Trospium Chloride in the Treatment of Overactive Bladder

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INTRODUCTION

Overactive bladder (OAB) is a symptom syndrome that refers to the layered, smooth muscle that surrounds the bladder, the detrusor muscle. This muscle contracts spasmodically, sometimes without a known cause, resulting in sustained, high bladder pressure and the urgent need to urinate.1 People with OAB often experience urination in inconvenient and unpredictable times. This urgency can interfere with daily routines, intimacy, and sexual function, all of which can lead to embarrassment, low self-esteem, and a diminished quality of life.

OAB affects men and women equally. Of an estimated 33.3 million adults in the U.S., 12.2 million have incontinence and 21.2 million do not.2 Tolterodine tartrate (Detrol™, Pharmacia) and oxybutynin chloride (Ditropan™, Ortho-McNeil) are anticholinergic drugs that are currently used for the treatment of OAB. Both of these drugs are potent, competitive antimuscarinic receptor antagonists. However, the need for compounds that are as effective at relieving symptoms of OAB as these, but with fewer unpleasant side effects, has triggered the development of a new anticholinergic agent, trospium chloride (Sanctura™, Indevus/Odyssey).

The Food and Drug Administration (FDA) approved trospium, an antispasmodic, antimuscarinic agent, in May 2004 for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.3 Key factors that characterize the older agents (tolterodine and oxybutynin) include extensive metabolism via the CYP-450 system and the formation of pharmacologically active metabolites, thus increasing the likelihood of metabolic drug interactions.4 Oxybutynin crosses the blood–brain barrier, inducing distinct central nervous system (CNS) effects and thereby affecting patients’ daily routines; in contrast, tolterodine and trospium lack distinct CNS effects, suggesting that they both act primarily in the periphery.5 In doses of 20 mg twice daily, trospium has demonstrated a better risk–benefit profile for long-term therapy than 5-mg, twice-daily doses of oxybutynin.6

ETIOLOGY

For proper urination to take place, the urinary tract and brain must work cohesively to control and initiate the process. The slight need to void urine is stimulated when the urine volume reaches about one-half of the bladder’s capacity. The need to void urine is suppressed by the brain until a person initiates micturition. Normally, when urination has been initiated, the CNS signals the detrusor muscle to contract into a “V” shape and expel urine. As the pressure in the bladder increases, the detrusor muscle remains contracted until the bladder empties. Upon emptying, pressure falls, and the bladder relaxes and returns to its normal muscle tone. However, people with OAB experience a malfunctioning detrusor muscle, resulting in spastic and uncontrollable urination.

OAB is not a disease state; it is a symptom associated with the following underlying conditions:1

- nerve damage caused by abdominal trauma, pelvic trauma, or surgery
- bladder stones
- adverse drug effects (ADEs)
- neurological disease (e.g., multiple sclerosis, Parkinson’s disease, stroke, or spinal cord lesions)

Another condition that produces symptoms similar to those experienced with OAB is a urinary tract infection (UTI), which most commonly occurs in women.

PHARMACOKINETICS

Less than 10% of the trospium dose is absorbed following oral administration; peak plasma concentrations (C_max) are achieved five to six hours after a single dose. Exposure causes a decrease in the C_max and an area-under-the-curve (AUC) concentration of up to 59% and 33%, respectively, for evening doses and morning doses. Because high-fat meals decrease the absorption of trospium by 70% to 80%, this agent should be taken one hour before meals or on an empty stomach.

Following a 20-mg oral dose of trospium, the apparent volume of distribution is 395 (± 140) liters, indicating that most of the 3H-trospium chloride, the radio-labeled form, is distributed in the plasma. At therapeutic concentrations, 50% to 85% of trospium is protein-bound.

It is hypothesized that the major metabolic pathway that trospium follows is ester hydrolysis, followed by conjugation of benzylic acid to form azonisapro-nortropanol with glucuronid acid. The main method of elimination of trospium is via active tubular secretion, with a mean renal clearance four-fold higher than the average glomerular filtration rate. The plasma half-life is approximately 20 hours in healthy people.3

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Special Populations

A person’s age does not affect the pharmacokinetic profile of trospium, but anticholinergic side effects unrelated to drug exposure were often seen in patients 75 years of age or older. The incidence of commonly reported anticholinergic ADs was higher among geriatric patients treated with trospium than among younger patients. Therefore, according to their tolerability, patients who are 75 years of age or older may receive a reduced dose of 20 mg once daily. Pharmacokinetic studies have not been performed in pediatric patients.3

TREATMENT OPTIONS

Therapeutic options for the management of OAB include both medication and behavioral therapy. Antimuscarinic agents with tertiary or quaternary amines remain the first-line (medicinal) therapy for the OAB. These agents reduce urge, stabilize detrusor overactivity, and increase bladder capacity.7,8 Patient education, keeping a voiding diary, managing fluid and diet, timed or prophylactic voiding, pelvic floor exercises, and delayed voiding are behavioral therapies that should be used in conjunction with medicinal therapy.9 Alternative treatments for OAB include bladder training, electrical stimulation, and surgery in severe cases, if all other treatments have failed.10

PHARMACOLOGY

Trospium chloride is a quaternary amine that antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs. It exhibits parasympatholytic action by reducing the detrusor tone of smooth muscle in the bladder as well as uncontrolled detrusor contractions that can cause OAB with incontinence.3

Although the anticholinergic drugs that are currently used to treat OAB have antimuscarinic activity, their affinity to bind to muscarinic subreceptors is variable. Muscarinic receptor subtypes include M1, M2, M3, M4, M5; M2 and M3 are associated primarily with bladder activity in a ratio of 80 to 20, respectively. When compared with other agents, trospium exhibits a higher relative binding to all receptors and is the most equipotent molecule at a ratio of M2:M3. Whereas anticholinergics inhibit M3 and M4 receptors associated with micturition, they also inhibit other muscarinic receptors associated with smooth muscle, secretory glands, bowel motility, ocular function, and the brain, producing unpleasant side effects.7

Efficacy Endpoint

The Zinner Study11

Patients who were 18 years of age or older and who had symptoms of OAB urge incontinence for at least six months were randomly assigned, in a ratio of 1:1, to receive 20 mg twice daily or matching placebo in a 12-week, multicenter, parallel, double-blind, placebo-controlled trial that was conducted at 51 sites. The outcome parameters in this study consisted of two primary efficacy variables: (1) the change in average number of toilet voids per 24 hours and (2) the change in the average number of urge incontinence episodes per 24 hours. The secondary efficacy variables included (1) the time to urgency urgency discomfort that abruptly stops all activity or tasks. Investigators concluded that patients taking 20 mg of trospium twice daily exhibited statistically significant improvements, compared with the placebo group, for the two primary efficacy variables as well as all secondary efficacy variables.

Another study that examined the effects of twice-daily trospium 20 mg used a similar design. The only difference between the two studies was the number of subjects enrolled in each. The
The Todorova Study

Todorova and colleagues conducted a phase 1, single-blind, randomized, placebo-controlled, four-arm, parallel-group clinical trial in 64 healthy, young male volunteers (18 to 35 years of age) to compare the potential CNS adverse effects of the three antimuscarinic drugs—tolterodine, oxybutynin, and trospium—with placebo. Subjects with clinically relevant acute or chronic diseases, a quantitative electroencephalogram (qEEG) outside of the normal range during screening, a history of headaches with qEEG abnormalities, poor EEG quality, laboratory values outside the normal range, positive drug tests, high blood pressure, or abnormal weight were excluded from the study.

Sixteen participants were assigned to receive one of the four trial medications administered in three successive doses every 5 hours:

- placebo given three times a day
- tolterodine 2 mg twice a day plus one placebo tablet
- oxybutynin 5 mg three times a day
- trospium 15 mg three times a day

The objective measures used to assess the effects of each treatment group on the CNS included drug-induced changes in the qEEG of the participants during two different resting conditions and under mental demand. The study results showed that tolterodine and trospium did not induce changes of the qEEG power in five of six frequency bands, compared with placebo (10% confidence interval). Oxybutynin produced significant power reductions in four frequency bands ($P < .01$) with a maximum effect one to two hours after administration, indicating that oxybutynin, which is a highly lipophilic tertiary amine, exerted distinct CNS effects.

Although tolterodine is a tertiary amine, its lipophilicity is 30 times less than that of oxybutynin; therefore, its penetration into the blood–brain barrier is low. The effects of tolterodine on the CNS did not differ significantly from those of trospium, which has a minimal ability to cross the blood–brain barrier. The findings thus suggest that both of these drugs act primarily in the periphery. Therefore, because oxybutynin has more pronounced CNS effects, its use in geriatric patients may be inappropriate.

The Madersbacher Study

Madersbacher et al. conducted a randomized, double-blind, multicenter trial to compare the efficacy, tolerability, and ADEs of trospium with those of oxybutynin HCl (Oxy). Ninety-five patients with spinal cord injuries and detrusor hyperreflexia were evaluated in this study. Individuals weighing more than 90 kg or who were younger than 18 years of age were excluded from the study. The study design consisted of a week without drugs and then two weeks of treatment with either trospium (20 mg twice daily) or Oxy (5 mg three times daily).

There were no statistically significant differences between the trospium and Oxy groups in terms of increasing maximum bladder capacity, compliance, and residual volume and decreasing maximum voiding detrusor pressure. However, the number of withdrawals from treatment and the number of reports of severe dry mouth were fewer for patients taking trospium than for those taking Oxy. Consequently, elderly patients who are more prone to dry mouth may benefit from taking trospium.

ADVERSE DRUG REACTIONS

Anticholinergic ADEs are common with trospium (Table 4). More than half of the patients in the clinical trials experienced one or more ADEs. The most commonly reported ADEs were dry mouth, constipation, abdominal pain (upper), constipation (aggravated), headache, and fatigue.
**CONTRAINDICATIONS AND PRECAUTIONS**

**Risk of Urinary Retention, Decreased Gastrointestinal Motility, and Controlled Narrow-Angle Glaucoma**

Trospium chloride is contraindicated in patients with urinary retention, uncontrolled narrow-angle glaucoma, or gastric retention and in patients who are at risk for the development of these conditions. Patients who have developed a hypersensitivity to trospium or its ingredients should not take it.3

Urinary retention, decreased gastrointestinal (GI) motility, and abnormal vision (mydriasis) are commonly associated with trospium.6 Therefore, this drug should be administered with caution in patients with clinically significant bladder outflow obstruction, GI obstructive disorders, ulcerative colitis, intestinal atony, and myasthenia gravis. Patients who are being treated for narrow-angle glaucoma should use trospium only if the potential benefits outweigh the risks. In such instances, careful monitoring is essential.3

**Renal and Hepatic Insufficiency**

Before they begin therapy with trospium, patients should be assessed for renal insufficiency and hepatic impairment. Patients with severe renal insufficiency (a creatinine clearance below 30 ml/minute) have experienced a 4.5-fold increase in the mean AUC and two-fold increase in the mean Cmax, respectively, as well as an additional elimination phase with a long half-life (approximately 33 hours). Because the Cmax is significant, patients with severe renal insufficiency should receive a single dose of 20 mg/day at bedtime. The pharmacokinetics of trospium has not been studied in patients with mild-to-moderate renal impairment (a creatinine clearance of 30 to 80 ml/minute).

After exposure, patients with mild and moderate hepatic impairment experienced increased Cmax concentrations of 12% and 63%, respectively, with an AUC concentration comparable to that of healthy subjects. Clinicians should take precautions when administering trospium to patients with moderate and severe hepatic dysfunction.3

**CONCLUSION**

Trospium chloride is the newest anti-spasmodic, anticholinergic agent to be approved by the FDA for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. As shown in Table 5, the recommended dose is 20 mg twice daily to be taken one hour before meals or on an empty stomach.14 Dosage modifications should be made for patients who have severe renal impairment with a dose of 20 mg once daily at bedtime. For geriatric patients 75 years of age or older, the dose may be titrated downward to 20 mg once daily, based on tolerability.

Like other available antispasmodic anticholinergic agents, trospium is effective for treating OAB and its symptoms; however, its side-effect profile proves more advantageous than that of older agents.12

**REFERENCES**


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**Table 5  Dosage and Cost of Agents Currently Used to Treat Overactive Bladder**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost*</th>
</tr>
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<tbody>
<tr>
<td>Oxybutynin chloride: average generic price</td>
<td>5 mg PO twice daily or three times daily</td>
<td>$22.20</td>
</tr>
<tr>
<td>Oxybutynin chloride (Ditropan™, Ortho-McNeil)</td>
<td>5 mg PO twice daily or three times daily</td>
<td>$60.60</td>
</tr>
<tr>
<td>Tolterodine tartrate (Detrol™, Pharmacia)</td>
<td>1–2 mg PO twice daily</td>
<td>$102.60</td>
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<tr>
<td>Trospium chloride (Sanctura™, Indevus/Odyssey)</td>
<td>20 mg PO twice daily</td>
<td>$89.33†</td>
</tr>
</tbody>
</table>

PO = by mouth.

*Cost for treatment of one month with the lowest recommended adult dosage, according to the most recent data (June 30, 2004) from retail pharmacies nationwide available from NDC Health, a health care information service company.

† Average wholesale price from the manufacturer.

Data from Med Lett 2004;46(1188):63–64.