Overactive Bladder — New Antimuscarinics for Treatment

a report by
Karl-Erik Andersson, MD, PhD
Professor and Chairman, Department of Clinical Pharmacology, University of Lund, Sweden

Summary

Antimuscarinics are the first-line pharmacological treatment of the overactive bladder (OAB). It is well known that this treatment is not always effective and that it is associated with side effects, limiting its clinical use. The clinical effectiveness of antimuscarinics has even been questioned. However, new antimuscarinics have recently been introduced that in several respects differ from those already available, and that may offer a possibility to optimize therapy with this class of drugs.

Rationale for Treatment

Muscarinic Receptor Mechanisms in OAB

Muscarinic receptors comprise five subtypes, M1–M5, all of which have been demonstrated in the bladder. M2 and M3 receptors are located preferentially on detrusor smooth muscle cells, whereas M1 (facilitatory) and M4 (inhibitory) can be found on cholinergic nerve terminals, where they influence acetylcholine release. On the human detrusor muscle cells, M2 receptors (75%) predominate in number over M3 receptors (25%), but the M3 receptors are mainly responsible for the normal micturition contraction, whereas the role for the M2 receptors in bladder function has not been established.

Muscarinic receptors can be found on other structures in the bladder that are believed to be of importance for bladder activity. They can be found on urothelial cells, on interstitial cells, and possibly on sensory nerves.

During the storage phase, acetylcholine may be released from both neuronal and non-neuronal sources (e.g. the urothelium), and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. This mechanism may be important in the pathophysiology of OAB/DO, and a possible target for antimuscarinics.

The common view is that, in OAB, antimuscarinics act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. However, antimuscarinic drugs act mainly during the storage phase, decreasing urge and increasing bladder capacity, and, during this phase, there is normally no activity in parasympathetic nerves. Furthermore,
Antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of acetylcholine, as during micturition, the effects of the drugs should be reduced, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. High doses of antimuscarinics can produce urinary retention in humans, but in the dose range needed for beneficial effects in OAB, there is little evidence for a significant reduction of the voiding contraction.

**New Antimuscarinic Drugs**

**Darifenacin**

Darifenacin is a selective muscarinic M₃ receptor antagonist. It is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolised in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6. Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5mg/d and 15mg/d.

Theoretically, drugs with selectivity for the M₃ receptor can be expected to have clinical effect in DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes. However, the clinical effectiveness and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

The clinical efficacy of darifenacin has been documented in several randomized controlled trials (RCTs). Haab et al. reported a multicenter, double-blind, placebo-controlled, parallel-group study that enrolled 561 patients with OAB symptoms for >6 months. Darifenacin 7.5mg and 15mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week two). This effect was sustained through week 12.

At this time, the number of incontinence episodes per week was reduced from baseline by 67.7% with darifenacin 7.5mg, and 72.8% with darifenacin 15mg, compared with 55.9% with placebo. Darifenacin...
NEW for overactive bladder

Help relieve their symptoms and your worries...

Simply brilliant.

Designed to work where it’s needed

- The only quaternary amine indicated for treating overactive bladder
- 75% to 83% median reduction in average number of daily urge incontinence episodes at week 12 vs placebo (50% to 54%)
- Up to 46% more effective than placebo in reducing daily toilet voids at week 12
- Minimally metabolized by the cytochrome P450 system based on in vitro data

SANCTURA is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Dosing is 20 mg bid on an empty stomach or 1 hour before meals.

SANCTURA is contraindicated in patients with or who are at risk of urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma and in patients who have demonstrated hypersensitivity to the drug or its ingredients.

The most common adverse effects for SANCTURA vs placebo were dry mouth (20% vs 6%), constipation (10% vs 5%), and headache (4% vs 2%).

Active tubular secretion is a major route of elimination for SANCTURA. Therefore there may be competition for elimination with other renally eliminated drugs.

www.SANCTURA.com

For product information or questions call 877-427-9068, ext 4.
Please see brief summary of prescribing information on adjacent page.
Sanctura™ (trospium chloride) 20-mg Tablets

Brief Summary: please see package insert for full prescribing information.

INDICATIONS AND USAGE
Sanctura is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

CONTRAINDICATIONS
Sanctura should not be used in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Sanctura is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

Geriatric Use
Of the 591 patients with overactive bladder who received treatment with Sanctura in the two U.S. placebo-controlled, efficacy and safety studies, 2975 patients were treated with Sanctura (N=1673), placebo (N=1056) or active control medications (N=248). Of this total, 1181 patients participated in two, twelve-week, Phase 3, U.S., efficacy and safety studies and a 9-month open-label extension. Of this total, 591 patients received Sanctura 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with Sanctura for at least 24 and 52 weeks, respectively. In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving Sanctura 20 mg bid and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with Sanctura or placebo, respectively, by the investigator.

Table 1 lists treatment emergent adverse events from the combined 12-week U.S. safety and efficacy trials that were judged to be at least possibly related to treatment with Sanctura by the investigator, were reported by at least 1% of patients, and were reported more frequently in the Sanctura group than in the placebo group.

The 2 most common adverse events reported by patients receiving Sanctura 20 mg bid were dry mouth and constipation. The single most frequently reported adverse event for Sanctura, dry mouth, occurred in 20.1% of Sanctura treated patients and 5.8% of patients receiving placebo. In the two Phase 3 U.S. studies, dry mouth led to discontinuation in 1.9% of patients treated with Sanctura 20 mg bid. For the patients who reported dry mouth, severe dry mouth was first observed during the first week of treatment.

The most common adverse events reported in the two Phase 2 placebo-controlled clinical trials in a total of 2975 patients, who were treated with Sanctura (N=1673), placebo (N=1056) or active control medications (N=248). Of this total, 591 patients received Sanctura 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with Sanctura for at least 24 and 52 weeks, respectively. In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving Sanctura 20 mg bid and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with Sanctura or placebo, respectively, by the investigator.

Table 1 lists treatment emergent adverse events from the combined 12-week U.S. safety and efficacy trials that were judged to be at least possibly related to treatment with Sanctura by the investigator, were reported by at least 1% of patients, and were reported more frequently in the Sanctura group than in the placebo group.

Management of Overdosage
Overdosage with Sanctura may result in severe anticholinergic effects. Treatment should be provided according to symptoms and supportive. In the event of overdosage, ECG monitoring is recommended.


For product information or questions call 877-427-9068, ext 4.

www.SANCTURA.com

J Urol
5.
6.
7.5mg and 15mg, respectively, was significantly superior to placebo for improvements in micturition frequency, bladder capacity, frequency of urgency, severity of urgency, and number of incontinence episodes leading to a change in clothing or pads.

The most common adverse events were mild-to-moderate dry mouth and constipation. However, no patients withdrew from the study as a result of dry mouth and discontinuation related to constipation was rare (0.6% placebo versus 0.9% darifenacin). There were no reports of blurred vision and the CNS and cardiac safety profile was comparable with placebo.

According to the assessment of the 3rd International Consultation on Incontinence (ICI) 2004, darifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

**Solifenacin**

Solifenacin (YM-905) is a long-acting (mean terminal half-life is approximately 50 hours) muscarinic receptor antagonist with some selectivity for M3 receptors (10–20-fold). It is a tertiary amine, well absorbed from the gastrointestinal tract (absolute bioavailability 90%). Solifenacin undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4).

The efficacy, safety, and tolerability of solifenacin in adult patients with OAB have been documented both in large-scale early trials and in several pivotal phase 3 studies. In one of these double-blind multinational trials, a total of 1,077 patients were randomized to 5mg solifenacin, 10mg solifenacin, tolterodine (2mg twice-daily), or placebo. Compared with placebo (-8%), mean micturitions/24h were significantly reduced with solifenacin 10mg (-20%), solifenacin 5mg (-17%), and tolterodine (-15%).

Episodes of urgency and incontinence were significantly reduced in patients treated with solifenacin 5mg and 10mg; tolterodine produced smaller, nonsignificant reductions in these endpoints. Mean volume voided per micturition was significantly increased with all active treatments. Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5mg, 21.3% with solifenacin 10mg, and 18.6% with tolterodine 2mg twice-daily.

According to the assessment of the 3rd ICI, solifenacin has a well documented effect in OAB and DO, and the adverse event profile seems acceptable.

**Trospium**

Trospium chloride is a quaternary ammonium compound with antimuscarinic actions and no selectivity for muscarinic receptor subtypes. Its biological availability is less than 10% and it is...
expected to cross the blood-brain barrier to a limited extent. In agreement with such an assumption, trospium seems to have no negative cognitive effects. It has a plasma half-life of approximately 20 hours, and is mainly (60%) eliminated unchanged in the urine by tubular secretion. It is not metabolized by the cytochrome P450 enzyme system. Generally, the recommended dose for adults is 20mg twice-daily.

Trospium has been available in Europe for more than 20 years and no safety concerns have been reported. Several studies have indicated that the drug is useful in the treatment of neurogenic and non-neurogenic OAB/DO. New documentation has further supported the effectiveness of the drug in OAB.

Zinner et al. treated 523 patients with symptoms associated with OAB and urge incontinence with 20mg trospium twice-daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo-controlled trial. Dual primary end-points were change in average number of toilet voids, and change in urge incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urge severity, urinations during day and night, time to onset of action, and change in incontinence impact questionnaire.

Trospium significantly decreased average frequency of toilet voids and urge incontinent episodes compared with placebo. It significantly increased average volume per void, and decreased average urge severity and daytime frequency.

All effects occurred by week one and all were sustained throughout the study. Nocturnal frequency decreased significantly by week four and incontinence impact questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%), constipation (9.5%), and headache (6.5%).

According to the 3rd ICI (2004) assessment, trospium has a documented clinical effectiveness and seems to be well tolerated. In more than 20 years of European experience, no safety concerns have been revealed. It is hoped that future clinical experiences will further establish the effectiveness of antimuscarinics in the treatment of OAB and are needed to demonstrate possible advantages of the newest antimuscarinic drugs.

Summary

Antimuscarinics are still the first line pharmacological treatment of OAB/DO. They may act not only on muscarinic receptors on the detrusor muscle cells (efferent side), but also on non-detrusor structures involved in the activation of the bladder (afferent side). This implies that they can influence the filling phase, decreasing symptoms of OAB with little effect on the voiding contraction.

Among the new drugs expected to become available for treatment in the US, darifenacin and solifenacin are tertiary amines. Both drugs are metabolized by the cytochrome P450 system. Darifenacin has higher selectivity for the M3 receptor subtype than other available drugs and is claimed to have few cardiovascular side effects, and little effect on CNS functions. Solifenacin has a moderate selectivity for M3 receptors and has a long plasma half-life (50 hours).

Both drugs have documented clinical effectiveness and seem to be well tolerated. Trospium is a quaternary amine with no selectivity for muscarinic receptor subtypes, and with limited ability to pass into the CNS. Since it is not metabolized by the cytochrome P450 system, no metabolic drug–drug interactions are expected. Trospium has a documented clinical effectiveness and seems to be well tolerated. In more than 20 years of European experience, no safety concerns have been revealed.

This article can be found with references in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).