



Solifenacin: a new drug for the treatment of overactive bladder and detrusor overactivity

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Overactive bladder is a prevalent and debilitating condition that affects many people. Drugs play a major role in treatment, together with bladder training and behavioral measures. Drugs are aimed at controlling the symptoms of overactive bladder, such as frequency, nocturia, urgency and urgency incontinence, preferably with as few side effects as possible. Solifenacin is a novel muscarinic receptor antagonist. It shows greater selectivity for the urinary bladder over salivary glands than tolterodine, oxybutinin and darifenacin. Solifenacin is long acting and therefore oral intake once-daily is sufficient. It can improve all symptoms of overactive bladder and results can be seen early into the treatment course. Dose adjustment is possible if needed. Long-term efficacy has been demonstrated.

There is a substantial interest in the health problem known as overactive bladder (OAB). The International Continence Society (ICS) defined the condition as a symptom syndrome suggestive of lower urinary tract (LUT) dysfunction comprising urgency, with or without incontinence, usually with frequency and nocturia [1]. The symptoms of bladder overactivity have been further defined by the ICS as:

- Urgency: a sudden, compelling desire to void that is difficult to defer
- Urgency incontinence: incontinence with urgency
- Frequency: voiding too often during the day (typically >8 voids/24 h)
- Nocturia: waking one or more times at night to void

These symptoms are not present with normal bladder function. Some can appear separately or in combination in different pathologies of the LUT as infection, stone disease, cancer and many more. These conditions have to be excluded to permit the diagnosis of OAB. Detrusor overactivity (DO) is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked.

It would appear that OAB/DO can occur as a result of several different mechanisms, myogenic and neurological. It is likely that both factors contribute to the development of the condition.

Approximately 22 million people across six European countries and 50–100 million people worldwide will have symptoms of OAB [2]. In the general population the prevalence of OAB in

people aged 40 years or over ranges between 12 and 22%. The prevalence increases with age, with the condition being present in 31–42% of people aged 75 years or over. However, OAB is not simply a condition affecting the elderly and should not be automatically accepted as a natural consequence of the aging process. It is a fact that OAB has a severe influence on the physical, social and psychological wellbeing of individuals [3].

Treatment of OAB is symptomatic, aiming at reducing the debilitating symptoms that influence quality of life (QoL) [4]. It is the aim of treatment to achieve improvement of the complaints, which are mostly apparent during bladder filling, with as little interference as possible to the function of other organs (high uroselectivity) whilst safeguarding micturition.

Currently, drugs play a major role in the treatment of OAB, an abundance of which have been used to date. For some, their use is based mainly on preliminary, open studies. Others have been studied more extensively. Many studies have shown a high placebo response which provides more information about the condition and its possible influence on the symptoms through behavioral measures such as keeping a voiding chart, focusing on the problem and discussion with colleagues.

Drugs used for OAB/DO

In the bladder there is a predominance of mRNAs encoding muscarinic receptors M2 and M3, although all five pharmacologically defined types have been found [5]. Although the M3 are considered the most important receptors for contraction, the M2 predominate in a

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Table 1. Drugs used for the treatment of overactive bladder.

Drug	Level of evidence*	Grade of recommendation†
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Propantheline	2	B
Atropine	3	C
Oxybutinin	1	A
Propiverine	1	A
Dicyclomine	3	C
Flavoxate	2	D
Imipramine	3	C

*1: Systematic reviews, meta-analysis, good quality randomized controlled trials;

2: Randomized, controlled trials, good quality prospective cohort studies;

3: Case-control studies, case series.

†A: Based on level 1 evidence (highly recommended); B: Consistent level 2 or 3 evidence (recommended); C: Level 4 studies or 'majority evidence' (optional);

D: Evidence inconsistent/inconclusive (no recommendation possible).

Adapted from the International Consultation on Incontinence report, 2004 [6].

ratio of at least 3:1. The role of the M2 receptor remains uncertain. A list of drugs used for the treatment of OAB to date, together with the level of evidence and the grade of recommendation for their use, as provided by the International Consultation on Incontinence (ICI) committee is currently available [5]. Part of this is provided in Table 1.

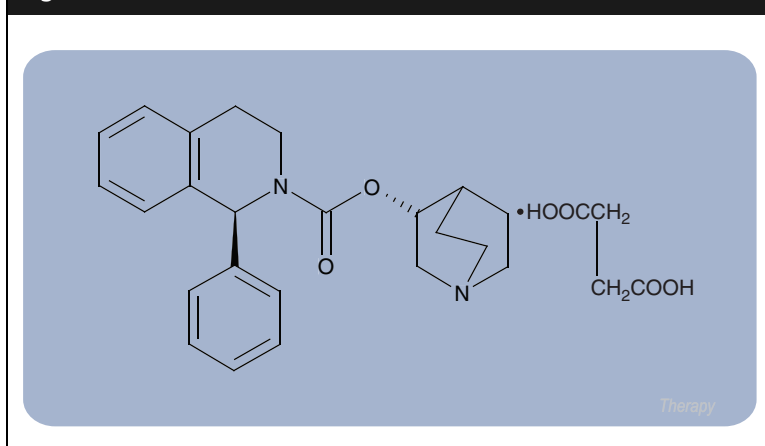
At the present time, muscarinic antagonists are the most widely used drug of choice for the treatment of OAB. These agents display a blocking activity at acetylcholine (ACh) muscarinic receptors. It is interesting, however, that the expected mode of action – the drug blocks the muscarinic receptor on the detrusor muscle, decreasing its ability to contract – does not correspond with the clinical facts. Antimuscarinics act mainly during the bladder storage phase, decreasing desire to void and increasing bladder capacity, while during this phase there is normally no parasympathetic input to the LUT. Antimuscarinics are mostly competitive antagonists. During micturition there is a massive release of ACh, and therefore the effects of drugs for OAB should be decreased to prevent the development of retention, which can be provoked by high doses of antimuscarinics. However, in doses normally used for the treatment of OAB/DO such an effect is seldom seen. Thus, there must be other mechanisms of action, such as blocking of the release of ACh during filling from both neuronal and non-neuronal sources and direct or indirect excitation of afferent

nerves in the suburothelium and within the detrusor, and recent studies in animals have provided data in favor of this hypothesis. In one such study, intravesical oxybutynin was shown to have a direct anesthetic effect within the bladder wall. It was shown to temporarily desensitize C fiber afferents, which could explain its clinical benefit in decreasing symptoms of bladder overactivity [6]. De Laet and colleagues showed in a rat model a decrease in afferent activity after systemic administration of oxybutynin for C and A-δ fibers and proved that the decrease in afferent spike rate is not the result of increased compliance [7]. Their findings strongly suggest that oxybutynin, either directly or indirectly, influences bladder sensory nerves, inhibiting the afferent part of the micturition reflex. In addition, similar effects have been demonstrated with tolterodine in healthy volunteers [8].

Antimuscarinics can be categorized into tertiary and quaternary amines, the former having higher lipophilicity and higher molecular charge [6]. Atropine, tolterodine, oxybutinin, propiverine, darifenacin and solifenacin are tertiary amines. They are generally well absorbed from the gastrointestinal (GI) tract and should, in theory, be capable of passing into the CNS. Quaternary amines, such as propantheline and trospium, are not well absorbed. In addition, they only cross the blood-brain barrier to a very small extent and thus exert minimal CNS side effects.

All currently used tertiary amines are metabolized by the cytochrome P450 (CYP) enzyme system which poses the possible risk of drug-drug interactions. Uroselectivity is lacking in currently used drugs causing side effects and creating contraindications for their use (such as untreated narrow-angle glaucoma). A complete overview of these drugs can be found in the International Consultation on Incontinence (ICI) report [5].

In addition to the antimuscarinics, there are a number of other agents that exert an antispasmodic action, and others still a mixed action. Agents acting on membrane channels include calcium antagonists and potassium channel openers; however, to date literature data has not shown these compounds to have any clinical value. Drugs with a mixed action include oxybutynin, dicyclomine, propiverine and flavoxate. Their level of evidence and the ICI recommendations for use are given in Table 1. There are a number of agents that are used off-license as α -blockers and β -agonists in addition to those that have been used, or are still used, as

Figure 1. Chemical structure of solifenacin succinate.

antidepressants (imipramine), and prostaglandin synthesis inhibitors. For example, intravesical vanilloids, which are still undergoing research, and botulinum toxin, which has been extensively evaluated to date.

Solifenacin succinate (VESIcare, Astellas) is a new, competitive, specific cholinergic antagonist (Figure 1). It has been shown to be a M3 receptor antagonist that has a higher binding affinity for exogenously expressed human M3 receptors than for M1 and M2 receptors [9]. This drug will be reviewed herein.

Pharmacokinetics

Animal experiments demonstrated that the half-life of solifenacin (YM905, (+)-(1*S*,3'*R*)-quinuclidin-3'-yl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate) is approximately 2–3 h [11–13].

Solifenacin is eliminated in urine and feces. A study showed that after a single oral dose of 10 mg solifenacin succinate over 26 days, approximately 70% of the radiolabel is excreted in urine, 23% is excreted in feces and 11% is recovered as unchanged drug in urine (18% as the *N*-oxide metabolite, 9% as the 4*R*-hydroxy-*N*-oxide metabolite and 8% as the active 4*R*-hydroxy metabolite). After a single dose of solifenacin succinate, the mean half-life varied between 47.4 and 68.2 h. These data support once-daily dosing. Similar values were obtained after multiple dosing (45.0–67.4 h) [Astellas, Data on file].

Solifenacin is mainly metabolized by the liver, mostly mediated by CYP3A4. In *in vitro* studies, solifenacin was shown to possess four metabolites, one pharmacologically active (4*R*-hydroxy solifenacin succinate) and three inactive (*N*-glucuronide, *N*-oxide and 4*R*-hydroxyl-*N*-oxide of solifenacin succinate [Astellas, Data on file].

In two trials in young men, a single-dose study evaluated seven doses ranging from 5 to 100 mg [14]. A multidose study evaluated 5-, 10-, 20- and 30-mg doses. In the single-dose study, mean time to maximal concentration and elimination half-life ranged from 3.3 to 4.8 and 40.2 to 57.6 h, respectively. In the multidose study, the corresponding ranges were 2.9–5.8 and 45.0–64.8. Plasma concentration and AUC values increased linearly with single doses in both trials. At steady state, a less regular increase was observed, with higher values in the 20- than the 30-mg group.

The product proved to be absorbed after oral administration with mean approximate bioavailability of 90%. It was also found to be bound to plasma proteins, primarily the α_1 -acid glycoprotein. Maximum plasma concentrations were reached after 3–8 h. The C_{max} and AUC values were dose-proportional over the range 5–40 mg. T_{max} is dose-independent. The slow absorption combined with slow disposition of solifenacin succinate results in an almost constant plasma concentration over a period of several hours [15].

The pharmacokinetics of solifenacin is not affected by food, as demonstrated in a randomized, two-period, crossover study by Uchida and colleagues in two groups of healthy men [16]. A single 10-mg dose of solifenacin was administered to the first group in the fasting state during period 1 and in the fed state during the period 2, and to the second group in the fed state during period 1 and in the fasting state during period 2. There was a 14-day washout between treatment periods. No statistically or clinically significant pharmacokinetic differences occurred between subjects in the fed and fasting states, suggesting that this drug may be administered with or without food. Solifenacin succinate has a high volume of tissue distribution [17].

Selectivity profile

Solifenacin acts mainly by blocking the muscarinic receptors on the detrusor muscle, preventing ACh from binding. It has relative selectivity for the M3 receptor subtype, which mediates cholinergic transmission of smooth muscles and exocrine glands (urinary bladder, ciliary muscle, salivary glands) [13]. Selectivity for urinary bladder over salivary glands has been evaluated in both *in vitro* and *in vivo* animal studies. Kobayashi and colleagues investigated the effects of solifenacin and current antimuscarinic drugs for the treatment of OAB (oxybutynin, tolterodine and darifenacin) on intracellular Ca^{2+} mobilization in

response to M3 muscarinic receptor activation in bladder smooth muscle and submandibular gland cells, isolated from cynomolgus monkeys. Solifenacin concentration-dependently inhibited carbachol-induced Ca^{2+} mobilization, with affinity constant values (pK_i) of 8.5 ± 0.053 in bladder smooth muscle cells and 8.2 ± 0.051 in submandibular gland cells ($n = 5$). The pK_i value of solifenacin was almost equivalent to the values of oxybutynin, tolterodine and darifenacin in bladder smooth muscle cells (8.7, 8.5 and 8.4, respectively), while being lower than those in submandibular gland cells (9.0, 8.7 and 8.8, respectively). Moreover, the bladder-selectivity index (K_i ratio: submandibular gland/bladder) for solifenacin (2.1) was statistically higher than those for oxybutynin, tolterodine and darifenacin (0.51, 0.65 and 0.46, respectively). These findings indicate solifenacin's selectivity for bladder smooth muscle cells over salivary gland cells in nonhuman primates, relative to oxybutynin, tolterodine and darifenacin [18]. Ohtake and colleagues found similar results when evaluating the *in vitro* and *in vivo* bladder selectivity profile of solifenacin over salivary glands in the rat, and comparing the results with those obtained for tolterodine, oxybutynin, darifenacin and atropine. Solifenacin exerted greater selectivity for urinary bladder over salivary gland than tolterodine, oxybutynin, darifenacin and atropine [19]. In a recent study in mice pilocarpine-induced salivary secretion was significantly reduced by oral administration of solifenacin. Although the suppression induced by solifenacin was more persistent than that due to oxybutynin, the antagonistic effect of solifenacin on the dose–response curves to pilocarpine was significantly weaker than that of oxybutynin [20].

Pharmacokinetics in special populations

The following data is currently on file at Astellas.

Age

No dosage adjustment based on patient age is needed. However, the pharmacokinetics have not been established in children and adolescents. These are the conclusions of a study by Krauwinkel and colleagues in 47 healthy adults (24 young/middle-aged: mean age 35; and 23 elderly: mean age 68; 12 males in each age group) enrolled in a single-center, multidose, open-label, crossover trial [21]. Solifenacin, 5 or 10 mg, was administered once-daily, during two, 14-day study periods separated by a wash-out period. Subjects were randomized to one dose in the first period and the other dose in the

second period. Primary outcome variables were C_{max} and AUC_{0-24} . Secondary parameters included terminal elimination half-life, time to T_{max} , fraction unbound, renal clearance, amount/percent of dose excreted in urine as solifenacin and its metabolites, and through plasma metabolite concentrations. Adverse events and other safety parameters were also evaluated. Although C_{max} and AUC_{0-24} were higher in elderly subjects than in younger subjects and there was a tendency toward longer T_{max} and half-life, these differences were small and not considered clinically relevant. The number of adverse events in elderly subjects was similar to that in younger subjects, indicating that no age-related dose adjustments are needed with this agent in the elderly.

Gender

Pharmacokinetic data are not influenced by gender, as shown in six clinical pharmacology studies and three Phase III patient studies. Mean values of T_{max} , C_{max} and AUC were similar in men and women.

Race

Pharmacokinetic data are not influenced by race. The pharmacokinetics determined in two Japanese studies was compared with those from Caucasian populations in Europe and USA.

Pharmacokinetics in special conditions

Renal impairment

Renal impairment was examined in a multicenter, open-label study in 24 patients [22]. In patients with mild-to-moderate renal impairment (clearance reduced by 20–25%) with an increase in half-life of approximately 30%, C_{max} was unaffected. In patients with severe renal impairment drug exposure was significantly greater than in controls, with increases in C_{max} of approximately 30%, AUC of more than 100% and half-life more than 60%. These data suggest that no dose adjustment is needed for patients with mild-to-moderate renal impairment (creatinine clearance > 30 ml/min). However, patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) should be treated with caution and should not receive more than 5 mg once-daily.

Hepatic impairment

Solifenacin succinate is metabolized extensively in the liver, primarily by CYP3A4. The effects of hepatic impairment on the pharmacokinetics, safety and tolerability of a single dose were exam-

ined in a single-center, open-label, parallel study of eight patients with moderate hepatic impairment and eight sex-, age- and weight-matched healthy controls. In these patients, the AUC increased by 60% compared with healthy controls. Therefore, patients with moderate hepatic impairment should be treated with caution and receive not more than 5 mg once-daily. No dose-adjustment is needed if only mild hepatic impairment has been demonstrated [23].

Kinetic interactions

Solifenacin does not significantly inhibit CYP1A1/2, 2C9, 2C19, 2D6 or 3A4 derived from human liver microsomes and is therefore unlikely to alter the clearance of drugs metabolized by these CYP enzymes. Solifenacin is extensively metabolized by CYP3A4, an isoenzyme that plays a major role in metabolism of a large number of drugs such as ketoconazole and warfarin. Coadministration of CYP3A4 substrates might alter the metabolism of solifenacin.

Simultaneous administration of ketoconazole (200 mg/day) resulted in a twofold increase of the AUC of solifenacin, and at a dose of 400 mg/day resulted in a threefold increase. Therefore, the maximum dose of solifenacin should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other strong CYP3A4 inhibitors [24].

Solifenacin was shown not to alter the pharmacokinetics of combined oral contraceptives ethinylestradiol and levonorgestrel (CYP3A4 substrates) contained in the combined oral contraceptive pill. A double-blind, placebo-controlled, crossover study investigated the effects of a combined oral contraceptive on the pharmacokinetics of solifenacin: no significant differences were seen in the pharmacokinetics of the components of the combined oral contraceptive with or without solifenacin [25].

Solifenacin does not alter the pharmacokinetics of *R*-warfarin (substrate for CYP3A4) or *S*-warfarin (substrate for CYP2C9). A double-blind study showed that repeated dosing of solifenacin 10 mg once-daily did not affect the pharmacokinetics of warfarin or their effect on prothrombin time. The combination was well tolerated.

Solifenacin (10 mg) did not interact in an open-label, one-sequence crossover study with digoxin (loading-dose 0.25 mg followed by 0.125 mg). Concomitant medication with other drugs with antimuscarinic properties may result in more pronounced therapeutic effects and undesirable effects.

An interval of approximately 1 week should be allowed between stopping treatment with solifenacin succinate and starting other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Contraindications & precautions

Solifenacin is contraindicated in patients with conditions making treatment with muscarinic relaxant drugs unsafe, including urinary retention, severe GI conditions (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.

Contraindications are also hypersensitivity to the active substance or to any of the excipients, haemodialysis, severe hepatic impairment, severe renal impairment or moderate hepatic impairment on treatment with a potent CYP3A4 inhibitor.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose–galactose malabsorption, should not take this medicinal product [15].

Symptoms of OAB can be caused by many different pathologies and these should be excluded or demonstrated before a pure symptomatic treatment is installed. A non-limitative list includes heart failure or renal disease, urinary tract infection, clinically significant bladder outflow obstruction at risk of urinary retention, GI obstructive disorders, risk of decreased GI mobility, hiatus hernia/gastroesophageal reflux

Clinical efficacy

Two controlled, Phase II studies evaluated the dose–response to four doses of solifenacin (2.5, 5, 10 and 20 mg once-daily). Solifenacin showed a clear distinction between placebo for micturition frequency and volume voided per micturition after 1 week of treatment, indicating a rapid onset of action with solifenacin [Data on file].

Several studies have been carried out to evaluate the clinical efficacy. Overall, these show that solifenacin 5 and 10 mg are effective in reducing the symptoms of OAB, such as micturition frequency, urgency, incontinence and nocturia.

Chapple and colleagues evaluated the dose–response relationship and safety, tolerability of solifenacin succinate in the treatment of OAB, and compared its efficacy and safety, tolerability with tolterodine 2 mg twice-daily. The study was multicenter and included a 2-week, single-blind, placebo run-in, a 4-week double-blind, placebo-controlled, active-treatment

phase, and a 2-week follow-up. Men and women with an OAB and urodynamic evidence of detrusor overactivity were randomized to placebo or solifenacin 2.5, 5, 10 or 20 mg once-daily, or tolterodine 2 mg twice-daily. Of 265 patients enrolled, 225 were randomized and 192 completed the study. Solifenacin 5, 10 and 20 mg produced statistically significant ($p < 0.05$) improvements in voids/24 h versus placebo, whereas tolterodine did not; the mean change with tolterodine was between those with solifenacin 2.5 and 5 mg. The outcome was similar for the mean change from baseline to end point in mean volume voided/void. For incontinence and urgency episodes/24 h the solifenacin dose groups showed numerically superior changes compared with placebo; the mean effects with tolterodine were generally smaller than with solifenacin. Most of the efficacy effect of solifenacin was evident at 2 weeks. QoL outcomes supported the efficacy results. Solifenacin 5 and 10 mg were well tolerated; there were no serious treatment-related adverse events [26].

In a Phase IIIa study, Chapple and the YM-905 study group investigated further. The study was an international, multicenter, randomized, double-blind, tolterodine- and placebo-controlled trial conducted at 98 centers. Adult patients with symptomatic OAB for 3 months or more were eligible. After a single-blind, 2-week, placebo run-in period patients were randomized equally to a 12-week, double-blind treatment with either tolterodine 2 mg twice-daily, placebo or solifenacin 5 or 10 mg once-daily. Efficacy variables included change from baseline in the mean number of urgency, incontinence and urge incontinence episodes, and change from baseline in voids/24 h and mean volume voided/void. In total, 1281 patients were enrolled, 1081 randomized and 1077 treated; 1033 were evaluated for efficacy. Compared with placebo, the change from baseline (-1.41, -32.7%) in the mean number of urgency episodes per 24 h was statistically significantly lower with solifenacin 5 mg (-2.85, -51.9%) and 10 mg (-3.07, -54.7%; both $p < 0.001$), but not with tolterodine (-2.05, -37.9%; $p = 0.0511$). There was a statistically insignificant decrease in episodes of incontinence with tolterodine (-1.14; $p = 0.1122$) but a significant decrease in patients treated with solifenacin 5 (-1.42; $p = 0.008$) and 10 mg (-1.45; $p = 0.0038$). Compared with placebo (-1.20, -8.1%) the mean number of voids/24 h was significantly lower in patients receiving tolterodine (-1.88, -15%; $p = 0.0145$), solifenacin 5 (-2.19,

-17%) and 10 mg (-2.61, -20%; both $p < 0.001$). The mean volume voided/void was also significantly higher with all three active treatments ($p < 0.001$) [27].

Cardozo and colleagues performed a multicenter, multinational, randomized, double-blind, placebo-controlled trial. Patients were randomized to 12-week, once-daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo. Compared with changes obtained with placebo (-1.59), micturitions per 24 h were statistically significantly decreased with solifenacin 5 mg (-2.37, $p = 0.0018$) and solifenacin 10 mg (-2.81, $p = 0.0001$). A statistically significant decrease was observed in the number of incontinence episodes with both solifenacin doses (5 mg, $p = 0.002$ and 10 mg, $p = 0.016$). This effect was also seen for episodes of urgency incontinence (5 mg, $p = 0.014$ and 10 mg, $p = 0.042$). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin. Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg (-0.71, -38.5%) versus placebo (-0.52, -16.4%, $p = 0.036$). Episodes of urgency were statistically significantly reduced with solifenacin 5 mg (-2.84, -51%, $p = 0.003$) and solifenacin 10 mg (-2.90, -52%, $p = 0.002$). Mean volume voided per micturition was statistically significantly increased with both solifenacin doses ($p = 0.0001$). Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo) [28].

Treatment over a period of up to 1 year was the main goal of the study by Haab and colleagues in order to examine safety and tolerability findings as primary end points, and efficacy outcomes as secondary end points of solifenacin [29]. The study was a 40-week, open-label extension of two 12-week, placebo-controlled, double-blind studies of solifenacin treatment in patients with OAB. Patients who completed the 12-week studies were offered participation in the open-label extension study. All patients who entered the open-label extension study initially received solifenacin 5 mg daily for 4 weeks, after which a flexible dosing regimen allowed patients to individualize their treatment (5 or 10 mg) at each of the three study visits. In total, 91% (1637/1802) of patients who completed the two 12-week, randomized studies chose to participate in the long-term, open-label extension study. A total of 81% of patients completed

40 weeks of open-label treatment. Improvements in major symptoms of OAB were noted for all patients for up to 52 weeks of treatment. In patients randomized to solifenacin in the double-blind studies, there were small incremental improvements in all efficacy parameters (reductions in episodes per 24 h of urgency, reductions in frequency and urge incontinence, and increases in volume voided per micturition) over the course of the extension study. Efficacy was confirmed when outcomes were assessed as a function of total solifenacin exposure. Patient satisfaction with solifenacin tolerability (85%) and efficacy (74%) were high [26].

Chapple and colleagues compared in a prospective, double-blind, placebo-controlled, two-arm, parallel-group, 12-week study, the efficacy and safety of solifenacin 5 or 10 mg and tolterodine extended release (ER) 4 mg once-daily in OAB patients. After 4 weeks of treatment, patients had the option to request a dose increase but were dummied throughout as approved product labeling only allowed an increase for those on solifenacin. Half of the patients requested a change. Solifenacin, with a flexible dosing regimen, showed greater efficacy to tolterodine in decreasing urgency episodes, incontinence, urge incontinence and pad usage and increasing the volume voided per micturition. More solifenacin-treated patients became continent and reported improvements in perception of bladder condition assessments. The majority of side effects were mild-to-moderate in nature, and discontinuations were comparable and low in both groups [30]. This study has caused some commotion with the exchange of letters in literature [31]. Discussions regarding the study design and interpretation of the results are interesting to read as they have a more general importance than related to this unique study. In this authors opinion, the importance of the study is that it shows that in many patients, dose titration of bladder-relaxing drugs may be indicated, which many clinicians will know. A presentation at the European Association of Urology (EAU) 2006 showed that in the STAR study the mean symptom severity at baseline was consistently worse in the groups requesting a dose increase and that these patients often had failed previous treatment [32].

A subgroup analysis of patients with OAB syndrome, assessing the efficacy of once-daily solifenacin succinate in patients with mixed urinary incontinence (MUI; n = 1041) or urge urinary incontinence (UUI; n = 1648) was only

published recently [33]. A greater proportion of patients receiving solifenacin achieved resolution of incontinence in both the MUI and UUI groups (MUI: 5 mg = 43%, 10 mg = 49%; UUI: 5 mg = 55%, 10 mg = 54%) compared with patients receiving placebo (MUI: 33%, UUI: 35%). Baseline to end point improvements in all other symptoms were statistically significant versus placebo for both solifenacin doses in both cohorts. The incidence of adverse events was comparable between the MUI and UUI cohorts. This analysis shows that once-daily solifenacin was as effective and well tolerated in patients with MUI as those with UUI.

Millard and Halaska recently completed a pooled analysis of the results in patients with severe symptoms of OAB [34]. Results from four multinational, Phase III studies of solifenacin with 2848 patients were pooled to determine the effects in patients with severe OAB symptoms at baseline. In these studies, patients were randomized to treatment with placebo or solifenacin 5 or 10 mg once-daily. Baseline severity was defined according to the number of incontinence episodes/24 h, number of urgency episodes/24 h and micturition frequency/24 h. The proportion of patients with restoration of continence, resolution of urgency and normalization of micturition frequency at end point was significantly greater with solifenacin than with placebo among patients with severe OAB at baseline. Solifenacin 5 and 10 mg were significantly ($p < 0.05$) more effective than placebo for reductions in the number of episodes of incontinence, urgency and micturition, and for the increase in volume voided/micturition among most subgroups of patients who were highly symptomatic at baseline.

During the EAU congress in Paris in March 2006, more data became available. Van Rey and Heesakkers showed significant results in a small group multiple sclerosis patients for frequency, median voided volume/void and median number of pads used per day [35].

New data from the SUNRISE study, which included almost 1000 patients at 105 sites across 14 European countries, were presented at EAU. This study has urgency as its primary end point. Using a validated grading scale, the Patient Perception of Intensity of Urgency Scale (PPIUS), where 0 represents 'no urgency' and 4 represents 'urgency incontinence', SUNRISE showed that urgency episodes graded 3 or 4 decreased by 2.58 on the scale with solifenacin compared with 1.81 with placebo ($p < 0.0001$). One of the secondary

variables in the study was urgency 'bother' – a measure of the inconvenience and distress caused by each urgency episode. Using a visual analog scale aimed specifically at urgency bother, where 0 represents 'no bother' and 100 represents 'worst possible bother', urgency bother was reduced by 35 on the scale with solifenacin and by 25 with placebo ($p < 0.0001$). A further outcome of the SUNRISE study was to show solifenacin has a rapid onset of action and impact on urgency episodes as early as day 3 following initiation of therapy, providing early reassurance for patients commencing therapy.

Side effects

Side effects were evaluated in two controlled trials of healthy young men [14]. All doses in the single-dose study were well tolerated. At steady state, only the 30-mg dose was not well tolerated. The most commonly reported adverse events were dry mouth, blurred vision, and headache. Solifenacin 5 and 10 mg, either as single doses or at steady state, had a minimal effect on salivary flow, visual near point, and the incidence of adverse events. Solifenacin was well tolerated up to single doses of 100 mg and after multiple doses of 20 mg.

In the study by Chapple and colleagues, solifenacin 5 and 10 mg were well tolerated; there were no serious treatment-related adverse events [26]. The incidence of dry mouth was 14% for solifenacin 5 and 10 mg, 2.6% for placebo and 24% for tolterodine. In the multicenter, Phase IIIa study by Chapple and colleagues, solifenacin was well tolerated; compared with placebo (4.9%), dry mouth (the most common side effect), mostly mild, was reported in 18.6% of patients receiving tolterodine, 14.0% receiving 5 mg and 21.3% receiving 10 mg solifenacin [27].

A study by Cardozo and colleagues showed that treatment with solifenacin was well tolerated [28]. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo).

Haab and colleagues found solifenacin treatment to be safe and well tolerated in their open-label study, and rates of anticholinergic side effects were relatively low. Only 4.7% of patients discontinued treatment owing to adverse events [29].

The SUNRISE study presented at the EAU 2006 conference confirmed existing knowledge on the safety profile of solifenacin with withdrawals due to adverse events at less than 3%. The adverse events observed were common to

antimuscarinics with rates of dry mouth at 12.2% with solifenacin 5 mg (15.8% solifenacin 5 and 10 mg), constipation at 5% with solifenacin 5 mg (6.9% solifenacin 5 and 10 mg), and no statistical difference between solifenacin and placebo for blurred vision.

Effects on QoL have been studied in a meta-analysis. QoL data using the King's Health Questionnaire (KHQ) were analyzed from two Phase III, 12-week studies (1984 patients) and a long-term extension of these studies (1637 patients) where patients received solifenacin for up to an additional 40 weeks (i.e., a 52-week exposure to solifenacin). The 12-week studies were multinational, multicenter, randomized, double-blind and placebo-controlled. The ten domains from the KHQ evaluated were general health perception, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity measures, and symptom severity. Changes from baseline to end point in QoL variables were assessed by analysis of variance, and from pooled outcomes of the 12-week studies by analysis of covariance. Descriptive statistics were used to evaluate data in the extension study. Solifenacin significantly improved the QoL in patients with OAB symptoms after 12 weeks of treatment, with further improvements during long-term administration up to 1 year. Clinical trial outcomes show a favourable balance of efficacy and tolerability with solifenacin; the present report further supports this efficacy and tolerability by providing evidence for both short- and long-term improvements in QoL [35].

Conclusion

Literature data on solifenacin allow us to state that:

- It is a competitive, specific and active antagonist of cholinergic muscarinic receptors
- It has a relative selectivity for the M3 receptor subtype
- It shows a greater selectivity for urinary bladder over salivary glands than tolterodine, oxybutynin and darifenacin in the doses studied
- It can be used once daily but some dose adjustment is possible if needed especially in those with more severe symptoms or previous failure with drug treatment
- Its action become notable within days
- Good effects are seen on the major symptoms of OAB including urgency and incontinence
- The side effects are acceptable in the dose of 5 and 10 mg

Highlights

- Solifenacin is a tertiary amine with muscarinic receptor blocking affinity.
- It has some uroselectivity compared with other drugs.
- Its action is comparable to that of the other available drugs.
- Side effects are mild or moderate in the dosage used and dry mouth less than in other available drugs.
- Dose adjustment is needed in cases of severe renal impairment and moderate hepatic impairment.

Expert commentary

Solifenacin does seem to do what the manufacturers claim. It can be a primary product for new patients and an alternative for those with OAB/DO who are not satisfied with their actual treatment. Solifenacin is not a new type of product and thus has to be positioned in the group of tertiary amines. The clinical experience is sufficient and the number of publications is steadily increasing. More studies with larger numbers on specific patient groups, as with neurologic overactivity, would be worthwhile. Studies evaluating the effect and effectiveness on the more probable ways of action of antimuscarinics in OAB such as the afferent innervation would be welcome. As in all studies with bladder-relaxing drugs little is available on clinical usefulness with higher

doses in patients in whom a complete abolition of bladder contractility would be the aim. Placebo effect is also clear in the studies with solifenacin though statistically better outcome has been shown with solifenacin than with placebo in most evaluations. It would be worthwhile to try to understand better why placebo effect is as high as it is in OAB treatment.

Outlook

There will be further evolution in the treatment of OAB/DO and it is likely that new formulations will explore effects on physiopathology mechanisms, which have become apparent in recent and future studies. It is not unlikely that more emphasis will be placed on the afferent arm of the mechanism involved in bladder filling pathologies, where for a very long time, the efferent arm was considered primordial. For some muscarinic antagonists, such effect has already been demonstrated in animal and human studies.

Information resources

The website of the ICS, under the documents standardization report of international continence society and ICI 2004 report published 2005, is a useful resource: www.icsoffice.org

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