TREATMENT OF THE OVERACTIVE BLADDER SYNDROME AND DETRUSOR OVERACTIVITY WITH ANTIMUSCARINIC DRUGS

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ABSTRACT

For decades, antimuscarinics have been the first line pharmacological treatment of urgency, frequency and urge incontinence, constituting the “overactive bladder syndrome” (OAB). These symptoms may or may not be associated with cystometrically demonstrated involuntary detrusor contractions (detrusor overactivity; DO). Treatment with antimuscarinics is not always effective and is associated with side effects limiting its clinical use. New antimuscarinic drugs have recently been introduced with the aim of improving the relation between efficacy and side effects. In this review, the rationale for the use of old and new antimuscarinics in the management of OAB/DO is re-examined and the results of treatment are discussed. (CONTINUENCE 1: 1-8, 2005)

Key Words: Muscarinic receptors, Pharmacokinetics, Darifenacin, Solifenacin, Trospium

The “overactive bladder (OAB) syndrome” has been defined by the International Continence Society as the symptoms of urgency, with and without urge incontinence, usually with frequency and nocturia.1 OAB may or may not be associated with cystometrically demonstrable involuntary detrusor contractions (detrusor overactivity; DO).2,4 Thus, in contrast to OAB, which is based on symptoms, a diagnosis of DO (neurogenic or non-neurogenic) requires cystometric investigation.1

In Europe and the USA, OAB has been estimated to occur in nearly 17% of the population, and the syndrome increases with age.3,6 Overall, the effects of OAB on quality of life are profound,6 but many affected individuals do not seek help from professionals.5 Appropriate management may significantly reduce morbidity and costs for management of the disorder.7,9

The first line pharmacological treatment of OAB/DO has been and still is antimuscarinic (anticholinergic) drugs.10 This treatment is not always effective and it is associated with side effects limiting its clinical use. However, new antimuscarinic drugs have recently been introduced, which in some respects differ from those already available, and which may offer a possibility to optimize therapy with this class of drugs. In this review, the rationale for using antimuscarinics in the treatment of OAB is discussed and also the clinical documentation of effects of the different drugs.

RATIONALE FOR TREATMENT

Muscarinic receptor mechanisms in OAB

Muscarinic receptors comprise five subtypes, M1-M5,11 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 M2 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 M1 receptors (25%), but the M1 receptors are mainly responsible for the normal micturition contraction, whereas the role for the M2 receptors in bladder function has not been established.12

Muscarinic receptors can be found on other structures in the bladder believed to be of importance for bladder activity. They can be found on urothelial cells,13,14 on interstitial cells,15,16 and possibly on sensory nerves.

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.

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.12,17

**ANTIMUSCARINIC DRUGS—GENERAL PHARMACOLOGY**

Antimuscarinics can be divided into two types based on the physicochemical characteristics. Tertiary amines (Figure 1) are well absorbed from the gastrointestinal tract, and can pass into the central nervous system (CNS). CNS adverse effects, manifested as changes in memory, disruption of sleep, hallucinations, confusion and delirium,20 may, at least theoretically, limit their use. Quaternary amines (Figure 2) are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS adverse effects. They still may produce well-known peripheral antimuscarinic adverse effects, such as dryness of mouth, tachycardia, constipation, and blurred vision.21

Antimuscarinic drugs will depress both voluntary and involuntary bladder contractions. They lack selectivity for the receptors in the bladder,12 even if some drugs have been claimed to have functional bladder selectivity, implying that the effects on the bladder are more pronounced than those on other organ systems. The non-bladder actions may result in dose-limiting adverse effects.

Many antimuscarinics (all currently used tertiary amines) are metabolized by the P450 enzyme system in the liver and gastrointestinal tract to active and/or inactive metabolites. The most commonly involved P450 enzymes are CYP2D6, and CYP3A4. The metabolic conversion creates a risk for metabolic drug–drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and/or interacting drug. Antimuscarinics secreted by the renal tubules may theoretically be able to interfere with the elimination of other drugs using this mechanism.

**CURRENT ANTIMUSCARINIC DRUGS—INDIVIDUAL DRUG PROFILES**

![Figure 1. Antimuscarinic drugs: tertiary amines.](image)

**Figure 1. Antimuscarinic drugs: tertiary amines.**

**Figure 2. Antimuscarinic drugs: quaternary amines.**

![Figure 2. Antimuscarinic drugs: quaternary amines.](image)

**Table 1. ICI assessments 2004: Oxford guidelines (modified)**

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
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</thead>
<tbody>
<tr>
<td>Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs)</td>
<td>Grade A: Based on level 1 evidence (highly recommended)</td>
</tr>
<tr>
<td>Level 2: RCTs, good quality prospective cohort studies</td>
<td>Grade B: Consistent level 2 or 3 evidence (recommended)</td>
</tr>
<tr>
<td>Level 3: Case-control studies, case series</td>
<td>Grade C: Level 4 studies or “majority evidence” (optional)</td>
</tr>
<tr>
<td>Level 4: Expert opinion</td>
<td>Grade D: Evidence inconsistent/inconclusive (no recommendation possible)</td>
</tr>
</tbody>
</table>
Many drugs with antimuscarinic properties have been tried for treatment of OAB/DO. For some of them, the effects have not been adequately documented in randomized controlled clinical trials.10 The drugs selected below have, according to assessments made by the International Consultation on Incontinence, held in Monaco in June 2004, a documented beneficial effect in OAB/DO (Table 1, 2).

Table 2. Drugs used in the treatment of detrusor overactivity. Assessments according to the Oxford system (modified)

<table>
<thead>
<tr>
<th>Antimuscarinic drugs</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Trosplum</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propantheline</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Atropine, hyoscyamine</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs with mixed actions</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>2</td>
<td>D</td>
</tr>
</tbody>
</table>

“PURE” ANTIMUSCARINICS

Propantheline

Propantheline bromide is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes. It has a low (5 to 10%) and individually varying biological availability. Propantheline is metabolized (metabolites inactive) and has a short plasma half-life (less than 2 h).25 It is usually given in a dose of 15 to 30 mg 4 times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages. The AHCPR (Agency of Health Care Policy and Research) clinical practice guidelines (Urinary Incontinence Guideline Panel) lists 5 randomized controlled trials with propantheline, showing a reduction of urge (percent drug effect minus percent effect on placebo) between 0 to 53%.

Controlled randomized propantheline trials (n=6) were also reviewed by Thüroff et al.,24 who confirmed a positive, but varying response.

Although the effect of propantheline on OAB/DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful.

Trosplum chloride is a quaternary ammonium compound with antimuscarinic actions and no selectivity for muscarinic receptor subtypes.25,26 Its biological availability is less than 10%,27,28 and it is expected to cross the blood-brain barrier to a limited extent. In agreement with such an assumption, tropium seems to have no negative effects on cognitive functions and on sleep.28-32 It has a plasma half-life of approximately 20 h, and is mainly (60%) eliminated unchanged in the urine by tubular secretion. It is not metabolized by the cytochrome P450 enzyme system. The usually recommended dose for adults is 20 mg twice daily.

Several studies have indicated that tropium may be useful in the treatment of neurogenic33,34 and non neurogenic35-39 OAB/DO.

Zinner et al.40 treated 523 patients with symptoms associated with OAB and urge incontinence with 20 mg tropium 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 volume per void, voiding urge severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire. Tropium significantly decreased average frequency of toilet voids and urge incontinent episodes compared to placebo. It significantly increased average volume per void, and decreased average urge severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 and Incontinence Impact Questionnaire scores improved at week 12. Tropium was well tolerated. The most common side effects were dry mouth (21.8%), constipation (9.5%) and headache (6.5%).

Tropium chloride has a documented effect in OAB/DO, and seems to be well tolerated.

Tolterodine

Tolterodine has no selectivity for muscarinic receptor subtypes. It is extensively metabolized by the cytochrome P450 enzyme system (CYP2D6) and has a major active metabolite with a similar pharmacological profile as the mother compound.21 This metabolite significantly contributes to the therapeutic effect of tolterodine.41,42 Tolterodine is rapidly absorbed and has a plasma half-life of 2–3 h, but the effects on the bladder seem to be more long lasting than could be expected from the pharmacokinetic data. The main metabolite also
has a plasma half-life of 2–3 h.42 The relatively low lipophilicity of tolterodine implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects.43,44 The dose of immediate release tolterodine is 2 mg twice daily. Tolterodine is available as an extended-release formulation, allowing once daily dosing (4 mg), and demonstrating potential advantages over the immediate release form in terms of either efficacy or tolerability.45,46

Several randomised, double blind, placebo-controlled studies on patients with OAB/DO (both idiopathic and neurogenic DO), have documented a significant reduction in micturition frequency and number of incontinence episodes.10,43,44 Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment), and the OPERA (Overactive Bladder: Performance of Extended Release Agents) studies, have further supported its effectiveness.

The OBJECT trial47 compared oxybutynin ER 10 mg once daily with tolterodine IR 2 mg twice daily in a 12-week randomized, double blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urge incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urge incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, extended-release oxybutynin was found to be significantly more effective than tolterodine in each of the main outcome measures adjusted for baseline. Dry mouth, the most common adverse event, was reported by 28% and 33% of participants taking extended-release oxybutynin and tolterodine IR, respectively. Rates of central nervous system and other adverse events were low and similar in both groups. The authors concluded that reductions in weekly urge incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with oxybutynin ER, but tolerability was otherwise comparable, including adverse events involving the central nervous system.

Tolterodine, in both the immediate and extended release forms, has a well-documented effect in OAB/DO. It is well tolerated and is currently, together with oxybutynin, first line therapy for patients with this disorder.

**Darifenacin**

Darifenacin is a selective muscarinic M3 receptor antagonist.49 It is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolised by the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6. The metabolism of darifenacin by CYP3A4 suggests that co-administration of a potent inhibitor of this enzyme (e.g. ketoconazole) may lead to an increase in the circulating concentration of darifenacin,50 indicating that the darifenacin dosage should be limited to 7.5 mg once daily when used concomitantly with a potent CYP3A4 inhibitor. Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg/d.

Theoretically, drugs with selectivity for the M3 receptor can be expected to have clinical efficacy in detrusor overactivity with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes.51 However, the clinical efficacy 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 have been documented in several RCTs.52-54 Haab et al.52 reported a multicentre, double-blind, placebo-controlled, parallel-group study which enrolled 561 patients with OAB symptoms for >6 months. Darifenacin 7.5 mg and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). 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 7.5 mg and...
72.8% with darifenacin 15mg compared with 55.9% with placebo. Darifenacin 7.5 mg and 15 mg, 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 to placebo.

The effects of darifenacin (3.75, 7.5, and 15 mg once daily) on cognitive functions were studied in 129 subjects, aged 65 years and older, with no/mild cognitive impairment. No effects on cognitive functions were demonstrated.

Darifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

**Solifenacin (YM-905)**

Solifenacin (YM903) is a long acting muscarinic receptor antagonist with some selectivity for M3 receptors (10–20 fold). It is a tertiary amine, well absorbed form the gastrointestinal tract (absolute bioavailability 90%). Solifenacin undergoes significant hepatic metabolism involving the cytochrome P-450 system (CYP3A4) into multiple metabolites. The plasma half-life of the oxybutynin metabolite, N-desethyloxybutynin, has pharmacological properties similar to the parent compound, but occurs in much higher concentrations after oral administration. It has been implicated as the major cause of the side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite.

Oxybutynin has several pharmacological effects, some of which seem difficult to relate to its effectiveness in the treatment of OAB/DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effects may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin was shown to have slightly higher affinity for muscarinic M1 and M3 receptors than for M2 receptors, but the clinical significance of this is unclear.

Oxybutynin is available not only in an immediate-release, but also as extended-release and transdermal preparations. The latter preparations allow once daily dosing, and have demonstrated potential advantages over the immediate-release form in terms of either efficacy and/or tolerability. The immediate release form of oxybutynin (OXY-IR) is recognized for its efficacy but also for frequ-
Propiverine has been shown to have combined antimuscarinic and calcium antagonistic actions.70 Propiverine has been shown to have beneficial effects in patients with DO of different etiology. Propiverine has a documented beneficial effect in the treatment of OAB/DO, and is, together with tolterodine, first line treatment for patients with this disorder.

**Propiverine**

Propiverine has been shown to have combined antimuscarinic and calcium antagonistic actions.70 The drug is rapidly absorbed (t<sub>max</sub> 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer on hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man.71 Several active metabolites are formed.72,73 Most probable these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified. The half-life of the mother compound is about 11 h.71 Several active metabolites are formed.72,73

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Propiverine has been shown to have beneficial effects in patients with DO of different etiology. Thriouff, et al.74 collected 9 randomized studies on a total of 230 patients, and found reductions in frequency (30%) and micturitions per 24 h (17%), a 64 ml increase in bladder capacity, and a 77% (range 33–80%) subjective improvement. Side effects were found in 14% (range 8–42%).

In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine’s superiority over placebo.70,74 Madersbacher, et al.75 compared the tolerability and efficacy of propiverine (15 mg t.i.d.) oxybutynin (5 mg b.i.d.) and placebo in 366 patients with urgency and urge incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin.

Dorschner, et al.76 investigated in a double-blind, multicentre, placebo-controlled, randomized study, the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years), suffering from urgency, urge incontinence or mixed urge-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg t.i.d.) or placebo (t.i.d.) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine-2 out of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes.

Propiverine has a documented beneficial effect in the treatment of OAB/DO, and seems to have an acceptable side effect profile.

**CONCLUSIONS**

Antimuscarinics are still the first line pharmacological treatment of OAB/DO. Differences in efficacy between the different agents recommended by the ICI seem difficult to establish. However, it cannot be excluded that there may be important differences in tolerability and safety between the drugs.

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