Oxybutynin for treatment of nocturnal enuresis in children

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Abstract

Question A 7-year-old child and his parents visit my clinic owing to the child's frequent bed-wetting. During the day, he has no problem controlling his urination. The family has tried behavioural methods but has failed to achieve dryness during the night. They ask to begin medical treatment. Is oxybutynin a safe and effective drug for treating nocturnal enuresis?

Answer Oxybutynin is an anticholinergic drug that has not been proven to be effective for treatment of nocturnal enuresis not accompanied by daytime symptoms, such as urgency. It can be added as a second-line drug and is effective for treating children with both daytime and nighttime wetting. Nevertheless, its common adverse effects, which can involve the central nervous system, should be considered when deciding whether or not to use it, especially in young children.

Résumé

Question Un enfant de 7 ans et ses parents me consultent à la clinique en raison d'une fréquente énurésie la nuit. Durant le jour, l'enfant n'a pas de problème à contrôler ses mictions. La famille a essayé des méthodes comportementales mais elles n'ont pas réglé le problème d'incontinence durant la nuit. Ils demandent de commencer un traitement médical. L'oxybutynine est-elle sûre et efficace comme traitement pharmaceutique de l'énurésie nocturne?

Réponse L'oxybutynine est un médicament anticholinergique dont l'efficacité n'a pas été prouvée pour le traitement de l'énurésie nocturne sans symptômes diurnes, comme l'impériosité. Elle peut être ajoutée comme médicament de deuxième intention et est efficace pour traiter les enfants incontinents pendant le jour et la nuit. Néanmoins, ses effets secondaires courants, qui peuvent toucher le système nerveux central, devraient être pris en compte dans la décision de l'utiliser ou non, surtout chez de jeunes enfants.

Nocturnal enuresis (NE) is the involuntary passage of urine during sleep beyond the age of anticipated nighttime bladder control, which is generally accepted to be 5 years of age. Approximately 15% of children wet the bed at night at age 5, and there is a spontaneous resolution rate of about 15% per year.[1] Nocturnal enuresis is classified as monosymptomatic or polysymptomatic. Most children (80% to 85%) with NE only have night wetting and are classified as monosymptomatic.[1] Children with polysymptomatic NE also have daytime bladder symptoms, such as urgency, frequency, or other signs of bladder instability.[2] Although it is a mostly benign and self-limiting condition, NE can cause considerable distress to the child and his parents, and successful treatment has been shown to improve the child's self-esteem and psychological function.[2] Nevertheless, treatment before the age of 6 years is rarely indicated.

Treatment options

The pathogenesis of NE is multifactorial and involves hormonal (low vasopressin levels), functional (bladder instability), sleep-related, and psychological factors. Treatments for NE address these different underlying pathogenic mechanisms. Desmopressin, a synthetic analogue of vasopressin, acts to decrease urine output by water retention.[1,3] Enuresis alarms are aimed to encourage awakening in response to full bladder sensation,[4] and oxybutynin targets bladder detrusor instability. Imipramine, a tricyclic antidepressant, is also used for NE treatment. It has been shown to improve symptoms, but its exact mechanism of action is not fully known.[1] Desmopressin is the first-line medical treatment choice in monosymptomatic NE; however, in 2007 the Food and Drug Administration issued an alert that restricts intranasal (but not oral) desmopressin use for NE in children owing to risk of severe hyponatremia and seizures.[5] Consequently, oxybutynin might be more frequently prescribed for NE.

Indications and effectiveness

Oxybutynin is an anticholinergic and antispasmodic agent that decreases uninhibited bladder contractions.[6]

It competitively antagonizes the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It also has direct spasmolytic effects on bladder smooth muscle as a calcium antagonist.[6] Oxybutynin is used successfully for treatment of urologic disorders such as urge incontinence[7] and neurogenic bladder.[8] Because detrusor hyperactivity plays a part in NE pathogenesis, oxybutynin is suggested to be effective when treating NE. The recommended dose is 5 to 10 mg at bedtime.[1]

Only 1 double-blinded study compared oxybutynin with placebo for treatment of NE.[9] Thirty children with primary monosymptomatic NE were given 10 mg of oxybutynin for 4 weeks. All children also received 4 weeks of placebo administration before or after the drug treatment period. Frequency of NE episodes did not differ between the drug regimen period and the placebo period. Although oxybutynin for monosymptomatic NE was shown to be no more effective than placebo, several studies demonstrated that it was effective for patients with polysymptomatic enuresis and for those with abnormal urodynamics.[3,10] In a multicentre study from Italy, oxybutynin was only given to children who had daytime symptoms (urgency or incontinence) in addition to enuresis.[10] Half of the children responded to treatment, increasing the number of dry nights to 5 to 7 a week; when oxybutynin was combined with desmopressin, 71% responded. Other studies that combined oxybutynin and desmopressin yielded similar results.[11,12] Oxybutynin was also shown to be more effective in combination with imipramine in a prospective study of 22 children between the ages of 6 and 12 years with primary monosymptomatic NE. The mean number of wet nights per week decreased from 6.1 to 1.7 ($P<.01$) after administration of the combined therapy.

Efficacy, defined as more than a 50% decrease in wet nights per week, was established in 20 patients (91%). Relapses occurred in 60% of patients during the follow-up period.[13]

The overall impression from these studies is that oxybutynin has a role as a second-line treatment, mainly as a combined drug when the child does not respond to first-line treatments or in cases of polysymptomatic NE.

Safety profile

Oxybutynin can cause anticholinergic adverse effects, including oral (dry mouth, dysphagia), visual (dry eyes, blurred vision), and gastrointestinal (diarrhea, constipation, distention) symptoms in up to 76% of patients.[14] However, the anticholinergic effects on the central nervous system (CNS) are of greater concern. Oxybutynin crosses the blood-brain barrier, as evidenced by its effects on quantitative electroencephalography in controlled studies.[15] A recent review of the Food and Drug Administration data regarding reported CNS adverse effects associated with oxybutynin revealed that 31% of pediatric reports involved the CNS (compared with 11% of adult reports).[16] Hallucinations (eg, sensing insects or beasts crawling on the body) were the most common CNS events reported among children, followed by agitation, sedation, confusion, amnesia, and abnormal dreams (eg, nightmares). Thirty percent of cases (excluding accidental exposures) involved oxybutynin prescribing in children younger than 5 years of age (when medical treatment of NE is rarely justified). In most cases the dose was 10 mg/d or less, and the events occurred within 1 month of beginning oxybutynin treatment. The authors were concerned that long-term administration of oxybutynin to young children might produce neurodevelopmental effects. Sommer et al performed neuropsychological function tests on 15 children with diurnal incontinence treated with oxybutynin and compared the results with those of 10 children receiving behavioural intervention only. Oxybutynin was not associated with cognitive impairment following the treatment.[17] Another study with 14 children found no negative long-term effects of oxybutynin on short-term memory and attention span.[18] However, those studies were small and lacked long-term follow-up.

Conclusion

Oxybutynin is proven to be effective when treating polysymptomatic NE, most probably through reduction of bladder instability. It could also be used as additive treatment to desmopressin or imipramine in children with monosymptomatic NE who are not responsive to first-line treatment. Nevertheless, oxybutynin can cause disturbing adverse effects involving the CNS and should be used with caution in young children.

Competing interests
None declared

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