International Journal of Pharmaceutical research and Applications
Volume 9, Issue 1, Jan.-Feb. 2024, pp:1165-1169 www.ijprajournal.com ISSN: 2456-4494

The Use of Solifenacin Succinate to Treat Overactive Bladder: A Review

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Date of Submission: 04-02-2024 Date of acceptance: 15-02-2024

ABSTRACT: **The common illness known as overactive bladder (OAB) has a negative impact on quality of life. More severe morbidity than that experienced by OAB patients who are continent is conferred when there is urgency incontinence. The main course of action for OAB and urgency incontinence is a combination of behavioral measures and antimuscarinic drug therapy. The optimum antimuscarinic medication should effectively treat OAB symptoms with the fewest possible negative effects.; it should be available as a once-daily sustained release formulation and in dosage strength that allows easy dose titration for the majority of sufferers. Solifenacin succinate was launched in 2005, and has been shown in both short and long term clinical trials to fulfill these requirements. A competitive M3 receptor antagonist with a lengthy half-life (45–68 hours), solifenacin. It comes in two dose strengths: a once-daily 5 or 10 mg pill [1].**

KEYWORDS: Solifenacin, urinary incontinence, overactive bladder,antimuscarinic, pharmacokinetics, detrusor overactivity.

I. INTRODUCTION

The Overactive Bladder Syndrome (OAB) was defined by the International Continence Society (ICS) as: urinary urgency, with or without urge incontinence, generally accompanied by frequency and nocturia. These symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity, but can be due to other forms of urethro–vesical dysfunction. These terms can be used if there is no proven infection or other obvious pathology.

It may affect people of both sexes, prevailing in women, and its incidence increases with age and impacts the quality of life of those who suffer from it. The prevalence in Europe ranges from 12% to 22% in people aged 40 and above . In the NOBLE study, the prevalence found was 16.5% in population aged 18 or older . An epidemiological study performed in Spain recorded a prevalence of symptoms compatible with OAB, in people aged 40 years or above, of 21.5% .

The main symptom of overactive bladder is urinary urgency, caused by involuntary contractions of the detrusor muscle, which takes place when the bladder is filling [2].

Muscarinic-receptor antagonists are the treatment of choice for OAB, as they reduce contractions of the bladder detrusor muscle, resulting in fewer episodes of urgency and incontinence. However, these agents are associated with adverse effects (AEs) such as dry mouth, constipation, drowsiness, and blurred vision, which may limit their clinical effectiveness.

Currently available antimuscarinic agents for the treatment of OAB in the United States include oxybutynin, tolterodine (TOL), trospium chloride, darifenacin, and solifenacin succinate (SOL). SOL is a competitive muscarinic-receptor antagonist that is taken orally once daily. It was approved by the US Food and Drug Administration in late 2004 for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency [3].

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II. Pathology of Overactive Bladder:

The etiology of OAB is multifactorial. Although a large proportion of cases are idiopathic, recognized contributing factors include lower urinary tract pathology (infection, calculi, and stones), neurological conditions (stroke, dementias, multiple sclerosis), systemic conditions (congestive heart failure, diabetes mellitus), functional and behavioral conditions (caffeine and alcohol consumption, mobility), and side effects of medication.

Involuntary detrusor muscle contractions may be associated with OAB. Bladder contraction is mediated by acetylcholine; a peripheral neurotransmitter which acts on muscarinic receptors of the detrusor muscle. Of the five known muscarinic receptor subtypes (M1–M5), M2 and M3 receptors are found in the bladder and M3 receptors appears to be the most important for bladder contractility. The true function of M2 receptors within the bladder is incompletely understood but it is thought that they may oppose sympathetically mediated smooth muscle relaxation or result in the activation of a non-specific cationic channel and activation of potassium channels. It is also thought that in certain disease states such as neurogenic bladder dysfunction the M2 receptors may become more important in mediating detrusor contractions [1].

The micturition reflex is a response to the autonomic spinal cord reflex, facilitated (or inhibited) by the pons of the brain-stem center. Micturition that is not mediated by autonomic stimulation and is accompanied by symptoms of urgency to void is known as urge urinary incontinence. Urge urinary incontinence occurs as a result of idiopathic or neurogenic detrusor muscle overactivity secondary to a neurologic condition (eg, diabetes mellitus) or decreased urethral activity. Additional types of urinary incontinence include stress incontinence and overflow incontinence. Patients may experience mixed incontinence, which includes >1 subtype, or functional incontinence, in which the patient's cognitive perception of the need to void is impaired or physical limitations result in an in ability to reach the toilet in time to void [3].

Regardless of the underlying etiology, the overactive bladder exhibits a characteristic set of signs. These include a sudden increase in intravesical pressure at low volumes during the filling phase, increased spontaneous myogenic activity, fused tetanic contractions, altered responsiveness to stimuli, and characteristic changes in smooth muscle ultrastructure [4].

III. Drug Profile: Solifenacin Succinate

Mechanism of Action: There are five subtypes of muscarinic receptors in the human body (M1–M5). The receptors M2 and M3 play a role in bladder function . Approximately 80% of the bladder muscarinic receptors are of the M2 subtype and 20% are of the M3 subtype. Although M3 receptors are more prevalent than M2 receptor in the healthy human bladder, M3 is the receptor primarily responsible for bladder contraction. Stimulation of M3 receptor causes a direct detrusor smooth muscle contraction through phosphoinositide hydrolysis. Although the practical function of the M2 receptor was not completely clarified, it appears that activation of the M2 receptor may oppose the smoothly mediated by sympathy muscle relaxation, thereby causing bladder contraction. The M2 receptor may play a more important role in bladder contraction than M3 receptor in disease states including neurogenic bladder dysfunction. It is the M3 receptor also present in salivary gland and intestine and, therefore, blockade of the bladder's M3 receptor results in blockade of M3 receptors in these organs. M3 receptor binding in the intestine and salivary glands leads to the most prevalent adverse effects of this agent and of this class of agents: xerostomia (dry mouth) and constipation [5].

Muscarinic receptor	Distribution
M1	Brain (cortex, hippocampus), glands, sympathetic ganglia
M2	Heart, hindbrain, smooth muscle
M3	Smooth muscle, glands, brain
M4	Brain (forebrain, striatum)
M5	Brain (substantia nigra), eye

Table 1: Muscarinic receptor distribution [6]

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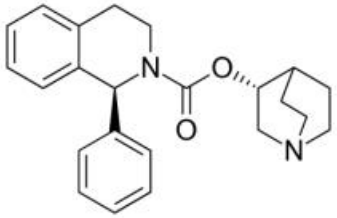
Drug Name	Solifenacin
Structure	
Molecular formula	C23H26N2O2
IUPAC name	(3R)-1-Azabicyclo [2 2 2] oct-3-yl (1S)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate
BCS class	BCS class I
Molecular weight	362.465 g/mol
Melting point	134-136˚C
Nature	Crystalline
Colour	White to pale-yellowish-white crystal or crystalline powder
Odour	Odourless
Taste	Extremely bitter
Category	Muscarinic antagonist recommended for the treatment of overactive bladder with urge to urinate incontinence, urgency, and urinary frequency.
Elimination half- life	45-68 hrs.
Protein binding	98%
Volume of Distribution	600L
Clearance	7-14 L/h
Lambda max	215 nm
Bioavailability	90%
Solubility	It is freely soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide, and methanol.

Table 2: Solifenacin drug profile [7]

IV. Pharmacokinetics

Absorption : Peak plasma levels (Cmax) of solifenacin are attained 3 to 8 hours after oral administration of VESIcare to healthy volunteers, and at steady state, varied from 32.3 to 62.9 ng/mL for the 5 and 10 mg VESIcare tablets, respectively. Solifenacin has a about 90% absolute bioavailability, and plasma concentrations are proportionate to the dose given.

Effect of food : It is possible to administer VESIcare without taking a meal. VESIcare was administered as a single 10 mg dose with food, increasing the Cmax and AUC by 4% and 3%, respectively.

Distribution : Approximately 98% (in vivo) of solifenacin is linked to human plasma proteins, primarily to alpha1-acid glycoprotein. The average steady-state volume of distribution of solifenacin in non-CNS tissues is 600L.

Metabolism: The liver extensively metabolizes solifenacin. Although there are other metabolic pathways, CYP3A4 is the main mechanism for removal. The N-oxidation of the quinuclidin ring and the 4R-hydroxylation of the tetrahydroisoquinoline ring are the two main metabolic pathways for solifenacin. After oral administration, human plasma contained three pharmacologically inactive metabolites (N-glucuronide, the N-oxide, and 4R-hydroxy-N-oxide of solifenacin) and one pharmacologically active metabolite (4R-hydroxy solifenacin), which occurs at low concentrations and is unlikely to significantly contribute to clinical activity.

Excretion : Healthy participants were given 10 mg of 14C-solifenacin succinate, and over the course of 26 days, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces. Less than 15% (as a mean value) of the dosage was found intact as solifenacin in the urine. N-oxide of solifenacin, 4R-hydroxy solifenacin, and 4R-hydroxy-N-oxide of solifenacin were the main metabolites found in urine, whereas 4R-hydroxy solifenacin was found in feces. After chronic dosage, the solifenacin elimination half-life ranges from 45 to 68 hours [8].

Drug Interaction: Oral solifenacin administration leads to the highest plasma amounts (Cma.) between 3 and 8 hours.

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Steady state levels of the drug in plasma range from 32.3 to 62.9 ng/mL for 5-mg and 10-mg doses, respectively [10] . Solifenacin's total bioavailability is 90%. With regular dosing, the half-life of elimination (t 112) of solifenacin is 45 to 68 hours.

Solifenacin is largely metabolized by the P450 (CYP) 3A4 cytochrome enzyme pathway. Therefore, solifenacin concentrations may be impacted by medications that affect this metabolic pathway. There are several prescribed agents that are significant CYP3A4 inhibitors (Table 3). For example, following the injection of 400 mg of ketoconazole together with 10 mg of solifenacin,a potent CYP3A4 inhibitor, the mean Solifenacin's Cmax and AUC rose by 1.5-2.7 times, respectively. Therefore, when combined with therapeutic doses of ketoconazole or other strong CYP3A4 inhibitors, it is advised not to exceed a daily dose of solifenacin of 5 mg.

Solifenacin has no noteworthy effect on either warfarin's pharmacodynamics or pharmacokinetics nor the steady-state pharmacokinetics of digoxin. An interaction of solifenacin with oral contraceptives containing ethinyl estradiol or levonorgestrel was not seen in a clinical trial.

Age has an impact on the pharmacokinetics of solifenacin which is minimal. In elderly patients (65-80 years old), a higher area under the curve (AUC 0_24) and Cmax of solifenacin have been noted, but dose adjustments are not warranted, and no reliable safety or tolerability issues have been associated with solifenacin use compared with younger patients (18-55 years old) [9].

Drug type	Indication	Example
Azole antifungal	Fungal infections	Fluconazole, ketoconazole, voriconazole, itraconazole
Calcium channel blockers	Hypertension	Diltiazem,Verapamil
HIV-I protease inhibitor	HIV, AIDS	Ritonavir,lopinavir/ ritonavir, atazanavir

Table 3: Common Potent Inhibitors of CYP3A4 that Require Caution if Coadministered with Solifenacin

V. Pharmacodynamics

Cardiac Electrophysiology

During the peak plasma solifenacin concentration, the effects of 10 mg and 30 mg solifenacin succinate on the QT interval were assessed in a multi-dose, randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg) experiment. Following sequential administration of the placebo and moxifloxacin, subjects were randomly assigned to one of two treatment groups.

Three more sessions of dosing with solifenacin 10, 20, and 30 mg were completed sequentially by one group (n=51) while concurrently by another group (n=25) completed a sequence of placebo and moxifloxacin. Study subjects were female volunteers aged 19 to 79 years. The solifenacin succinate dose of 30 mg, which is three times the maximum advised dose, was used in this investigation because it produces a solifenacin exposure that is equivalent to that produced by the co-administration of 10 mg of VESIcare with 400 mg of a powerful CYP3A4 inhibitor (such as ketoconazole). Baseline EKG readings and the last QT evaluation (of the 30 mg dose level) were 33 days apart because of the study's sequential dose escalation design.

When compared to placebo, the median difference in heart rate between the 10 and 30 mg doses of solifenacin succinate was 2 and 0 beats/minute, respectively.

Because there was a noticeable period effect on QTc, the parallel placebo control arm was used to investigate the QTc effects rather than the originally intended intra-patient analysis. Representative results are shown in table 4.

Drug/Dose	Fridericia method (using mean difference)
Solifenacin 10 mg	2 (-3,6)
Solifenacin 30 mg	8 (4,13)

Table 4: QTc deviations from baseline at Tmax (compared to placebo) in msec (90%CI)

Given the length of the trial, moxifloxacin was used as a positive control and its impact on the QT interval was assessed over the course of three sessions.

In each of the three sessions, the moxifloxacin mean changes in QTcF (90% CI) were 11 (7, 14), 12 (8, 17), and 16 (12, 21), respectively.

In comparison to the 10 mg dose of solifenacin, the QT interval lengthening effect seemed to be more pronounced with the 30 mg dose. Despite the fact that the effect of the greatest dose of solifenacin (three times the maximum therapeutic dose) investigated did not seem to be as significant as the effect of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This

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study was not designed to draw direct statistical conclusions between the drugs or the dose levels [8].

VI. Marketed formulation

Description and Use

VESIcare is used to treat overactive bladder, which manifests as urge incontinence, urgency, and frequent urination.

Dosage and Administration

VESIcare should only be taken in doses of 5 mg once daily. The dose may be increased to 10 mg once daily if the 5 mg dose is well tolerated. VESIcare needs to be swallowed whole and taken with beverages. You can take VESIcare with or without food.

How Supplied

VESIcare is supplied as round, film-coated tablets, available in bottles and unit dose blister packages as follows:

Strength	5 mg	10 mg
Colour	Light yelow	Light pink
Debossed	Logo,150	Logo,151

Store at 25 ºC (77 ºF) with excursions permitted from 15 ºC to 30ºC (59 °F-86 ºF) [10].

Side effects of Solifenacin

1. Dry mouth
2. Headache
3. Experiencing vertigo, sleepiness, or a spinning sensation
4. Having diarrhea or being ill (vomiting)
5. Constipation
6. (Wind) Farting and burping
7. Abdominal pain
8. Dry eyes
9. Blurred vision
10. Difficulties or pain during urinating, as well as an inability to empty your bladder [11].

Contraindications

1. Urinary retention
2. Gastric retention
3. Wide-angle glaucoma that is not under control
4. Among patients who have shown a drug's hypersensitivity [12].

VII. Conclusion

Solifenacin is a potent antimuscarinic that has low side effects when used to treat OAB. Solifenacin medication can assist patients with OAB wet or dry, improving USS, frequency, nocturia episodes, and bladder capacity without reducing voiding effectiveness. 13.0% of individuals only experienced minor side effects, usually dysuria [13].

The anti-muscarinics are first-choice drugs in overactive bladder syndrome therapy , as well as the benefit-risk ratio is largely dependant on numerous types of selectivity subtypes of muscarinic receptors. Solifenacin shows greater chooser for the bladder M3 receptors, which affords it advantages over other drugs in the group.

Only the CYP3A4 enzyme can break down solifenacin, producing three inert byproducts and one with activity close to that of the original molecule. By acting on the urothelium receptors, the active metabolite and the unmodified portion of solifenacin that are excreted in urine can support therapeutic efficacy [2].

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