Article ▸ Ocular Side Effects of Oxybutynin and Other Oral Anticholinergics Used In the Management of Overactive Bladder Syndrome: A Review

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ABSTRACT

Oxybutynin and other oral anticholinergic medications are used in the treatment of patients with overactive bladder syndrome. However, side effects including blurred vision can occur through an extension of this same therapeutic effect. The most common ocular side effects of oral anticholinergics are reduced lacrimation (leading to ocular surface dryness) and cycloplegia (leading to accommodative deficiencies). The oral anticholinergic with the highest likelihood of causing these side effects is oxybutynin as it most easily crosses the blood-brain barrier. Eye care providers are likely to encounter patients on these types of medications and should be aware of possible ocular complications from this class of drugs. A review of this class of medications and their respective side effects is presented here.

Keywords: anticholinergic, antimuscarinic, cycloplegia, ocular dryness, overactive bladder syndrome, oxybutynin

Introduction

Oxybutynin is an oral anticholinergic/antimuscarinic medication developed and researched in the 1950-1960s as a possible musculotropic antispasmodic drug. It has subsequently found a place in contemporary medicine, predominantly for urinary incontinence, overactive bladder syndrome, and pediatric enuresis and secondarily to treat hyperhidrosis complaints.[1-13] Overactive bladder syndrome (OBS) affects 10-17% of adults overall and up to 31% of women and 42% of men over 75 years old. Younger populations including children and young adults can also be affected.[5,6,13-16]

The mainstay of treatment of OBS is the anticholinergic class of medications, including oxybutynin, which all have known possible ocular and systemic side effects.[2,3,5,10,11,13-15,17,18] Oxybutynin chloride is one of a series of acetylenic amino esters that possesses moderately potent anticholinergic, antispasmodic, and local anesthetic actions.[1] It is one-tenth as potent as atropine in causing anticholinergic antispasmodic actions on smooth muscle tissue, and it has been shown to be only 4% effective with mydriasis as compared to the potency of atropine.[1] Even in light of this reduced potency, oral anticholinergics can cause ocular issues by the same mechanism of action. Cycloplegia and ocular surface dryness are the most common patient complaints encountered by eye care providers.[4,7,14-16] The side effect/complaint of blurred vision due to OBS medications is considered to be relatively rare and has been reported in only 3.8% of patients receiving this anticholinergic treatment.[10,16]

Pupil Pharmacology and Innervation Review

The pupils are innervated by both sympathetic and parasympathetic nerve fibers, which are responsible for mydriasis and miosis, respectively. Accommodation of the crystalline lens for near point activities is controlled by the parasympathetic nerve fibers. Muscarinic receptors play an important role in this tug-of-war between the sympathetic and parasympathetic systems to regulate pupillary tone and accommodation. There are five known subtypes of muscarinic receptors in humans: M1-M5. Currently, no physiologic function has been

identified for the M5 subtype.[5-7,17,19] Muscarinic receptor agonism by the parasympathetic nervous system leads to active iris sphincter contraction (miosis) and accommodation of the crystalline lens, while muscarinic receptor antagonism will cause passive mydriasis of the pupil and decreased accommodation. These actions are seen with most nonselective, well-known topical ophthalmic anticholinergic drugs like atropine, scopolamine, homatropine, and tropicamide.[17,19]

Mechanism of Action and Side Effects

Oxybutynin and the other oral anticholinergics used in OBS exert their action by specifically inhibiting the M3 receptors located on the bladder smooth muscle tissue.[7,11] Oxybutynin is selective for both M1 and M3 receptors. M1 is believed to play a crucial role in modulating cognitive function of the brain. M3 also plays an important role in pupil size, accommodation, binocular convergence, and initiating lacrimation of the lacrimal gland.[4,6-8,11,13] This is important with regard to ocular side effects. Since the M3 receptor is located on the ciliary body, the iris sphincter muscles, and the lacrimal gland, when this receptor is blocked by the oral anticholinergics, a blurred-vision cascade occurs stemming from mild mydriasis, cycloplegia, and/or ocular surface dryness.[1-4,6-8,11,13] Other reported ocular side effects in the literature with this class of medications include compensatory accommodative esotropia and acute angle-closure glaucoma in patients with narrow angles due to the inherent mydriatic and cycloplegic effects.[2,3,9,20] Notably, the other systemic side effects commonly attributed to these medications (e.g., dry mouth, constipation, etc.) are also a result of the drugs' interactions with the M3 receptor.[4,6-8,11,13]

Oxybutynin is a relatively non-toxic agent similar to atropine in most cases, but it is only about 1/10th as potent on systemic smooth muscles and only about 1/25th as potent regarding its cycloplegic and mydriatic effects on the eyes.[1] Typical starting doses of oxybutynin start between 3.9 mg and 5 mg, but doses of 10-20 mg are possible.[7,10,14,16,21] As expected, the higher the dose (≥10 mg), the more side effects tend to occur, specifically with regard to the blurred-vision cascade. Therefore, knowing the dose is important in order to gauge the risk of potential ocular side effects.[7,10,14,16,21] In fact, of all the oral anticholinergics available to treat OBS, oxybutynin has the highest risk of causing both systemic and ocular side effects (Table 1).[5,10,14-16] Discontinuation rates due to side effect profiles with the oral anticholinergics are extremely varied and tend to be very unhelpful in general, as discontinuation rates have been reported ranging anywhere between 4 and 88%.[11,14,22]

Table 1. Oral OBS Anticholinergic Medications and their Relative Risk of Causing Ocular and/or Other Side Effects (subtle variations per study)[5,10,14-16]

Anticholinergic Medication	Highest Risk of Causing Side Effects
oxybutynin	Highest
propiverine	High
fesoterodine	Intermediate
solifenacin	Intermediate
tolterodine	Intermediate/Low
darifenacin	Intermediate/Low
trospium	Low

When it was originally being developed, oxybutynin was described as having no limiting CNS actions and as being noticeably free of cardiovascular activity. This makes this drug seemingly have a wide margin of safety.[1] However, we now know that this is false, as a mountain of newer research comparing all of the antimuscarinic agents used in OBS has shown that oxybutynin consistently is the oral anticholinergic agent with the most CNS penetrance.[4-7,15] These CNS side effects are more prominent in the elderly than in the younger population due to the blood-brain barrier weakening as aging occurs. This weakening allows greater drug penetration into the cerebral tissues.[6-8] If antagonism of the

M1 receptor (predominantly found in the brain tissue) is too severe, it can lead to Alzheimer's-like complications in patients taking these anticholinergic medications.[6]

The most common side effects of anticholinergic drugs such as oxybutynin are dry mouth, ocular burning sensation and surface dryness, blurred vision, constipation, tachycardia, impaired REM sleep leading to somnolence/insomnia, hallucinations, confusion, headache, dizziness, memory impairment, and decreased accommodative amplitudes.[3,4,6-8,10,12,15,16,18] For eye care providers, the two most important ocular side effects are ocular surface dryness and decreased accommodation.[4,7,14-16] Blurred vision can confidently be determined to represent a marker of CNS penetration due to reduced accommodation.[6] Decreased accommodation greater than 1.00 diopter has been reported in 7% of patients on oxybutynin compared to 3% of patients on tolterodine[23] and appears to be most likely to occur within the first 4 weeks of initiating oxybutynin therapy.[18] As the lacrimal gland is predominantly stimulated by the M3-subtype muscarinic receptor and is blocked by anticholinergics, one can logically see how dry eye syndrome and/or tear film insufficiencies can occur with the use of these anticholinergic medications due to decreased lacrimation from involvement of the peripheral nervous system.[7,18] Ocular surface disease could lead to degradation of the tear film and increased corneal irregularities, compromising the optical system. The patient would then be susceptible to blurry vision complaints.

In order to cause CNS effects, any anticholinergic drug must first pass through the blood-brain barrier, which is formed by the endothelial cells that line cerebral capillaries and their continuous tight junctions.[6,7,16] Oxybutynin, a tertiary amine, likely has the greatest CNS effect because of its small molecular size, high lipophilicity, and neutral polarity. This allows it to pass through the blood-brain barrier more easily than any of the other related molecules of this same family of drugs.[4,6,7,16] In contrast, the other OBS anticholinergic medications are larger-sized, have moderate polarity, and have lower lipophilicity, which inhibits their ability to cross the blood-brain barrier as readily as does oxybutynin. This leads to a lower risk of CNS side effects.[4,6,7,16] All of the anticholinergic OBS medications available are tertiary amines except for trospium, which is a quaternary amine. Trospium is a large, positively charged, hydrophilic molecule that does not easily pass through the blood-brain barrier. This explains why it has the fewest CNS side effects of all the OBS anticholinergic medications.[7,16]

Efflux transporters, specifically the P-glycoproteins (P-gp) on the membranes of the cerebral endothelial cells making up the blood-brain barrier, do possess the ability actively to transport some substances back into systemic circulation after those substances specifically pass through the blood-brain barrier.[7] However, oxybutynin is not a P-gp substrate, and once it passes the blood-brain barrier, it cannot be pumped back into systemic circulation, leading to a larger risk of toxicity and side effects in comparison to the other OBS medications.[4-7,15]

Other available antimuscarinics used for patients with OBS are darifenacin, fesoterodine, propiverine, solifenacin, tolterodine, and trospium chloride.[4-6,14,16,21] A newer drug, imidafenacin, is a muscarinic-selective anticholinergic medication that cuts down on extraneous side effects from this class of medication. It has a high affinity for bladder muscarinic receptors, specifically, but not other receptors in the body like those in the submaxillary gland, the lacrimal gland, the ciliary body, and the parotid gland.[4] Of all of the OBS medications listed above, oxybutynin appears to be the drug responsible for the majority of adverse side effects and has the highest rate of dropout due to side effects.[7,16,21]

As the oral anticholinergics used in OBS are largely metabolized in the intestinal wall and the liver by first-pass metabolism and are then

excreted via the kidneys, patients with decreased hepatic and/or renal function may be at higher risk of overdose or of experiencing side effects than patients with normal hepatic and/or renal function.[7] Interestingly, co-administration of medications that can inhibit the P-450 enzymes in the liver responsible for metabolizing a variety of substances and medications can lead to a build-up of toxic by-products of anticholinergic OBS medications.[7] Specifically, medications like buproprion, fluoxetine, paroxetine, terbinafine, quinidine, cimetidine, ritonavir, ketoconazole, itraconazole, verapamil, cyclosporine, erythromycin, clarithromycin, and fluconazole, and even grapefruit juice, can lead to a faster build-up of toxic levels of OBS anticholinergics.[7]

A thorough case history and understanding of the drugs which can exacerbate the anticholinergic toxicities is important for eye care providers to know and to understand. Working through the treating physician to determine if decreasing the overall dosage is appropriate is a key step. If the dose cannot be reduced or stopped, or if the patient is still symptomatic despite reducing the dose, then low-plus spectacle prescriptions and/or vision therapy should be strongly considered for those patients with accommodative dysfunction or compensatory binocular vision problems.

Pharmacology – ANTICHOLINERGIC & NEUROMUSCULAR BLOCKING AGENTS (Used with Permission from Speed Pharmacology)

Conclusion

Eye care providers need to be aware of possible ocular complications stemming from systemic anticholinergic use in patients with OBS. Simple reassurance and acknowledging the drug's known ocular side effects to the patient is all that is needed in the vast majority of instances. However, in the presence of proven ocular side effects from oral ingestion of these anticholinergics, the prescribing physician should be notified by the managing eye care provider.

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