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An Overview on Silodosin and Doxazosin in Treatment of Benign Prostatic Hyperplasia

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Abstract

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are highly prevalent in older men. Medical therapy is the first-line treatment for LUTS associated with BPH. Mainstays in the treatment of male LUTS and clinical BPH are the α1-adrenergic receptor antagonists. Silodosin is a new α1-adrenergic receptor antagonist that is selective for the α1A-adrenergic receptor. By antagonizing α1A-adrenergic receptors in the prostate and urethra, silodosin causes smooth muscle relaxation in the lower urinary tract. Since silodosin has greater affinity for the α1A-adrenergic receptor than for the α1B-adrenergic receptor, it minimizes the propensity for blood pressure-related adverse effects caused by α1B-adrenergic receptor blockade. In the clinical studies, patients receiving silodosin at a total daily dose of 8 mg exhibited significant improvements in the International Prostate Symptom Score and maximum urinary flow rate compared with those receiving placebo. Silodosin showed early onset of efficacy for both voiding and storage symptoms. Furthermore, long-term safety of silodosin was also demonstrated. Retrograde or abnormal ejaculation was the most commonly reported adverse effect. The incidence of orthostatic hypotension was low. Doxazosin, a quinazoline derivative, is a highly selective alpha 1-adrenoceptor antagonist that should be an excellent candidate for the pharmacological management of BPH. Doxazosin binds with high affinity to all alpha 1-adrenoceptor subtypes, including the alpha 1c-receptor believed to be the predominant alpha 1-adrenoceptor subtype in the prostate. The long plasma half-life (22 hours) of doxazosin allows for once daily dosing.

Keywords: α1A-adrenoceptor antagonist, silodosin, Doxazosin, benign prostatic hyperplasia, lower urinary tract symptoms.

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1. Introduction

BPH is the most common benign tumor in men, and incidence is age related. BPH is a common urological disease among the older men. According to American Urology Association (AUA), BPH has become the most frequent disease that is closely related to aging man. It is demonstrable in 30–40% of men in the 4th decade of life, and its prevalence increases significantly to 70–80% in those older than 80 years [1]. There is some evidence to suggest prevalence varies by race and ethnicity. Other factors associated with BPH include metabolic syndrome, obesity, increased BMI, dyslipidemia, diabetes, cardiovascular disease, acute and chronic prostatic inflammation, treatment for cardiac disease, antidepressant use, calcium antagonist use, erectile function or dysfunction, high concentrations of prostate -specific antigen, family history of bladder cancer, family history of prostatic disease, whereas an inverse association has observed with increased physical exercise, Alcohol consumption, and smoking [2].

2. Silodosin

Silodosin is a drug used to treat symptomatic BPH and help the passage of ureteric stones. It acts as an alpha-1 adrenergic receptor antagonist. Silodosin, is the most selective antagonist of the α1A-adrenoreceptors (ARs) family. The most common side effect is a reduction in the amount of semen released during ejaculation [3]. During the 1990s, Shibata, et al., [4] discovered that the investigational drug silodosin had approximately 10-fold higher affinity at the cloned human alpha α1-AR than at the cloned rat alpha α1-AR. Subsequently, silodosin developed in the treatment of BPH/LUTS. Silodosin received its first marketing approval in Japan in May 2006, under the brand name Urief, which is marketed by Kissei Pharmaceutical and Daiichi Sankyo. Kissei licensed the US, Canadian, and Mexican rights for silodosin to Watson Pharmaceuticals (now Allergan) in 2004. The FDA and Health Canada approved silodosin under the brand name Rapaflo in October 2008, and January 2011, respectively [5] Silodosin structure (Figure 1).

3. Pharmacology

1-Mechanism of action

It works by blocking receptors called alpha1A adrenoreceptors (α1A-ARs) in the prostate gland, the bladder and the urethra. The α1A-ARs belong to the family of G

protein-coupled receptors. Phospholipase C is activated by the binding of norepinephrine and epinephrine, which results in the production of second messengers such as inositol triphosphate and diacylglycerol. Finally, they cause smooth muscle contraction and intracellular calcium level rises. Blocking α1A-ARs causes prostatic and urethral smooth muscle to relax, which may alleviate voiding symptoms. Silodosin, however, also acts on symptoms of bladder over activity & storage by targeting afferent nerves in bladder [7].

2-Pharmacokinetics

The absolute bioavailability after oral intake is 32%. Food has little effect on the drug bioavailability. The drug has a volume distribution of 49.5 L and is ≈97% plasma proteins bound. Its main metabolite is silodosin glucuronide (liver glucuronidation) which inhibits the α_{1A} receptor with 1/8 of the affinity of the parent substance. 91% of the glucuronide are bound to plasma proteins. Silodosin is almost completely excreted in the form of metabolites; 33.5% via the urine and 54.9% via feces. Biological half-life (t1/2) of approximately 13 hours and that of glucuronide is 18 hours or 24 hours [8].

- ***Indications***

1) BPH and LUTS

LUTS are very common disorders affecting both sexes adversely affecting the QOL. Silodosin is indicated for treatment of the signs and symptoms of BPH and LUTS [3].

2) Silodosin monotherapy

A pooled analysis of 2 RCTs revealed significant and rapid recovery in patients treated with silodosin in terms of IPSS score and Q max compared with placebo. Within 3 to4 days of commencing treatment, patients receiving silodosin achieved significant improvement in total IPSS score as well as irritative and obstructive sub scores. Significant improvement in urinary flow rate occurred at 2–6 hours. The proportion of orthostatic hypotension was similar in both groups [9].

3) Silodosin Combination Therapy

The co-administration of silodosin with sildenafil or tadalafil was clinically significant in the treatment of BPH in healthy men with no history of symptomatic hypertension. A total of 103 patients with LUTS /BPH and IPSS >8 after ≥4 weeks of silodosin treatment were further treated with silodosin 4 mg twice daily (BID) or silodosin 4 mg BID plus tadalafil 5 mg once daily (QD). After 8 weeks of treatment, the analysis revealed that the IPSS ,OAB symptom score and Qmax scores showed a greater improvement in the silodosin plus tadalafil combination therapy than monotherapy group. Further subgroup analysis in patients with overactive bladder (n= 55) also showed significantly greater improvements in the IPSS storage symptom sub score, IPSS urgency sub score, and OABSS urgency sub score in the combination therapy than mono-therapy group [10].

4) Nocturia in BPH/LUTS

Among patients with BPH, approximately 85% experience two or more episodes per night. Several studies have shown the efficacy of silodosin in reducing nocturia. Silodosin reduced the incidence of nocturia in patients with BPH after 12weeks of treatment. There were also improvements in the IPSS and QOLtotal score [11].

5) Chronic Prostatitis/Chronic Pelvic Pain Syndrome

About 35–50% of men have symptoms suggesting prostatitis during their life time. The EAU guidelines recommend the use of α-blockers for patients with prostate pain syndrome [12].

6) Premature Ejaculation

Premature ejaculation (PE) is the most common sexual disorder in men and affects 30% of men, though it is not fatal. It is assumed that contractile dysfunction of seminal vesicle and spermatic duct is major cause of onset of ejaculation. Acomparison of α1-blockers in patients with PE demonstrated that the success rate of treatment was silodosin, 69.6% with tamsulosin, 45.5% with alfuzosin, 52.4% with terazosin and 66% with doxazosin. There were statistical improvements in intra vaginal ejaculation latency time, QOL scores and decrease in premature ejaculation profile (PEP) in patients treated with silodosin compared with other group [13].

7) Ureteral Calculi

Medical expulsion therapy (MET) with α1-blockers is recommended for the treatment of ureteral stones >5 mm as per the latest EAU guidelines. Kumar et al demonstrated that patients treated with silodosin had significantly higher stone expulsion rate compared with tamsulosin and tadalafil. The mean stone expulsion time was significantly less in silodosin-treated groups Compared with tamsulosin and tadalafil. There was a decrease in the average episodes of colicky pain with silodosin. The analgesic requirements were also significantly less with silodosin than other drugs. Thus, the authors concluded that the use of silodosin increases ureteric stone passage significantly along with better control of pain and lesser analgesic requirement [14].

8) Prostate Cancer Post Brachytherapy-Induced Progression

In patients with LUTS who received α1-blockers after 1 year of brachytherapy. The patients administered with tamsulosin and naftopidil reported a worsening of health condition than those receiving silodosin. These findings suggest that silodosin may have an added advantage in management of LUTS after125 I prostate brachytherapy compared with other α1-blockers [15].

4. Interactions

Combining silodosin with strong inhibitors of the liver enzyme CYP3A4, such as ketoconazole, significantly increases its concentrations in the blood plasma and its area under the curve (AUC). Less potent CYP3A4 inhibitors such as diltiazem have a less pronounced effect on this parameters, which is not considered clinically significant., alcohol dehydrogenases, and aldehyde dehydrogenases, as well as the transporter P-glycoprotein, may also influence silodosin concentrations in body. Digoxin, which is transported by P-glycoprotein, not affected by silodosin [8]. Co-administration of digoxin with silodosin is safe and no dose adjustment required. Similarly, administration of antihypertensive drugs with silodosin causes no clinically significant orthostatic effects and is considered safe. Higher but insignificant orthostatic hypotension was observed on concomitant administration of tadalafil with silodosin in healthy men. The co-administration of sildenafil or both tadalafil and silodosin

may be an appropriate treatment for patients who experience erectile dysfunction. Therefore, its concomitant treatment with PDE5 inhibitors needs to be closely monitored, particular in patients with symptomatic hypotension. No relevant interactions with antihypertensive drugs or with PDE5 inhibitors have been found in studies; although combination with other α_1-antagonists is not well studied [3].

5. Side effects

- Anejaculation is the main drawback of silodosin which faces many patients (Specially, sexually active men) to stop silodosin loss of seminal emission. This seems to be caused by silodosin's high selectivity for α_{1A} receptors responsible for the contraction of ejaculatory duct [8].
- Ophthalmologic: Patients taking silodosin are prone to a complication known as floppy iris syndrome during cataract surgery. The manifestations of floppy iris syndrome are pupil constriction, fluttering, and billowing of the iris stroma with a propensity of the iris to prolapse during cataract surgery. Adverse outcomes of the surgery are greatly reduced by the surgeon's prior knowledge of the patient's history with this drug, and thus having the option of alternative techniques [16].

Other common adverse effects (in more than 1% of patients) are dizziness, orthostatic hypotension, diarrhea, and clogged nose. Less common (0.1–1%) are tachycardia (fast heartbeat), dry mouth, nausea, skin reactions, and erectile dysfunction. Hypersensitivity reactions occur in less than 0.01% of patients. There have reports about intraoperative floppy iris syndrome during cataract extractions. These side effects are similar to those of other α_1 antagonists [17].

6. Dosage and administration

The dose of silodosin recommended by both the FDA and EMA is 8 mg once a day [18].

7. Doxazosin

Doxazosin, sold under the brand names Cardura among others, is a medication used to treat symptoms of benign prostatic hyperplasia (enlarged prostate) and hypertension (high blood pressure). For high blood pressure, it is a less preferred option [3]. It is a α_1-selective adrenergic blocker in the quinazoline class of compounds.

8. History

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study stopped its arm of trial looking at alpha blockers, because doxazosin was less effective than a simple diuretic, and because patients on doxazosin had a 25% higher rate of cardiovascular disease and twice rate of congestive heart failure as patients on diuretics. Pfizer, aware of results before publication, launched a marketing campaign in early 2000, and sales largely unaffected, despite dangers highlighted by study [19]. Doxazosin was patented in 1977 and came into medical use in 1988 fig 2. It is available as a generic medication. In 2020, it was 209th most commonly prescribed medication in the United States, with more than 2 million prescriptions [20].

9. Pharmacology

1-Mechanism of action Doxazosin

Doxazosin is a quinazoline derivative that acts as a competitive alpha1-antagonist at the post-synaptic receptor.

- In Hypertension

Selectively inhibits postsynaptic alpha-1 receptors on vascular smooth muscle by nonselectively blocking the alpha-1a, alpha-1b, and alpha-1d subtypes, This action on blood vessels decreases systemic peripheral vascular resistance, reducing blood pressure, exerting minimal effects on the heart rate due to its receptor selectivity [22].

- In Benign Prostatic Hyperplasia

Norepinephrine-activated alpha-1 receptors located on the prostate gland and bladder neck normally cause contraction of regional muscular tissue, obstructing urinary flow and contributing to the symptoms of benign prostatic hypertrophy. Symptoms of BPH are caused by mechanical or dynamic obstruction of urine flow through the urethra. Mechanical obstruction is mostly due to prostate size. Dynamic obstruction is associated with an increase in smooth muscle tone at the neck of the bladder and the prostate. Doxazosin works by blocking alpha1 receptors, thereby decreasing urethral resistance and improving urine flow [23].

2-Pharmacokinetics

- ***Absorption***

Doxazosin is rapidly absorbed in the gastrointestinal tract and peak concentrations are achieved within 2-3 hours after administration. The bioavailability is about 60%-70%.The intake of food with doxazosin is not expected to cause clinically significant effects.
Route of administration: oral
Bioavailability: 65%
Protein binding: 98%
Metabolism: liver
Elimination half-life: 22 hours

- ***Indications***

1-Benign Prostatic Hyperplasia

There is also an extended-release formulation of doxazosin. It utilizes the gastrointestinal therapeutic system (GITS). It is FDA-approved for treatment of BPH and LUTS but does not have approval for treatment of hypertension. One benefit of extended-release formulation is stable drug concentrations throughout the day & decreased incidence of orthostatic hypotension/syncope. Doxazosin is indicated to treat symptoms of benign prostatic hypertrophy, which may include urinary frequency, urgency, and the nocturia, among other symptoms. In addition, doxazosin is indicated alone or in combination with various antihypertensive agents for management of hypertension. Off-label uses of the doxazosin include treatment of pediatric hypertension [24]. Doxazosin is considered to be effective in reducing urinary symptom scores and improving peak urinary flow in men with BPH.

2- Hypertension (immediate release only)

The immediate-release formulation can be a second-line agent for the management of hypertension in patients with concomitant BPH [25]. If combination therapy is needed to achieve blood pressure control, the recommendation is to combine it with a diuretic for optimal effectiveness. There is an opinion that doxazosin can be used as mono-therapy for hypertension in a patient with LUTS or BPH; however, the American Urologic Society states that mono-therapy with doxazosin is not optimal and hypertension should have separate management [26].

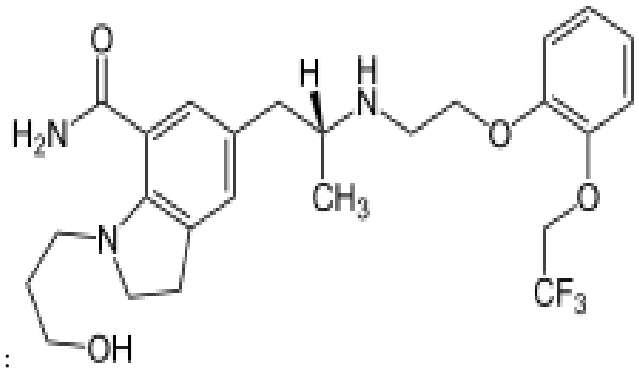

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Figure (1): Structure of silodosin C25H32F3N3O4 [6].

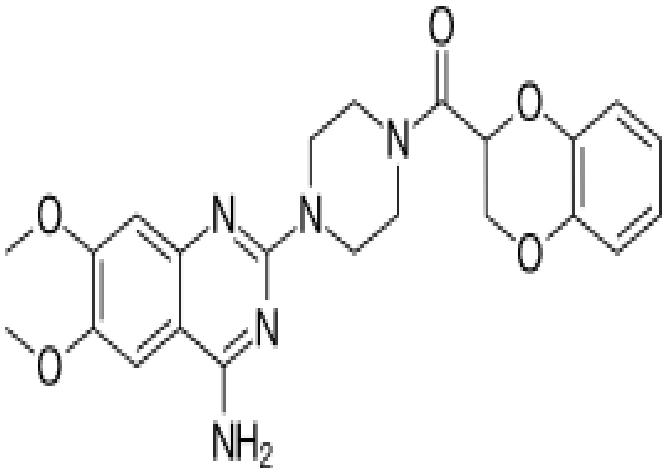

Figure 2: Doxazosin Mesylate Monograph for Professionals" $C_{23}H_{25}N_5O_5$ [21].

Doxazosin usually added to other antihypertensive therapy such as calcium channel antagonists, diuretics, beta-adrenoreceptor antagonists & angiotensin-converting enzyme inhibitors. Like other alpha-1 receptor antagonists, it has role in the perioperative management of the pheochromocytoma [27].

3- Ureteral Stones

The use of alpha1-antagonists, including doxazosin, for the treatment of ureteral calculi is recommended by US and European guidelines. The tamsulosin has the most evidence, but doxazosin has demonstrated efficacy in the expulsion of ureteral calculi less than 10 mm as medical therapy alone or in combination with the shockwave lithotripsy [28].

4- Posttraumatic Stress Disorder (PTSD) Associated Nightmares

Like prazosin, doxazosin has an off-label use for the treatment of PTSD-associated nightmares. There have been numerous small studies and case reports that have shown that doxazosin is effective in treating PTSD-related nightmares [29]. The benefits of doxazosin over the prazosin are a longer half-life and a gastrointestinal therapeutic (GITS) availability system (in the extended-release form), allowing for a more gradual absorption of the drug, thereby reducing the peak to trough concentration ratio. This characteristic permits higher initial doses without risk of hypotension. Extended-release the doxazosin dosing initially starts at the 4 mg daily [30].

10. Dosage and administration

➢ ***Formulations***

- ***Tablet, Oral***
  - 1 mg, 2 mg, 4 mg
- ***Tablet, Oral, as mesylate***
  - 8 mg
- ***Tablet Extended-Release 24 Hour, Oral***
  - 4 mg, 8 mg
  - As with all extended-release formulations, this formulation should not be crushed to pass through a nasogastric, orogastric, or PEG tube.

➢ ***Dosing***

- ***Benign Prostatic Hyperplasia***

- Oral Immediate Release: Initiate at 1 mg once daily. The dose may be titrated up at 1- to 2-week intervals up to a maximum dose of 8 mg once daily. This titration should take place by doubling the dose while monitoring for response and tolerability.
- Oral Extended Release: Initiate at 4 mg once daily. The dose may be titrated up at 3- to 4-week intervals up to a maximum dose of 8 mg once daily. The clinician should titrate by doubling the dose while monitoring for response and tolerability.
- The re-initiation of Therapy: If therapy discontinues for several days, reinitiate therapy at the initial dose and titrate according to the initial dose regimen.

- ***Hypertension***

- Oral Immediate Release: Initiate at 1 mg once daily. The dose may be titrated up to 16 mg once daily; this should occur while monitoring for response and the tolerability.

11. Adverse Effects

11.1. Dose-related Adverse Effects

- Orthostatic hypotension/syncope can occur, especially when combined with another antihypertensive, nitrates, or a PDE-5 inhibitor.
- These adverse effects occur most commonly after initial dose or following re-initiation of therapy; this requires patients to follow a multistep titration regimen to avoid syncope.

11.2. Common Adverse Effects

- Dizziness
- Fatigue
- Headache
- Weakness
- Tachycardia
- Upper respiratory tract infection
- Edema
- Rhinitis
- Dyspnea
- Allergic reactions

In a research study, researchers randomly assigned a total of 3,047 men were randomly assigned to groups of a placebo, doxazosin, or combination therapy with the finasteride. Adverse effects of the orthostatic hypotension and dizziness occurred significantly more in the groups taking the doxazosin and combination treatment compared to placebo group. Rates of adverse effects were reported to peak at year one during a mean duration of 4.5 years of the treatment [31].

12. Contraindications

- Hypersensitivity to doxazosin or other quinazolines.
- Pregnancy: Doxazosin is Pregnancy Category C, meaning that there is no adequate data on the safety of doxazosin in pregnant women.

13. Monitoring

Effective therapy with doxazosin for its various indications requires titration based upon response and tolerability. Open communication between patients and providers is crucial for successful treatment. Patients should receive education on the different common side effects of doxazosin, and provider should conduct a thorough review of other medications for possible interactions, paying particular attention to other antihypertensives, nitrates, and PDE-5 inhibitors.

14. Toxicity

Symptoms of overdose include hypotension, changes in heart rate, and drowsiness. Administer supportive treatment in case of an overdose with doxazosin [32].

15. Interactions

- The metabolism of Doxazosin can be decreased when combined with Abiraterone. Or Verapamil
- The metabolism of Doxazosin can be increased when combined with Acetaminophen
- Acebutolol may increase the orthostatic hypotensive activities of Doxazosin.

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