suggesting its potential in aiding the passage of ureteric stones. This effect was attributed to the smooth muscle relaxant properties of silodosin (Dellabella M, 2010 Mar;). Furthermore, a systematic review and meta-analysis conducted and assessed the efficacy of silodosin in medical expulsive therapy for ureteral stones. The analysis demonstrated that silodosin significantly increased the stone expulsion rate and reduced the time to stone expulsion. These findings further support the notion that silodosin's smooth muscle relaxation properties contribute to its potential effectiveness in facilitating ureteric stone passage (Xiong T, 2017).

PHARMACOKINETICS OF SILODOSIN:

Absorption: Silodosin is well-absorbed after oral administration, with a bioavailability of approximately 32%. It reaches peak plasma concentrations within 2-4 hours after dosing (Abrams P, 2011;).

Distribution: Silodosin has a moderate volume of distribution and is highly bound to plasma proteins, primarily to albumin. It crosses the blood-brain barrier poorly due to its lipophilic nature (Takasu T, 2009).

Metabolism: Silodosin undergoes extensive metabolism in the liver, primarily via the cytochrome P450 (CYP) enzyme system, specifically CYP3A4 and CYP2D6. The major metabolites formed are pharmacologically inactive (Hänseler E, 2012;).

Elimination: Silodosin is eliminated mainly via hepatic metabolism, with less than 1% of the dose excreted unchanged in the urine. The elimination half-life of silodosin is approximately 13 hours (Yamaguchi O, 2012;).

Role of Silodosin in Ureteric Stones: Silodosin has been investigated as a potential medical expulsive therapy (MET) for ureteric stones, aiming to facilitate stone passage by relaxing the smooth muscles in the ureter (Porpiglia F, 2010;), (Seitz C, 2013;).

ADVERSE EFFECTS OF SILODOSIN:

Retrograde ejaculation: Retrograde ejaculation, characterized by the entry of semen into the bladder instead of being expelled through the urethra during ejaculation, is a well-known adverse effect of silodosin due to its mechanism of action on the smooth muscle in the prostate and bladder neck (Gacci M, 2012;). Orthostatic hypotension: Silodosin can cause a decrease in blood pressure, especially upon standing up from a sitting or lying position, resulting in dizziness or fainting. Patients should be cautious when transitioning between positions (McVary KT, 2007;). Nasal congestion and rhinitis: Some individuals may experience nasal congestion or rhinitis (inflammation of the nasal mucosa) as a side effect of silodosin (Roehrborn CG e. a., 2002;). Headache: Headache is a commonly reported adverse effect associated with silodosin use, although its incidence is generally low. Gastrointestinal disturbances: Some patients may experience gastrointestinal adverse effects, such as nausea, diarrhea, or abdominal pain, while taking silodosin (Fovargue D, 2010;).

CONCLUSION:

Urinary stones are typically composed of various minerals, with the most common types being calcium oxalate, calcium phosphate, uric acid, and struvite stones. Tamsulosin and Silodosin are both alpha-blocker medications commonly prescribed to help with the passage of distal ureteric stones, particularly in cases where the stones are smaller in size and can be managed conservatively. Both medications work by relaxing the smooth muscle in the ureter, which can facilitate the passage of the stone and alleviate associated symptoms. Studies have been conducted to compare the effectiveness of Tamsulosin and Silodosin in promoting stone passage and relieving symptoms. The results of these studies have been mixed, with some trials showing a slight advantage of one medication over the other, while others have found no significant difference between the two drugs. It's important to note that individual responses to medications can vary, and the choice between Tamsulosin and Silodosin may depend on factors such as a patient's medical history, overall health status, and any other medications they may be taking.

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