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The newer antimuscarinic drugs: Bladder control with less dry mouth

ABSTRACT

Two newer antimuscarinic anticholinergic drugs—tolterodine and extended-release oxybutynin—are approximately as effective in treating overactive bladder as immediate-release oxybutynin, but are more tolerable. I review clinical trial data on the newer agents.

KEY POINTS

The principal anticholinergic side effect of immediate-release oxybutynin is dry mouth, which may be due to one of its metabolites.

Both tolterodine and extended-release oxybutynin produce significantly less dry mouth than immediate-release oxybutynin, although for apparently different reasons.

As tolterodine was slightly less effective than immediate-release oxybutynin in reducing urge incontinence in clinical trials, it is recommended for patients with mildly overactive bladder, but for improvement in frequency and urgency rather than urge incontinence.

TWO NEWER muscarinic receptor antagonists are replacing immediate-release oxybutynin (Ditropan) for treatment of overactive bladder: tolterodine (Detrol, Detrol LA) and extended-release oxybutynin (Ditropan XL). These seem to be approximately as effective as immediate-release oxybutynin, but are associated with significantly lower rates of dry mouth, the principal side effect.

In this article, I review clinical trial data comparing the newer agents with the longtime gold standard, immediate-release oxybutynin.

Because primary care physicians now write most of the prescriptions for overactive bladder, knowing when and how to incorporate these newer drugs into practice is essential.

OVERACTIVE BLADDER: SCOPE OF THE PROBLEM

Overactive bladder affects more than 17 million people in the United States, making it more common than asthma, osteoporosis, or diabetes mellitus, according to some estimates.[1]

Symptoms of overactive bladder are urinary frequency, urgency, and urge incontinence. Individual patients may present with any combination or only one of these symptoms.

Although behavioral and surgical interventions can be used to treat overactive bladder, most physicians use drug therapy as the first intervention. The drugs of choice have been anticholinergics with antimuscarinic activity, although other drugs may be used in association with them, such as the tricyclic antidepressant imipramine or the antispasmodic dicyclomine.

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Immediate-release oxybutynin has been the gold standard drug for overactive bladder for 30 years, and in testing new drugs for overactive bladder, researchers use either immediate-release oxybutynin or placebo in the control group. However, its side effects (dry mouth, constipation, blurred vision, heat intolerance) interfere with its efficacy, prompting efforts to develop agents that are as effective but more tolerable, so that patients can continue taking them in the long term.

TOLTERODINE

Safety

Tolterodine is closely related to terodiline, a drug marketed in Europe in the late 1980s and found to be associated with arrhythmias and acute cardiac events. At that time, clinical studies of terodiline in the United States were halted.

In view of these adverse events with terodiline, patients in trials of tolterodine were very closely monitored with electrocardiography and other cardiovascular measures. The trials demonstrated no safety concerns with tolterodine, and it has an excellent safety profile.[2]

Study goals

Studies of tolterodine for treating overactive bladder looked at three main measures of efficacy:

- How many times patients void per day (goal: a 20% reduction from baseline, approximately the amount of improvement seen with immediate-release oxybutynin)
- The number of episodes of urge incontinence per day (goal: a 50% reduction)
- The volume voided at each micturition (closely related to the number of incontinent episodes).

Efficacy of tolterodine

In four studies of tolterodine[2] (two studies comparing it with immediate-release oxybutynin and two studies comparing it with placebo), tolterodine met the goal of reducing the frequency of urination by about 20%, similar to immediate-release oxybutynin. After 12 weeks, tolterodine 2 mg twice daily was equivalent to oxybutynin 5 mg three times daily.

Tolterodine was not quite as effective as immediate-release oxybutynin in reducing urge incontinence, reducing episodes by about 45% compared with 50% with oxybutynin, although the difference was not statistically significant.

On the basis of these results, tolterodine can be recommended for patients with mild overactive bladder ("dry" overactive bladder), but specifically to reduce frequency and urgency rather than urge incontinence.

Long-term efficacy of tolterodine

So many patients stop taking immediate-release oxybutynin because of dry mouth that it is difficult to make a valid comparison of efficacy, particularly over the long term.

For a patient to notice a clinically significant improvement from baseline, he or she needs to take tolterodine for 5 to 8 weeks.[2] The reason for the delay in effect is not known; a number of other drugs, including oxybutynin, begin to provide some relief earlier.

Symptoms continue to improve during the first 6 months of therapy. In addition, this improvement was sustained for at least 1 year in one study.[3] A decrease in incontinent episodes and an increase in volume voided over an extended period are the most significant and important benefits of tolterodine, and they last as the patient stays on the medication.

Overactive bladder may be more common than asthma, osteoporosis, or diabetes

Tolerability of tolterodine

Patients tolerated tolterodine significantly better than immediate-release oxybutynin: fewer patients complained of dry mouth, fewer withdrew from the studies, and fewer required dosing reductions.[2] Patients reported that dry mouth was less intense than with oxybutynin when it did occur.[2,4,5]

Why less dry mouth with tolterodine?

An animal study[6] suggested that tolterodine causes less dry mouth than immediate-release oxybutynin because tolterodine is somehow more selective, inhibiting muscarinic receptors in the bladder rather than those in the salivary glands, though the reason for this is not understood.

Dosage of tolterodine

The usual adult dosage of tolterodine is 2 mg twice a day, or 1 mg twice a day for patients who are elderly, are concurrently taking a drug that inhibits cytochrome P450, or have hepatic or renal impairment. Dosages as high as 8 mg twice a day have been used in clinical studies.

In the four studies reviewed above, more patients withdrew who were taking placebo compared with tolterodine 1 mg twice daily.[2] Slightly more patients withdrew with 2 mg twice daily compared with placebo, but the difference was not statistically significant.

LONG-ACTING TOLTERODINE

A recent study[7] compared immediate-release tolterodine (2 mg twice a day) with a newer, long-acting form of tolterodine (4 mg once a day). Incontinent episodes were reduced by 53% from baseline with the long-acting form, which was slightly better than with the twice-daily form. This difference was not statistically significant when the results were given as the arithmetic mean continence score. However, when presented as the median rather than the mean number of incontinent episodes, the reduction from baseline in incontinent episodes was 71%, which was statistically significantly greater than with the twice-a-day formulation.[8]

Antimuscarinics reduce urge incontinence by about half

Potential drug interaction. The long-acting form of tolterodine uses a different method of controlled release than extended-release oxybutynin and is pH-dependent. This may be a disadvantage in patients who are taking antacids, for example, since a higher gastric pH may cause the tolterodine capsule to release its medication early, thereby drastically shortening the duration of its effect.[9]

EXTENDED-RELEASE OXYBUTYNIN

Oxybutinin metabolism: Location matters

The molecule responsible for dry mouth with immediate-release oxybutynin therapy may be its metabolite *N*-desethyloxybutynin, not oxybutynin itself.[10]

One study[11] showed that drug delivery routes that bypass the upper gastrointestinal tract may result in much less metabolite formation and fewer anticholinergic side effects. Immediate-release oxybutynin is metabolized by the cytochrome P450 system in the liver and in the gut wall, especially in the upper gastrointestinal tract. This metabolic step results in high levels of the metabolite and limits the amount of oxybutynin that reaches its muscarinic receptors in the bladder.

Extended-release oxybutynin is formulated to be absorbed mainly in the lower gastrointestinal tract (the large bowel), avoiding P450 metabolism. As a result, less metabolite is produced and more oxybutynin is available.

Antimycotic drugs are known to suppress P450 enzyme activity. A study by Chancellor et al[11] tried to determine whether concomitant use of ketoconazole would suppress production of oxybutynin's metabolite and, thus, its side effects. The study showed that ketoconazole suppresses metabolite levels and side effects more with standard oxybutynin than with the extended-release form; this supports the contention that metabolite levels are higher with the standard formulation. The study also showed that, when patients stopped taking ketoconazole, metabolite levels and side effects increased more in those taking standard oxybutynin than in those taking the extended-release form.

Efficacy of extended-release oxybutynin

Studies[12,13] showed that extended-release oxybutynin reduced urge incontinence (the primary clinical end point) and also reduced urinary urgency and frequency, well surpassing immediate-release oxybutynin. Extended-release oxybutynin produced an 83% decrease in the mean incidence of weekly accidents, compared with a 49% reduction with immediate-release oxybutynin.

Adverse effects

In a 1-year US study,[14] more than 1,000 patients who were not prescreened and were from diverse communities treated themselves with extended-release oxybutynin, beginning with a 5-mg tablet each day and increasing the dosage every week as needed. The dosage titration was based on the patient's own assessment of adverse effects and efficacy; those who experienced adverse effects chose either to stop using the medication or to con-

tinue. More than half the patients were over age 65. The incidence of adverse effects related to the central nervous system (eg, deficit in mental acuity or memory) was very low, and during the study 5.7% of patients reported severe anticholinergic side effects, including 3.8% reporting severe dry mouth resulting in discontinuation of the drug.

A double-blind, placebo-controlled study of extended-release oxybutynin in geriatric patients in long-term nursing home care[15] showed a 90% reduction in episodes of urge incontinence per week and an 86% decrease in pad use. These results are clinically important because urinary incontinence is the second leading cause of patient admissions to nursing homes.[16]

Some experts have speculated that oxybutyinin gets into the brain and so, therefore, has more central nervous system effects than tolterodine, but we have no evidence of this. Dmochowski and Appell[17] demonstrated that the incidence of central nervous system side effects in a large patient population given extended-release oxybutynin is quite small. Moreover, any tertiary amine (including tolterodine) crosses the blood-brain barrier.

Chief advantage of the new drugs: less dry mouth

Evaluation of diurnal saliva output

Patients taking immediate-release oxybutynin 5 mg showed a significant reduction in saliva output, but those taking extended-release oxybutynin 10 mg did not.[18]

Another study,[19] which compared tolterodine and both forms of oxybutynin, found no significant differences between tolterodine and extended-release oxybutynin. Saliva production seemed to increase throughout the day, as other studies showed in patients taking placebo. However, saliva production in both the immediate-release oxybutynin and tolterodine groups decreased markedly at about 2 hours after dosing, then gradually returned to normal. Patients taking extended-release oxybutynin had a constant level of saliva output.

SELECTING AN ANTIMUSCARINIC

We recently performed a double-blind, 3-month study in 380 patients, comparing extended-release oxybutynin and tolterodine.[1] The tolerability of both drugs was similar and excellent. At the end of the study, extended-release oxybutynin was more effective than tolterodine as measured by urge incontinence (6.1 ± 9.7 vs 7.8 ± 11.1 episodes per week, respectively), total incontinence (7.1 ± 12.0 vs 9.3 ± 13.4 episodes per week), and frequency of voiding 67.1 ± 22.1 vs 71.5 ± 20.5 per week). While all of these differences were statistically significant, both drugs improved symptoms of overactive bladder significantly from baseline ($P < .001$), demonstrating that, while both drugs are efficacious, extended-release oxybutynin potentially helps more people to a greater extent without compromising safety or tolerability.

Selection of which drug for which patient is based on several factors:

- Degree of incontinence
- Concomitant medications and risk of drug-drug interactions
- Need for dosing flexibility (extended-release oxybutynin approved for 5–30 mg/day; tolterodine for 2–4 mg/day)
- The patient's perception of efficacy and tolerability.

While anticholinergic drugs can help patients with overactive bladder, they have inherent limitations. Newer treatments are under development that target other important mechanisms thought to be responsible for this condition.

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