Palliative Care Rounds

Sublingual Atropine Drops for the Treatment of Pediatric Sialorrhea

Adam Rapoport, MD, FRCPC, MHSc
Max and Beatrice Wolfe Children’s Centre, Temmy Latner Centre for Palliative Care, Mount Sinai Hospital, and Division of Pediatric Medicine, Hospital for Sick Children, Toronto, Ontario, Canada

Abstract
Excess oral secretions or sialorrhea is a common problem affecting children and adults with neurological disorders, as well as those approaching the end of life because of a variety of underlying illnesses. Systemic anticholinergic medications are often prescribed in an attempt to improve quality of life and reduce complications; yet, response rates are variable, and a sizable proportion of patients discontinue these drugs as a result of intolerable side effects. This report describes the successful use of a local treatment, sublingually delivered ophthalmic atropine drops, to reduce sialorrhea in a child receiving palliative care. In addition, medical evidence for the safety and efficacy of traditionally prescribed systemic medications for the treatment of pediatric sialorrhea is reviewed.

J Pain Symptom Manage 2010;40:783–788. © 2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Sialorrhea, drooling, excess oral secretions, anticholinergic medications, atropine, death rattle, palliative care, pediatrics

Introduction
Excess oral secretions or sialorrhea is a significant problem in children with complex neurodevelopmental disorders. Sialorrhea varies in prevalence depending on the underlying disorder; estimates range between 10%1 and 78%2 in children with cerebral palsy and 28% in a cohort of children with neurological impairment because of a variety of causes.3 Significant drooling can negatively impact the quality of life of affected children and their caregivers3,4 and may cause local skin maceration, perioral infection, aspiration, and dehydration.1,5–7 In children approaching the end of life, the problem of excess oral secretions is both common and particularly challenging to manage. This is not only true for those dying from underlying neurological disorders8,9 but also for children dying of other causes, including cancer without neurological involvement.10

Although many treatments are available for drooling, no reliably effective therapy has emerged. Evaluations of surgical procedures and injections with botulinum toxin have demonstrated variable success, and each of these interventions carries a risk of serious complications.11–14 Anticholinergic medications, including glycopyrrolate, scopolamine (hyoscine), and benztropine, have all been shown to decrease drooling, but their use is...
limited by a wide range of side effects resulting from systemic absorption.\(^5,7,15,16\) Recently, sublingually administered ophthalmic atropine has been used to treat excess oral secretions in adults.\(^17–22\) This case report describes the successful use of sublingual atropine to reduce sialorrhea in a child with metachromatic leukodystrophy (MLD) receiving palliative care.

**Case Report**

A 14-year-old boy with MLD, a metabolic disease resulting in progressive neurological deterioration, was admitted to hospital with recurrent intussusception around his gastrojejunostomy tube. MLD is a life-limiting condition that invariably leads to feeding intolerance and difficulty swallowing as neurological status declines. As this was the fourth intussusception in four months, the patient was admitted for temporary parenteral nutrition and hydration support while a plan could be formulated that was consistent with the overall goals of care.

The family believed that the patient enjoyed a good quality of life with minimal suffering before the recurrent intussusceptions; however, in light of his underlying disease trajectory, all care was focused on measures to optimize comfort. During this admission, it became evident that a major source of suffering for both the patient and family was his excess oral secretions. The patient required frequent suctioning throughout the day and night, his secretions often resulted in prolonged desaturations, and it was suspected that he chronically aspirated on his own saliva. Systemic medications and surgical options for the treatment of sialorrhea were discussed with the family, but concerns about side effects, drug interactions, and risks of anesthesia made all of these treatments unattractive.

The patient’s family agreed to a trial of sublingually delivered 0.5% ophthalmic atropine after a literature review suggested that it might be efficacious and have few, if any, adverse effects. Atropine was given as one drop (0.25 mg) sublingually every six hours as needed. The patient was monitored for adverse reactions, including common anticholinergic effects such as facial flushing, tachycardia, behavioral changes, urinary retention, and constipation.

Within 24 hours of starting atropine, the patient’s family and nurses felt that the drug had significantly reduced his oral secretions. The onset of action was perceived to be between 15 and 30 minutes, and the duration of action was approximately four hours, based on noticeable changes in the need for oral and pharyngeal suctioning. Without altering his total fluid intake, the need for suctioning reduced from his previous baseline of 10–15 times daily to zero to two times over nearly five weeks of observation. On most days, the patient required no suctioning at all. Oxygen desaturations below 90%, previously a regular occurrence, all but discontinued and served as a reminder that the patient was due for another dose. On a few occasions, the patient’s mother left the hospital for brief periods. On returning, she was consistently able to determine whether her son had received the atropine during the past six hours based on the presence or absence of noisy respirations and drooling.

After more than two weeks of treatment without adverse effects, the atropine was withheld because of the acute development of tongue fasciculations and dystonia. Nearly six hours after the last dose of atropine was given, the family and staff noted a significant increase in the need for suctioning and the frequency of desaturations, both of which occurred at least once per hour. The tongue fasciculations and dystonia resolved on cessation of intravenous metoclopramide, which had been prescribed only 24 hours before the onset of these symptoms to promote gastrointestinal motility and feeding tolerance. Sublingual atropine was restarted shortly thereafter, with complete resolution of desaturations and the need for suctioning within one hour of the initial dose. Neither the tongue fasciculations nor dystonia returned on reestablishing the atropine.

No obvious adverse effects were identified. Before initiating the atropine, the patient had repeated episodes of urinary retention believed to be secondary to his underlying MLD, which resulted in an indwelling Foley catheter. As such, urinary retention could not be assessed. There was no facial flushing or constipation, and his behavior never deviated from baseline. The patient’s cardiac monitor did not capture any significant tachycardia.
Discussion

The management of excess oral secretions is a challenge in adults and children who are living or dying with this problem. Regardless of the age or the underlying condition, the cause of sialorrhea is the inability to handle one’s own saliva, rather than hypersalivation. Yet, because the cause is often irreparable, treatment is aimed at reducing the production and consistency of saliva to a more manageable state.

Atropine (DL-hyoscyamine) is an anticholinergic medication that reduces saliva production by blocking the muscarinic (M3) receptor sites on the salivary glands. Although long recognized as an antisialogogue, atropine never gained wide acceptance as a treatment for chronic drooling. Instead, alternative anticholinergics, including glycopyrrolate, scopolamine, and benztropine, have become the drugs of choice for sialorrhea as a result of their superior ability to decrease salivation and reduced adverse effect profiles. Nonetheless, these medications may still cause significant adverse effects that necessitate their discontinuation (Table 1).

The most researched drug for the treatment of drooling in children is glycopyrrolate. A retrospective review describing its use in 37 children with cerebral palsy found that 46% experienced various side effects. In this study, 27% chose to discontinue glycopyrrolate because of intolerable adverse effects despite acknowledgment of the drug’s efficacy in reducing oral secretions. A randomized controlled trial investigating the efficacy and safety of glycopyrrolate in neurologically impaired children with sialorrhea also found a high rate of adverse effects. Sixty-nine percent of children in this study experienced adverse effects while receiving glycopyrrolate, which resulted in nearly 20% choosing to drop out. Interestingly, in spite of the generally held belief that glycopyrrolate is unable to penetrate the blood-brain barrier, behavioral changes were the most common side effects described in this study, including drowsiness, irritability, restlessness, and mood changes. Adverse central nervous system effects of glycopyrrolate in children also have been reported elsewhere.

Scopolamine is an attractive drug for use in children because it can be delivered via transdermal patch. Unfortunately, scopolamine’s clinical efficacy as a treatment for sialorrhea may be marred by unwanted adverse effects secondary to its systemic absorption. In a randomized, controlled, crossover trial involving 11 children with problematic drooling, two-thirds developed clinically relevant pupillary dilation and three children had increased mouthing behaviors. Fewer than half of the children remained on the scopolamine patch after study completion; however, the reason for discontinuation was not provided. A study comparing transdermal scopolamine to botulinum toxin for the treatment of pediatric sialorrhea reported side effects in over 80% of subjects receiving scopolamine. In addition to pupillary dilation, subjects in this study experienced xerostomia, restlessness, somnolence, and confusion; almost

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended Dosing</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrrolate</td>
<td>Oral: 40–100 mcg/kg/dose, three to four times daily</td>
<td>Drowsiness, irritability, restlessness, and mood changes</td>
</tr>
<tr>
<td></td>
<td>IV/SC: 4–10 mcg/kg/dose, every three to four hours</td>
<td>Dry mouth or thick secretions, urinary retention, flushing, and constipation</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>IV/SC: 6 mcg/kg/dose, every six to eight hours, (maximum dose: 0.3 mg/dose) or 1.5–2.5 mcg/kg/hour continuous</td>
<td>Pupillary dilatation and mouthing behaviors</td>
</tr>
<tr>
<td></td>
<td>Transdermal (must be &gt;12 years): Apply one patch (1 mg) behind ear, every 72 hours</td>
<td>Restlessness and somnolence</td>
</tr>
<tr>
<td>Benztropine</td>
<td>IV/SC/oral: 0.02–0.05 mg/kg/dose, one to two times daily</td>
<td>Irritability, vomiting, stereotypical behaviors, and pupillary dilation or visual disturbances</td>
</tr>
<tr>
<td>Atropine</td>
<td>SL: 1–2 drops of 0.5% ophthalmic solution, every four to six hours</td>
<td>Facial flushing; constipation; tachycardia; other anticholinergic effects</td>
</tr>
</tbody>
</table>

IV = intravenous; SC = subcutaneous; SL = sublingual.


*No adverse effects were experienced by the patient in this case report.
10% dropped out because of the adverse effects of scopolamine. Esotropia is an additional ocular side effect that has been described in a child on the scopolamine patch for sialorrhea. Based on clinical observations alone, one publication recommended avoiding scopolamine patches in hot weather to avoid heat sensitivity from decreased perspiration. Finally, case reports of acute confusion and hallucinations in children using scopolamine patches to control nausea and vomiting has led to the term “scopolamine psychosis.”

Benztropine was found to be effective for the treatment of sialorrhea in a randomized, controlled, crossover trial in which 27 participants with neurodevelopmental disorders were enrolled, 14 of whom were pediatric. At least three (11%) patients dropped out of the study because of adverse reactions to benztropine, which included irritability, vomiting, stereotypical behaviors, and pupillary dilatation. Four additional patients dropped out of the study; it is uncertain whether adverse effects from benztropine may have contributed to this decision. In a case series of N-of-1 trials involving three children with cerebral palsy and excess drooling, one child discontinued benztropine because of an intolerable visual disturbance despite significant improvement in drooling.

The frequent adverse effects associated with medications used to treat drooling in children have resulted in some clinicians electing to avoid this form of therapy altogether. Over a 30 year experience, Crysdale et al. chose to medicate only 14 of 1487 children, preferring to treat the bulk of patients through surgical intervention instead. “[W]e do not believe in utilizing a systemic medication long term in children for what we perceive basically as a localized problem” was offered as justification. Yet, the risk of anesthesia, anatomical considerations, and/or procedural complications may preclude surgical- or injection-based interventions in medically complex children or those receiving palliative care for advanced illness.

The management of excess oral secretions may be particularly relevant for pediatric patients at the end of life. Noisy breathing or “death rattle” is a frequent symptom encountered in dying children, which can be very distressing to caregivers. Because it results from airflow through an upper respiratory tract filled with secretions, noisy breathing in dying patients is generally treated using the same anticholinergic medications prescribed for sialorrhea. At present, no studies have investigated the use of anticholinergic medications in children with death rattle; dying adults with this symptom, however, demonstrate variable responses to these drugs, with up to 40% having no response at all.

Sublingual atropine has many potential advantages over other interventions for excess oral secretions: it is easy to deliver, noninvasive, fast acting with reversible effects, and inexpensive. Despite the fact that no serious adverse effects have been reported in the small body of literature on sublingual atropine, its effectiveness for the treatment of sialorrhea remains uncertain. One adult case series reported “immediate relief” and “instantaneous” results of clozapine-induced sialorrhea with the use of one drop of 1% ophthalmic atropine solution given at bedtime. Two additional case reports described similar findings. A pilot study involving adults with sialorrhea secondary to Parkinsonism found both subjective and objective improvements with one drop of 1% solution given twice daily.

At this time, only one randomized controlled trial has investigated the efficacy of atropine to reduce sialorrhea. In this crossover design involving 22 adults receiving palliative care for esophageal or gastric cancer, no difference was observed between placebo and treatment with two drops of 0.5% sublingual atropine every six hours. Although the results of this trial contribute to the body of evidence regarding the efficacy of sublingual atropine, they should not be taken as definitive. There are a number of potential reasons for a negative study result: inadequate sample size, heterogeneous variation in response among participants, inaccurate measurement, and so forth. The authors of this study suggest that their equivocal findings may have been caused by insufficient dosing. Multiple studies will be required to conclusively determine if, and under what circumstances, sublingually delivered atropine is effective for the treatment of sialorrhea.

The optimal dosing of sublingual atropine in children and adults remains unknown. It is reasonable to assume that the pharmacodynamics of sublingual atropine fall somewhere between those of the intravenous and the oral routes of
administration. Studies using intravenous atropine for the treatment of infantile hypertrophic pyloric stenosis have shown a cumulative daily dose of 0.1 mg/kg/day to be safe. Side effects, including mild facial flushing, tachycardia, and transient elevation of serum alanine aminotransferase (ALT) to less than twice normal values, were well tolerated and resolved without intervention. Oral atropine appears to be safe and well tolerated at doses of 0.03 mg/kg. The duration of action of sublingual atropine is likely similar to that of oral and intramuscular delivery up to four hours.

In the case described above, sialorrhea was identified as a key symptom negatively impacting the quality of life of an adolescent with a life-limiting metabolic disease. Nonetheless, the family was reluctant to try any traditional treatments because of their associated adverse effects and the potential for interactions with the patient’s multiple systemic medications. A trial of sublingual atropine was suggested on the patient’s multiple systemic medications. A dosing frequency of every six hours (as needed) was chosen to promote patient safety. However, with a presumed duration of action of four hours, it is not surprising that the family and staff felt that he would have benefited from more frequent dosing.

This is the first known case report describing the successful use of sublingually delivered ophthalmic atropine to control excess oral secretions in a pediatric patient. Family members and health care providers found atropine to be fast acting, well tolerated, and devoid of observable adverse effects. Although no validated objective measures were used, it may be argued that, particularly in palliative patients, a subjective improvement in any symptom causing suffering is perhaps the most important outcome. Despite this patient’s positive response, the effectiveness of sublingual atropine for the treatment of sialorrhea remains unproven. Nevertheless, it appears to be both safe and worthy of consideration, particularly in patients at risk of anticholinergic adverse effects, such as men with prostatic hypertrophy or individuals with cardiac arrhythmias.

References


15. Jongerius PH, van Tiel P, van Limbeek J, Gabreels FJ, Rotteveel J.J. A systematic review for...


