

Oral glycopyrrolate for the treatment of chronic severe drooling caused by neurological disorders in children

Marian L Evatt

Department of Neurology, Atlanta Veterans Administration Hospital and Emory University School of Medicine, Atlanta, GA, USA

Abstract: Excessive drooling may complicate the care of children with chronic neurological conditions by socially isolating both patients and families and by causing secondary dermatitis and infection. Normal control of saliva requires normal integrity of oral structures, normal oropharyngeal sensation, and motor functioning, as well as normal cognitive awareness and rate of salivary production. Glycopyrrolate is an anticholinergic medication with a quaternary structure that recently received Food and Drug Administration approval to treat sialorrhea due to neurological problems in children ages 3–16 years. This review summarizes the few published studies of safety and efficacy of glycopyrrolate for drooling in children with chronic neurological conditions.

Keywords: drooling, sialorrhoea, sialorrhea, children, glycopyrrolate

Introduction

The persistence of drooling in children older than age 3 years is abnormal, occurs in a wide variety of neurological disorders, and has no standard treatment. The prevalence of neurological disorders in children that are associated with severe and chronic drooling is difficult to estimate, in part because of a varied clinical spectrum of such disorders; the list of these disorders includes severe developmental delay, cerebral palsy, autism spectrum disorders, sensory impairments, traumatic brain injuries, as well as neurogenetic and metabolic disorders. Persistent and severe drooling is socially disabling for patients and families, complicates hygiene care, and causes secondary dermatologic and infectious problems. Chronic drooling is a common management issue, with reported prevalence rates varying from 10%¹ to almost 40%.² Most reports focus on children with cerebral palsy but may include patients with other neurological disorders. For example, a recent registry study of 1357 children in the Northern Ireland cerebral palsy register reported that approximately one in five (22%) children aged 5 years with cerebral palsy experienced drooling.³ Because the synthetic anticholinergic glycopyrrolate does not easily cross the blood–brain barrier, it theoretically may avoid central nervous system side effects and decrease production of saliva, thereby improving drooling caused by neurological disorders in children. This review summarizes published studies of the safety and efficacy of glycopyrrolate used for the treatment of sialorrhea in children.

Saliva production, handling, and function

The viscosity and production of saliva is typically regulated by such extrinsic stimuli as vision, smell, and taste and regulated intrinsically by both the sympathetic and

Correspondence: Marian L Evatt
1841 Clifton Rd NE, Atlanta,
GA 30329, USA
Tel +1 404 728 4952
Fax +1 404 728 4892
Email mevatt@emory.edu

parasympathetic nervous system. Whereas stimulation of the sympathetic nervous system tends to thicken saliva, stimulation of the parasympathetic nervous system tends to induce production of less viscous saliva. In addition to providing enzymes (α -amylase and lipase) for initiation of carbohydrate digestion, saliva fluid and salivary production serve several important homeostatic functions including maintaining optimal oral lubrication and acid-base balance, as well as providing a bacteriostatic and bactericidal function. Thus, disruptions in normal saliva production and handling can have oral, dermatologic, and infectious sequelae beyond the social disability associated with chronic drooling.

Though data is lacking for children, adults normally produce about 1–1.5 L of saliva daily and, with normal oral sensation and reflex swallowing, saliva is swallowed automatically and without difficulty. Disturbances in the parasympathetic pathways (including pons and medulla in the brainstem) that control excitatory salivary production as well as sensory deficits, oropharyngeal motor weakness, cognitive deficits, medications, or chronic tracheostomy may disrupt normal production and handling of saliva, resulting in chronic and severe drooling. Because both intrinsic and extrinsic factors affect saliva production and handling, quantization of both salivary production and drooling is problematic; studies often use varying methods, thus making comparisons between studies difficult. Often subjective rating scales that are completed by family and/or caregivers are used, but many have not undergone rigorous validity testing. Estimates of salivary production in children are scarce, but Senner et al found that children with cerebral palsy have lower salivary production than control (normally developing) children,⁴ suggesting that drooling in children with chronic neurological conditions may stem predominantly from issues other than excess saliva production. In spite of these observations, a common approach to management of drooling is aimed at reducing saliva production.

Glycopyrrolate – pharmacologic properties

Glycopyrrolate is a quaternary ammonium structure that competitively inhibits acetylcholine receptors in salivary glands and other peripheral tissues. Thus, indirectly, it may decrease salivary production. Originally approved for adjunctive use in peptic ulcer disease, it has also been used as a preanesthetic agent to decrease secretions. Because of its' quaternary structure, glycopyrrolate does not cross the blood–brain barrier well, a characteristic that theoretically makes it more tolerable in patients with central nervous system impairments. Taken orally, the drug has relatively low and variable bioavailability

and is excreted largely unmetabolized via the kidneys. After oral administration, glycopyrrolate half-life is about 3 hours⁵ and drug excretion in patients with renal insufficiency is significantly impaired, so dose adjustments in such patients may be required.^{6,7} Until 2010, glycopyrrolate was only available in oral tablet form or intravenous solution (Robinul® and Robinul® Forte; Shionogi Pharma, Inc, Florham Park, NJ and injectable Robinul®; Baxter Healthcare Corporation, Deerfield, IL) and oral solutions were compounded from the tablets for patients who could not swallow pills or needed smaller dosing. Cober et al have demonstrated such compounded solutions are stable for 90 days when stored at 23°C–25°C.⁸ However in July 2010, the Food and Drug Administration (FDA) approved an oral solution of glycopyrrolate (Cuvposa™; Shionogi Pharma, Inc) for the treatment of chronic severe drooling in children aged 3–16 years, so both oral pill and liquid formulations are now available.

Methods

Search strategy

Studies discussed in this review were identified by searching English language PubMed citations from 1950 to July 2011 using keywords “glycopyrrolate” and “drooling” or “sialorrhea” or “sialorrhoea.” Results were limited to humans aged 0–18 years and referenced articles in search results also screened to look for additional clinical trials of glycopyrrolate. Two unpublished studies in children are described in the Cuvposa™ package insert and are discussed in this review because so few clinical studies in children are published.

Results

Of the 10 manuscripts identified, two were excluded as irrelevant to this topic (one had a primary focus on parotidectomy,⁹ the other glycopyrrolate for drooling caused by clozapine¹⁰) and four were review articles. The remaining four articles discussed below are listed in Table 1, along with the two unpublished studies discussed in the package insert for oral glycopyrrolate solution.⁷ Of these four, only one was a double-blind study. Of the two unpublished preapproval studies, study methods and results were incompletely described in the package insert, but may be gleaned from the FDA Review Summary as noted in Table 1. All four published studies allude to or discuss potential problems with blinding and known issues with lack of uniform assessment tools and subjectivity of assessment tools. However, such quantitative measures of sialorrhea as measuring weight of saliva absorbed into cotton dental pads are not easily accomplished and do not measure patients' physical discomfort or social embarrassment.¹ Blasco and Stansbury suggest that subjectivity

Table I Summary of clinical trials that investigated efficacy and safety of glycopyrrolate in children with drooling

Reference	Study design	Subjects	Dose range	Duration	Outcome measure(s)
Blasco and Stansbury ¹⁵	Open-label, dose-ranging	40 children and young adults (4–27 years, mean 12.5 years)	0.01–0.082 mg/kg/day, median 0.09 mg/kg/day, split into 1–5 times daily	8 months–4 years	Change in drooling quantity (“better, worse, same”) and side effects
Stern ¹⁶	Open-label	24 children (3–23 years, mean 13.4 years) and young adults with moderate to profuse drooling	0.04–0.1 mg/kg/day with maximum of 0.175 mg/kg/day, given as once daily dose	Up to 28 months	Questionnaire and drooling scale of Thomas-Stonell and Greenberg ²¹
Bachrach et al ¹³	Open-label, retrospective	37 patients with cerebral palsy (9 months–20 years, mean 8.3 ± 4.8)	0.01–0.04 mg/kg/dose, “most commonly” given tid (ie, 0.03–0.12 mg/kg/day)	1–34 months	5-point rating scale of Camp-Bruno ²² and side effects (Teacher Drooling Scale)
Mier et al ¹⁹	Double-blind, dose-ranging	39 children (4.33–19 years, mean 10.75 years) mixed neurological disorders, mostly cerebral palsy	0.04 mg/kg/dose to 0.2 mg/kg/dose, mean 0.22 mg/kg/dose in tid dosing Subjects <30 kg: 0.6 mg, increasing each week up to 2.4 mg, split into tid dosing Subjects >30 kg: 1.2 mg, increasing each week up to 3.0 mg, split into tid dosing	8 weeks placebo or glycopyrrolate, 1 week washout then 8 weeks in reciprocal treatment	Parental/caregiver and investigator evaluation of change in sialorrhea on 9-point drooling scale, modified Teacher Drooling Scale (0 = never drools to 9 = profuse drooling)
Package insert study 1 ⁷	Double-blind, placebo-controlled	20 subjects with cerebral palsy, mental retardation, or other neurologic condition associated with problem drooling defined as drooling in the absence of treatment so that clothing became damp on most days (approximately 5–7 days per week)	0.02 mg/kg/dose to 0.1 mg/kg/dose tid, not exceeding 3 mg tid	Up to 4 week titration plus 4 weeks at maximum tolerated dose	9-point modified Teacher Drooling Scale ⁶ (0 = dry, never drools to 9 = profuse, clothing, hands, tray, and objects frequently become wet)
Study 2 ⁷	Open-label	151 patients (20 patients from study 1 plus additional 131 patients)	Not stated in package insert; per FDA Summary Review, ¹⁸ max 3 mg tid 0.02 mg/kg, 0.04 mg/kg, 0.06 mg/kg, 0.08 mg/kg, 0.1 mg/kg	Not stated in package insert; per FDA Summary Review, 24 weeks	Not stated in package insert; per FDA Summary Review, ¹⁸ 9-point modified Teacher Drooling Scale

Abbreviations: FDA, Food and Drug Administration; tid, three times a day.

may have clinical validity, and reviews of glycopyrrolate and drooling^{11–14} also discuss issues related to appropriate outcome measure for drooling intervention studies.

Open-label studies

Blasco and Stansbury¹⁵ report a prospective study of open-label glycopyrrolate in 40 children and young adults who had either motor and/or cognitive difficulties associated with

severe drooling. Dosing was initiated at 0.5 mg daily to twice daily. Patients were assessed every 5–10 days to ascertain response and side effects. The primary outcome measure was the subjective answer to the question, “is the drooling worse, better, or the same?” Of the 40 subjects, two had immediate allergic responses and of the remaining 38 subjects, 36 reported drooling was improved. However, in no subject was glycopyrrolate successful for eliminating drooling. Nine

of 40 subjects (22.5%) discontinued glycopyrrolate due to side effects.

Stern¹⁶ conducted a small open-label trial of glycopyrrolate in 24 children and young adults with once daily dosing of glycopyrrolate. Dose titration was not specified, other than patients were initiated at 0.04 mg/kg/day and increased to 0.1 mg/kg/day with a maximum of 0.175 mg/kg/day. The author states that “the majority of subjects show improvement in both severity and frequency of drooling while taking glycopyrrolate.” Details of statistical analyses do not include quantitation of improvements though the changes on glycopyrrolate were reported as highly significant for both frequency and severity. Side effects reported were relatively mild. From the discussion, it appears that three children (12.5%) discontinued the drug due to lack of effectiveness at lower dose rather than from glycopyrrolate side effects.

Bachrach et al first reported in abstract form,¹⁷ and subsequently in manuscript form,¹³ on their retrospective, open-label experience using glycopyrrolate in children with cerebral palsy. In their retrospective survey of 1437 patients, about one-third (34%) reported drooling sometimes and 16% reported drooling was often a problem. Of 54 patients for whom antisialorrheic medications were prescribed, the authors were able to obtain questionnaire data for 41 (76%). Of these 41 patients, most (37 patients, 90%) had used glycopyrrolate and almost half (46%) reported side effects, with almost a third (10/37, 27%) discontinuing glycopyrrolate due to side effects.

Another open-label study of 151 children is referred to in the package insert⁷ and the listing of side effects in the package insert are reportedly from both the placebo-controlled trial as well as the 24-week open-label extension, but no other details of methodology nor details of results are provided in the package insert. Some details are available from the FDA Summary Review and are included in Table 1.¹⁸

Double-blind studies

Two double-blind studies of glycopyrrolate were identified, only one of which has been published. Mier et al performed a double-blind dose-ranging study of glycopyrrolate in 39 children with developmental disabilities and “bothersome” drooling who were seen in pediatric hospital outpatient clinics.¹⁹ Most of the subjects in this report (34/39) had cerebral palsy. Dosing was determined by weight: for subjects less than 30 kg, dosing was initiated at 0.6 mg/dose three times daily and increased at weekly intervals to 1.2, 1.8, and 2.4 mg/dose. For subjects weighing more than 30 kg, initial dosing was 1.2 kg/dose three times daily and was increased as tolerated at weekly intervals to 1.8, 2.4, and 3.0 mg. Doses of 0.10 mg/kg per dose appeared effective at reducing sialorrhea as measured by parental/caregiver and

investigator evaluation on a nine-point scale. However, even at low doses, 20% of children exhibited adverse events severe enough to warrant discontinuation of the medication.

Summary

For children with chronic neurological conditions, drooling may result from disturbances of saliva production, oral motor or sensory deficits, or diminished cognitive awareness. Chronic drooling is common, may be socially disabling, and may cause such secondary problems as dermatitis, skin maceration, or infection. Management options to help individuals with saliva control have included practicing oral motor exercises, using intraoral devices, prescribing anticholinergic medications, repeatedly injecting botulinum toxin in the salivary glands, and performing surgical interventions on the salivary glands. Of available anticholinergic medications, the synthetic anticholinergic glycopyrrolate is appealing because of its’ poor central nervous system penetration and theoretically reduced likelihood of causing centrally-mediated side effects.

However, remarkably few formal studies have explored the efficacy and safety of glycopyrrolate for sialorrhea in this population; only four clinical investigations of glycopyrrolate have been published and only one of these was double-blind. Except for the unpublished, open-label study referred to in the Cuvposa™ package insert, none of the studies included more than 40 subjects treated with glycopyrrolate.

While authors consistently report a positive response to glycopyrrolate, in three of the four studies over 20% of subjects discontinued the medication due to side effects. Furthermore, constipation is consistently mentioned as a common side effect, with Bachrach et al noting a case of pseudo-obstruction.¹³ Thus, for children with prior history of severe constipation or pseudoobstruction, clinicians may want to try other modalities before considering glycopyrrolate or other anticholinergic medications.

No studies have compared the various anticholinergic medications head-to-head, nor have studies compared medical and other treatment modalities with each other prospectively. Clinicians are thus left to consider the relative severity each patient’s comorbidities and their own clinical experience when considering and choosing management options for chronic drooling. It is not surprising that with limited published data, surveys of clinicians treating patients with drooling have reported varying prescribing patterns.^{13,20} Scopolamine is reported the most common first-line therapy in the UK²⁰ whereas glycopyrrolate is the most commonly used anticholinergic agent in the US.¹³

Clinicians trying to interpret the clinical data are also hampered because the available studies use different outcome

Table 2 Suggested outcome measures – sialorrhea treatment studies

Drooling Impact Scale ²⁴
Drooling Severity and Frequency Scale ²¹
Modified Teacher Drooling Scale ^{18,7}
Caregivers/patients are willing to continue the treatment short-term and long-term
Caregiver/patient assessment of whether the treatment improves overall quality of life

measures. While the scale described by Thomas-Stonell and Greenberg (Drooling Severity and Frequency Scale [DSFS])²¹ and the Teacher Drooling Scale²² (TDS) are easy to use, advocated for clinical practice,²³ and had outcome measures evaluated in one or more of the studies listed in Table 1, neither has undergone rigorous clinimetric testing. The Drooling Impact Scale²⁴ (DIS) has been developed as a validated, semiquantitative assessment of drooling that will also be responsive to interventions. Even with the high variability in clinical symptoms in this patient population, the DIS appears a reasonable semiquantitative, validated assessment scale appropriate for use as an outcome measure. However, the DIS has not yet been used in multiple studies of drooling. To allow comparisons to existing studies, future investigators may consider using the DIS along with such other outcome measures as DSFS, TDS, or practical assessments listed in Table 2 when trying to assess efficacy of an intervention.

Thus, while glycopyrrolate is available in both oral tablet and as a solution and is an option for treating patients with chronic drooling due to neurological conditions, caregivers should be advised that patients may not tolerate glycopyrrolate and the medication will help control, but not likely abolish pathological drooling.

Disclosure

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