New Drug Review

Glycopyrrolate for Chronic Drooling in Children

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ABSTRACT

Background: Sialorrhea, or drooling, is seen in the pediatric population, especially in patients with cerebral palsy and other neurodevelopmental disabilities. If medication use is warranted, anticholinergic agents are the drug of choice; however, adverse effects limit their use. Glycopyrrolate, a synthetic anticholinergic that acts at peripheral muscarinic receptors, has been used off-label for excessive drooling in children with neurodevelopmental disabilities for years. Product formulations restricted the use of glycopyrrolate. However, an oral solution was approved by the US Food and Drug Administration for children ages 3 to 16 years with neurologic disorders for chronic severe drooling in 2010; it became available for use in 2011.

Objective: This article provides an overview of the pharmacology, clinical efficacy, and tolerability of glycopyrrolate when used for sialorrhea in children.

Methods: To evaluate the efficacy and safety profile of glycopyrrolate for the treatment of sialorrhea in children, a comprehensive search was performed of the MEDLINE database (1966–February 25, 2012) and International Pharmaceutical Abstracts as well as references from additional review articles identified. Searches were conducted using the terms *glycopyrrolate, sialorrhea, drooling, secretion,* and *pediatrics*. The terms *drug-induced* and *Parkinson disease–associated sialorrhea* were excluded from the search. The pharmaceutical manufacturer of the oral solution was contacted for medical and study information.

Results: Oral bioavailability of glycopyrrolate varies widely, with a median of 3.3%. Mean C_{max} in children was determined to be 0.37 μg/mL, and mean T_{max} was 3.1 hours. The clearance in children ranges from 0.6 to 1.43 L/kg/h. The $t_{½}$ ranges from 22 to 130 minutes and 19 to 99 minutes in infants and children, respectively. Six studies describing the use of glycopyrrolate for drooling in children were identified. A double-blind, crossover trial of 27 patients (age range, 4–19 years) demonstrated a reduced mean drooling score (modified Teacher's Drooling Scale [1 = never drools to 9 = clothing, hands, and objects frequently become wet]) for glycopyrrolate (mean highest tolerated dose, 0.11 mg/kg) compared with placebo of 1.85 versus 6.33 ($P < 0.001$). In a parallel study of 36 patients (age range, 3–16 years), 14 of 20 patients randomized to receive glycopyrrolate solution showed improvement in the mean modified Teacher's Drooling Scale score compared with only 3 patients receiving placebo (−3.5 vs −0.1, respectively). Glycopyrrolate was initiated at 0.02 mg/kg per dose orally TID (Max dose: 3 mg) and titrated over a 4-week period. Adverse effects identified in studies include dry mouth (9%–41%), constipation (9%–39%), and behavioral changes (18%–36%).

Conclusions: Glycopyrrolate is effective in decreasing sialorrhea in children with cerebral palsy or other neurodevelopmental disabilities. Adverse effects did occur, more frequently at higher doses, and should be monitored. (*Clin Ther*. 2012;34:735–742)

Key words: anticholinergic, children, drooling, glycopyrrolate, pediatrics, sialorrhea.

INTRODUCTION

Sialorrhea, or drooling, is seen in the pediatric population and is defined as saliva that unintentionally goes beyond the lip margin.[1] Drooling is normal in infants and decreases as they develop oral motor skills, usually at ~18 months of age. However, the occurrence of continual drooling after 4 years of age should be evaluated.[1] Sialorrhea is most commonly seen in patients

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with cerebral palsy (10%–25%) and other neurodevelopmental disabilities.[1]

Saliva is primary produced by the submandibular and sublingual glands during normal body activity. Its role is to maintain the oral pH; aid in bacterial growth, dental health, and lubrication; and assist with the digestion of food.[1] When the parotid gland is stimulated secondary to eating, it releases a large amount of saliva. Patients who have excess production of saliva or the inability to swallow large amounts tend to exhibit drooling. Although it is not a life-threatening condition, drooling is associated with physical, social, and psychological issues.

Speech or physical therapy with oromotor or behavioral exercises may be beneficial for some patients with neurodevelopmental disabilities and is generally used first.[1] Medications that decrease the volume of saliva are usually the subsequent treatment option, with surgical intervention as a last-line resort. Anticholinergic agents are primarily the drugs of choice; however, adverse effect profiles have limited options due to the inability to restrict the antimuscarinic activity to specific sites. Glycopyrrolate is a synthetic quaternary ammonium similar to atropine that inhibits acetylcholine at parasympathetic sites such as secretory glands.[2–4] It has been used off-label for excessive drooling because it reduces the volume of saliva and has fewer adverse effects due to its inability to cross the blood–brain barrier.[3,4] General dose recommendations for controlling drooling with glycopyrrolate include the following: oral doses, 40 to 100 μg/kg per dose administered TID to 4 times daily without regard to food; intramuscular/intravenous injection, 4 to 10 μg/kg per dose administered TID to 4 times daily.[4] Glycopyrrolate is available in brand* and generic tablet and injectable solution formulations. However, the injectable product contains benzyl alcohol, which has been associated with a "gasping syndrome" in neonates and should be used with caution.[4] Because an oral liquid was not available, product formulation availability may have restricted the use of glycopyrrolate in patients. To circumvent this issue, tablets could be crushed and administered or the injectable formulation could be used in enteral therapy in an inpatient setting. Recipes for making an extemporaneous suspension have been available but had a shorter shelf life. A newly published stability study of a compounded suspension (0.5 mg/mL) determined 90-day stability at room temperature for this formulation.[5]

However, in June of 2010, an oral solution† (1 mg/5 mL) was approved by the US Food and Drug Administration for use in children ages 3 to 16 years with neurologic disorders for chronic severe drooling.[6] This is the first approval of a glycopyrrolate product for excessive drooling. The manufacturer recommends an initial dose of 0.02 mg/kg per dose administered orally TID. Doses may be increased by 0.02 mg/kg every 5 to 7 days to a maximum of 0.1 mg/kg per dose TID or 1.5 to 3 mg per dose. A detailed dose titration table is provided in the package insert from the manufacturer.[6] It is formulated as a clear, cherry-flavored solution and should be stored at room temperature. The drug was made available for use in April 2011. However, for a patient to receive the solution, the physician must order the medication through a specialty pharmacy (Diplomat Specialty Pharmacy, Flint, Michigan), and it is then shipped directly to the patient or to the physician's office.[7]

This article provides an overview of the pharmacology, clinical efficacy, and tolerability of glycopyrrolate when used for sialorrhea in children.

METHODS

Relevant reports pertaining to the use of glycopyrrolate for drooling or sialorrhea in children were identified through a MEDLINE database (1966–February 25, 2012) and International Pharmaceutical Abstracts search. Searches were conducted using the terms *glycopyrrolate, sialorrhea, drooling, secretion,* and *pediatrics*. The terms *drug-induced* and *Parkinson disease–associated sialorrhea* were excluded from the search. References in review articles identified were also screened for additional publications. Abstract data were not included. The pharmaceutical manufacturer of the oral solution was contacted for medical and study information.

RESULTS

Clinical Pharmacology

Oral bioavailability of glycopyrrolate varies widely. One study in 6 healthy children (median age, 10 years) found a range of 1.3% to 13.3%, with a median oral bioavailability of 3.3%.[8] The manufacturer recommends that the oral solution be administered at least 1

*Trademark: Robinul® and Robinul Forte® (Shionogi Pharma, Inc., Florham Park, New Jersey).

†Trademark: Cuvposa™ (Shionogi Pharma, Inc.).