OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Pharmaceutics**

Exploring Sensitivity and Significance of Tamsulosin as Modified Release in Benign Prostatic Hyperplasia

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DOI: 10.36348/sjmps.2024.v10i03.007 | **Received:** 07.02.2024 | **Accepted:** 12.03.2024 | **Published:** 14.03.2024

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Abstract

This abstract outline the use of Tamsulosin, a selective α (1A and 1D)-adrenoreceptor blocker, to treat benign prostatic hyperplasia (BPH). The study's background highlights the most prevalent symptoms and prevalence of BPH in elderly men. The research objective and goal are to better understand the mechanism of action, pharmacokinetics, dose, clinical efficacy, safety, and tolerance of Tamsulosin, particularly in its modified release (MR) version. Considering evidence-based medicines have recently been made available, the treatment approach for current cases of benign prostatic hyperplasia has evolved. Considerations including therapeutic benefits, potential for morbidity, likely long-term effectiveness, and expenses must be made before selecting a therapy to relieve symptoms. When individuals with benign prostatic hyperplasia report with symptoms related to the lower urinary tract, the main treatment option is α1-adrenergic receptor antagonists. The technique includes a review of the literature on Tamsulosin's development, discovery, and approval, as well as its pharmacodynamics and pharmacokinetics. The findings show that Tamsulosin MR is successful in treating BPH, with a preference for the 0.4mg once-daily dose.

Keywords: Tamsulosin, Benign prostatic hyperplasia, modified release, α-1 adrenoreceptors antagonist.

INTRODUCTION

Benign prostatic hyperplasia also termed as enlarged prostate is a non- malignant medical condition due to which urine flow is blocked in males causing difficulty in urination. Urine flow obstruction results from the prostate pressing against the bladder and urethra due to this hypertrophy. This issue is more common in older men. [1]. Common symptoms includes: frequent urination at night, urinary retention, incontinence, pain with urine or blood during urination, and weak urine stream [2]. To treat this condition, α-1 adrenoreceptor blockers are mostly used.

Tamsulosin is used effectively in the treatment of benign prostatic hyperplasia (lower urinary tract symptoms) as a modified release drug. Tamsulosin is a selective α (1A and 1D) adrenoreceptor blocker. Prostatic gland, prostatic capsule, prostatic urethra, and bladder are the primary locations for α (1)-receptors. Patients with benign prostatic hyperplasia (BPH) report better maximal urine flow and a reduction in lower urinary tract symptoms (LUTS) when their smooth muscles in the prostate and bladder relax [3]. Tamsulosin has shown to be an effective therapy for BPH. Compared to α1B- receptors, it exhibits a 20–38-fold higher affinity for α1Aadrenergic receptors. The absence of interaction between tamsulosin and antihypertensives and its mild cardiovascular adverse effects are thought to be caused by this selectivity of α1Asubtype adrenergic receptors. It was the first medication created especially to treat BPH-related LUTS alone [4].

Discovery and Approval

Tamsulosin is marketed under the brand name Flomax. In 1996, tamsulosin was initially made available for commercialization under the brand name Flomax. October 2009 marked the expiration of the US patent [5]. Generics were authorized by the U.S. Food and Drug Administration (FDA) in March 2010 [6]. In the UK, tamsulosin was sold over-the-counter in 2010 [7].

It is marketed under license by a number of companies, most notably those of Boehringer Ingelheim

and CSL. Tamsulosin hydrochloride extended-release capsules are sold under various brand names such as Urimax 0.4 (India), Tamlocept 0.4 (India), Flomax, Mecir LP (France), Urimax, and Pamsvax. Even though generic, unmodified-release capsules are still approved and marketed in many countries (like Canada). It is marketed as Omnic by Astellas Pharma Europe in Egypt, Italy, Russia, and Iceland. Tamsulosin is primarily produced by Synthon BV in the Netherlands. In Bangladesh, tamsulosin hydrochloride is sold under the brand names Tamisol MR, Prostanil MR, Uromax, and Tamsin [8-11].

Modified Release of Tamsulosin

In order to accomplish particular therapeutic goals that are not possible with conventional immediate release dosage forms when delivered in the same way, modified release dosage forms are formulations that control the rate and/or site of release of the active component.

A drug that is initially made available to the body in a quantity that is sufficient to produce the desired pharmacological response as quickly as is consistent with the drug's properties and that allows for the maintenance of activity at the initial level for a desired number of hours is known as a prolonged or sustained release product [19]. Compared to traditional dose forms, prolonged release systems release the active ingredient more gradually. In comparison to traditional dosage forms, they often have a greater dose of the active component and require less frequent administration. Increased safety margin, less severe local or systemic adverse effects, better patient convenience and compliance, and less time spent by staff members dispensing, administering, and monitoring patients are just a few benefits of sustained release formulations. However, they have a few drawbacks, including lower systemic availability, a poor correlation between in vitro and in vivo, and a greater formulation cost [20].

The literature review finds that tamsulosin hydrochloride was developed as a controlled release delivery method, pellets, and oral controlled delivery system [21-24].

Mechanism of action

The adrenoceptors alpha-1A and alpha-1D are blocked by tamsulosin. In the prostate, the alpha-1A subtype accounts for around 70% of alpha-1 adrenoceptors. The prostate's smooth muscle relaxes and urine flow is enhanced when these adrenoceptors are blocked. The detrusor musculature of the bladder relax when alpha-1D adrenoceptors are blocked, preventing storage symptoms. Tamsulosin's specificity concentrates its effects on the intended location while reducing its impact in other places [12].

Pharmacodynamics

With a preference for the α-1A and α-1D subtypes, which are more prevalent in the prostate and submaxillary tissue, tamsulosin is an alpha adrenoceptor blocker.1. The aorta and spleen are the primary locations for the final subtype, alpha-1B.1. Tamsulosin binds to α-1A receptors with a selectivity that is 3.9–38 times greater than that of α-1B and 3–20 times greater than that of α-1D.1. Due to its selectivity, there is less chance of side effects including orthostatic hypotension while yet having a sizable impact on urine flow [12].

Pharmacokinetics

A MR capsule formulation of tamsulosin was developed since an immediate-release formulation shows fast absorption and a rapid rise in plasma concentration upon oral delivery, potentially causing cardiovascular adverse effects [25, 26]. This formulation uses a dual layer coated pellet technique. The pellets contain a medication core and MR properties are provided by the coating around them. The medication is released after being hydrated in the GI tract [28].

Absorption- Patients who are fasting absorb 90% of the oral tamsulosin. For an oral dosage of 0.4 mg, the AUC is 151-199 ng/mL*hr, and for an oral dose of 0.8 mg, it is 440-557 ng/mL*hr. For an oral dosage of 0.4 mg, the highest concentration in the blood is 3.1-5.3 ng/mL; for an oral dose of 0.8 mg, it is 2.5-3.6 ng/mL. Tamsulosin maximizes plasma concentration between 40–70% and enhances bioavailability by 30% when taken with food, but it also lengthens the period to the optimal concentration from 4 to 7 hours [13, 14].

Volume of Distribution- 16L after intravenous administration.

Protein binding: 94%-99% protein bound, mostly to α-1-acid glycoprotein.

Metabolism: Cytochrome P450 (CYP) 3A4 and 2D6 metabolize tamsulosin mostly in the liver, with some additional CYPs metabolizing it as well. CYP2D6 is in charge of hydroxylating tamsulosin to the M-3 metabolite and demethylating tamsulosin to the M-4 metabolite, whereas CYP3A4 is in charge of de-ethylating tamsulosin to the M-1 metabolite and oxidative deamination to the AM-1 metabolite. Furthermore, an unidentified enzyme may hydroxylate tamsulosin at another location to produce the M-2 metabolite. Before being excreted, the M-1 and M-3 metabolites can undergo sulfate conjugation to generate additional metabolites. The M-1, M-2, M-3, and M-4 metabolites can also be glucuronidated [12-14].

Route of Elimination: According to research, 97% of an oral dose is recovered within 168 hours, with 76% of it appearing in the urine and 21% in the faeces. Tamsulosin that has not been digested excretes 8.7% of the dosage.

Half-life: In patients who are fasting, the half-life is 14.9±3.9 hours. In healthy subjects, the elimination half-life is 5-7 hours while the apparent half-life is 9–13 hours. The apparent halflife of tamsulosin in patients who need it is 14–15 hours.

Dosage and Clinical efficacy

A European Phase II trial comparing dosages of 0.2, 0.4, and 0.6 mg once-daily [29] and two US Phase III studies comparing 0.4 and 0.8 mg once-daily [30, 31] examined the dosedependency of tamsulosin MR's clinical effects. Studies show that 0.4 mg once-daily is most beneficial for the majority of people. Therefore, this is the sole registered dose in European countries. Doses can be increased to 0.8 mg once daily in the US, however 0.2 mg once daily is suggested in Japan and other Asian nations [31].

Normal adult dose for Benign prostatic hyperplasia is 0.4mg once per day which can be increase to 0.8mg for the patients doesn't respond to the lower dose after administering for a particular period of time. But 0.4mg dose is the optimal dose as it has minimised side effects when compared to the 0.8mg [31].

Dosage of tamsulosin is formulated and prescribed as low dose to prevent excessive accumulation and maintain safe bloodstream levels. Also, Tamsulosin can produce an abrupt drop in blood pressure, therefore starting with a lower dose can help lessen the risk of dizziness or fainting during first treatment or following dose adjustments.

Side effects

Common side effects involves cough, fever, chill, lower back pain, painful and difficult urination. Chest pain can also be observed sometimes. In rare cases, it can cause dizziness, faintiness, spinning sensation, prolonged painful erection of penis.

Safety profile of tamsulosin in women and children

Four studies explicitly included women, with an average age ranging from 7.3 to 76.8 years. Women commonly experienced side effects (AEs) such as abdominal pain, asthenia, constipation, dizziness, dry mouth, drowsiness, dyspepsia, headache, incontinence, nasal congestion, nausea, orthostatic hypotension, and somnolence. In this group treated with tamsulosin for varied illnesses and symptoms, there were no unexpected adverse events (AEs) [39].

Three studies involved children. The safety profile in children found to be consistent with that in males suffering from lower urinary tract symptoms caused by BPH. Patients quit tamsulosin largely because of adverse events or insufficient response [39].

Safety and tolerance

Tamsulosin MR's safety and tolerability have been evaluated in multiple randomized controlled trials, including one Phase II [29], two European Phase III [32], two US Phase III [30, 31], and several more. Open-label post marketing surveillance studies have evaluated the tolerability of tamsulosin MR in subgroups of patients, including those with comorbidities and multiple medicines. Clinical pharmacology studies were conducted on a small number of subjects to better understand the tolerability of tamsulosin. These investigations focused on adverse effects, including BP-lowering and abnormal ejaculation.

Comparitive studies with other α-1- blockers

Tamsulosin 0.4 mg once-daily had similar adverse event rates to alfuzosin 2.5 mg three times daily [33], extended-release alfuzosin 10-15 mg once-daily [34], terazosin 5 mg once-daily after titration [35], and a small study with tamsulosin 0.4-0.8 mg compared to doxazosin 4-8 mg [36]. In contrast, a study comparing 0.2 mg tamsulosin to terazosin 1-5 mg in a Korean population [37] and terazosin 2 mg in Chinese patients [38] found that tamsulosin had a reduced incidence of adverse effects.

Since the introduction of α1-AR antagonists for hypertension treatment, clinical trials have focused on side effects associated to blood pressure lowering. Tamsulosin did not significantly lower systolic or diastolic blood pressure in placebo-controlled trials conducted in Europe and the United States [30-32].

Since α1-adrenereceptor antagonists were first introduced to treat hypertension, clinical trials have explicitly addressed side effects connected to reducing blood pressure. Tamsulosin did not significantly lower systolic or diastolic blood pressure in placebo-controlled trials conducted in Europe and the United States [30-32]. Tamsulosin MR 0.4 mg treatment did not significantly reduce symptomatic orthostatic hypotension compared to placebo [30-32]. One study identified a minor but statistically significant difference in the incidence of orthostatic hypotension with the tamsulosin 0.8-mg dose, while another US experiment did not [30, 31].

SUMMARY AND CONCLUSION

Males with benign prostatic hyperplasia, commonly referred to as an enlarged prostate, have a blockage in the flow of urine, making it difficult for them to urinate. Urinary retention, incontinence, pain, weak urine stream, and frequent urination are common symptoms. BPH is treated with tamsulosin, a selective α-1 adrenoreceptor blocker with a 20–38-fold higher affinity for α1A-adrenergic receptors. Its selectivity is thought to be the cause of its mild adverse effects on the cardiovascular system. Tamsulosin, initially marketed under the brand name Flomax, was authorized for generics by the FDA in 2010. It is marketed under license by Boehringer Ingelheim and CSL, and extended-release capsules are sold under various names. In some countries, generic, unmodified-release capsules are still available. Tamsulosin is primarily produced by Synthon

BV in the Netherlands. To accomplish particular therapeutic objectives, modified release dosage forms regulate the rate and/or site of active component release. Products with prolonged or sustained release release the active ingredient more gradually, in larger doses, and with fewer administration intervals. They provide a greater safety margin, fewer side effects, improved patient convenience, and reduced patient care time. They do, however, have disadvantages such as poorer in vitro and in vivo correlation, lower systemic availability, and higher formulation costs. Tamsulosin is an alpha adrenoceptor blocker that relaxes the prostate's smooth muscle and enhances urine flow. It binds to α-1A and α-1D receptors with selectivity 3.9-38 times greater than α-1B and 3-20 times greater than α1D, reducing the risk of side effects like orthostatic hypotension. A MR capsule formulation was developed to address potential cardiovascular adverse effects. Tamsulosin is absorbed 90% of the time, with an AUC of 151-199 ng/mL*hr for oral dosages of 0.4 mg and 440-557 ng/mL*hr for 0.8 mg. It maximizes plasma concentration and enhances bioavailability by 30% when taken with food. Tamsulosin is metabolized by CYP 3A4 and 2D6 in the liver, with some additional CYPs also involved. Research shows 97% of an oral dose is recovered within 168 hours, with 76% appearing in urine and 21% in faeces. The apparent half-life of tamsulosin is 14-15 hours in fasting patients. Tamsulosin MR is a medication used to treat benign prostatic hyperplasia. It is prescribed as a low dose to prevent excessive accumulation and maintain safe bloodstream levels. Common side effects include cough, fever, chill, lower back pain, painful urination, chest pain, and dizziness. Tamsulosin's safety and tolerability have been evaluated in multiple randomized controlled trials, with patients often stopping due to adverse events or insufficient response.

Tamsulosin, a α-1-blocker, has similar adverse event rates to other α-1-blockers, but has a reduced incidence of adverse effects. Clinical trials have focused on side effects related to blood pressure lowering, but tamsulosin does not significantly lower systolic or diastolic blood pressure.

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