There are currently five antimuscarinic (reversible muscarinic receptor antagonists) used clinically to treat the symptoms of an embarrassing disorder referred to as overactive bladder (OAB): oxybutynin, tolterodine, darifenacin, trospium, and solifenacin. Overactive bladder is estimated to afflict up to 20 million persons in the United States. This condition has previously been reviewed (Kosier, Newton, & Smith, 2000). Solifenacin (VESIcare®) produced by Yamanouchi Pharmaceutical Co. with marketing partner GlaxoSmithKline was FDA approved in November, 2004. Darifenacin (Enablex®) and trospium (Sanctura™) were also FDA approved in 2004. Solifenacin is a once-daily (5-10 mg) drug to treat symptoms of this condition such as urgency, frequency, and urge incontinence (involuntary loss of urine).

The pharmacologic strategy of targeting the cholinergic system in treating OAB stems from the prominent role of the parasympathetic nervous system in controlling the urinary bladder and the process of micturition. Lumbosacral parasympathetic innervation provides motor control of the smooth muscle of the urinary bladder (detrusor) via acetylcholine activation of M2/M3 muscarinic receptors. The M3 receptors are mainly responsible for detrusor muscle contraction via coupling to calcium entry into the cells by activation of L-type calcium channels on the smooth muscle cell membrane (Scheider, Fetscher, Krege, & Michel, 2004). New evidence also points to an important role of muscarinic receptors on the urothelium and suburothelial interstitial cells. They mediate the release of various neurotransmitters which function as modulators of both detrusor muscle contraction as well as mediate sensory information to the central nervous system when triggered by stretching the bladder wall (De Groat, 2004; Gillespie, Harvey, & Drake, 2003). OAB is thought to involve an imbalance within one or more aspects of this cholinergic control system resulting in overstimulation of the detrusor muscle and the observed symptoms of OAB (De Groat, 1997). Symptoms are urinary frequency (having to urinate eight or more times daily), urgency (the need to urinate immediately), and urinary incontinence (leaking or wetting accidents).

Solifenacin relieves the symptoms of OAB by relaxing the smooth muscle of the bladder. It competitively antagonizes the muscarinic receptors in the urinary bladder (primarily M3) leading to smooth muscle relaxation. Solifenacin possesses marginal selectivity for the M3 receptor subtype not seen with tolterodine, which does not have selectivity towards any of the five muscarinic subtypes (Gillberg, Sunquist, & Nilvebrant, 1998). In animal studies, greater bladder-to-salivary gland selectivity was reported for both tolterodine and solifenacin compared to oxybutynin (Ikeda et al., 2002).

**Pharmacokinetic Profile**

The absolute bioavailability of solifenacin is 90% with peak plasma levels reached within 3 to 8 hours. The presence of food does not affect the pharmacokinetics of the drug significantly (Uchida, Krauwinkel, Mulder, & Smulders, 2004). Solifenacin is 98% bound to human plasma proteins and is extensively metabolized in the liver primarily via the CYP3A4 pathway. This hepatic metabolism involves N-oxidation and hydroxylation pathways yielding three inactive and one active metabolite. The elimination half-life after single or multiple doses from 5 to 60 mg in healthy males is 40 to 68 hours (Smulders, Van Alphen, Vissar et al., 2002).

Dosage: 5 mg po daily. If 5 mg is tolerated, the dose may be increased to 10 mg po daily. This is adult usage only as the drug has not been tested in children. If a patient has moderate liver impairment or renal disease with a creatinine clearance of 30 ml/minute or less, do not increase the dose to 10 mg.

Clinical studies. The clinical efficacy and safety of solifenacin (5-10 mg qd) in treating symptoms of OAB have been extensively studied. These studies have demonstrated that solifenacin is an effective and well-tolerated treatment for OAB symptoms (Kosier, Newton, & Smith, 2000; Smulders, Van Alphen, Vissar et al., 2002). The drug is generally well-tolerated, with the most common side effects being dry mouth, constipation, and urinary retention. The incidence of these side effects is generally lower than with other antimuscarinic agents. Solifenacin is contraindicated in patients with known hypersensitivity to the drug or its components. It is also contraindicated in patients with narrow-angle glaucoma or urethral stricture.

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OAB has been investigated in four 12-week double-blind, randomized, placebo-controlled, multicenter trials involving 3,027 patients. The endpoints of these trials were the mean change in baseline in the number of micturitions over 24 hours, number of incontinent episodes/24 hrs and mean volume of urine voided per micturition. The results of these trials showed a significant improvement in the above parameters reflecting a decrease in symptoms of OAB compared to placebo controls (Chapple, Khullar, Gabriel, & Dooley, 2005).

A recent comparison study (STAR trial) between solifenacin (5-10 mg qd) and tolterodine ER (4 mg qd) demonstrated that flexible dosing with solifenacin (5 mg to start and increased to 10 mg if well tolerated) was superior to tolterodine ER in most OAB treatment outcomes (Chapple, Martinez-Garcia et al., 2005). Adverse effects were similar for both drugs.

Adverse Effects and Precautions

The major side effects from the use of solifenacin include constipation, blurred vision, urinary retention, and dry eyes with dry mouth being the most common complaint. These anticholinergic side effects are similar in the other four antimuscarinic drugs approved for treating OAB. The incidence of dry mouth is about 20% in most trials at the 10 mg dose but was less (about 10%) with the 5 mg dose (Chappel, Khullar et al. 2005). Solifenacin should be prescribed with caution in patients with renal or hepatic disease, controlled narrow-angle glaucoma, bladder outflow obstruction, and decreased GI motility. Higher doses of the drug (10 mg and 30 mg) prolong the cardiac QT interval and thus should be used with caution in patients with a history of QT prolongation. There is an increased risk of serious cardiac arrhythmias in patients who are taking other medications that prolong the QT interval. The lower dose of 5 mg should be prescribed in patients with a creatinine clearance of less than 30 ml/minute. Known inducers or inhibitors of CYP3A4 may require dose adjustments in solifenacin.

Contraindications

Solifenacin is contraindicated in patients with urinary or gastric retention, uncontrolled narrow-angle glaucoma, severe hepatic impairment, or patients who have demonstrated a hypersensitivity to the drug. The drug should not be used during pregnancy or during breastfeeding.

Nursing Considerations

- Assess bladder function.
- Monitor drug effects.
- Watch for urinary retention if the patient has bladder outlet obstruction.
- Monitor the patient for decreased GI motility and constipation.
- Blood levels and half-life may be increased in the elderly even though safety and effectiveness remain the same.

Patient Teaching

- Swallow the tablet with liquid.
- The drug may be taken with or without food.
- Take the drug only once per day.
- If a dose is missed, start taking the drug the next day rather than trying to “make up” missed doses.
- If an overdose is taken, call the emergency department or Poison Control Center.
- If blurred vision is experienced, do not drive or undertake potentially hazardous activities.
- Dry mouth may be experienced.
- Call the prescriber if severe abdominal pain or constipation lasting 3 days occurs.
- Heat prostration may be experienced in hot environments due to increased sweating.
- Avoid taking other medications that may cause blurred vision, dry mouth, constipation, or urinary retention.
- Read the information that comes with each refill of solifenacin because it may contain updated information.
- Store the bottle of medication at room temperature with bottle closed and out of the reach of children.

References


