

Treatment of Sialorrhea With Glycopyrrolate

A Double-blind, Dose-Ranging Study

Richard J. Mier, MD; Steven J. Bachrach, MD; Ryan C. Lakin, MS; Tara Barker, BS; Judith Childs, PhD; Maria Moran, MS

Objective: To determine the safety and efficacy of glycopyrrolate in the treatment of developmentally disabled children with sialorrhea.

Design: Placebo-controlled, double-blind, crossover dose-ranging study.

Setting: Outpatient facilities in 2 pediatric hospitals.

Patients: Thirty-nine children with both developmental disabilities and excessive and bothersome sialorrhea.

Main Outcome Measures: Parent and investigator evaluation of change in sialorrhea and adverse effects.

Results: Glycopyrrolate in doses of 0.10 mg/kg per dose is effective at controlling sialorrhea. Even at low doses, 20% of children may exhibit adverse effects severe enough to require discontinuation.

Conclusions: Glycopyrrolate is effective in the control of excessive sialorrhea in children with developmental disabilities. Approximately 20% of children given glycopyrrolate may experience substantial adverse effects, enough to require discontinuation of medication.

Arch Pediatr Adolesc Med. 2000;154:1214-1218

SIALLORRHEA, or drooling, is the unintentional loss of saliva from the mouth and is a normal phenomenon in infancy, usually subsiding by 18 to 30 months of age as oromotor maturation occurs. Sialorrhea is a problem for developmentally disabled children and adults, particularly those with cerebral palsy. Prevalence of moderate or severe sialorrhea in this population is estimated at between 10% and 37%.^{1,2} Five factors may contribute to sialorrhea in this group, including the integrity of the oral structures, oropharyngeal motor function, orofacial sensory perception and feedback, rate of saliva secretion, and cognitive awareness of salivary spill.³ Consequences are both medical and psychosocial and include irritated and macerated facial skin, dehydration,⁴ constant wetness and foul odor of clothing, interference with interpersonal relationships, lowering of self-esteem, and restricted vocational options. Environmental surfaces such as printed material and electronic devices can become wet enough to cause damage and hinder communication. Sialorrhea is a constant source of frustration for patients and caregivers.

Attempts to control sialorrhea in populations of children with neurological dysfunction have included oromotor therapy, surgery, and medications. None are completely successful, and surgery and medications often carry with them unacceptable adverse effects. Oromotor therapies have included various types of behavior modification, often emphasizing sensorimotor feedback.⁵ Surgical techniques have included removal of the salivary glands, ligation or repositioning of the salivary ducts, and division of secretomotor nerves. Improvements in drooling are often outweighed by significant postoperative complications, including airway obstruction, excessively dry mouth, development of ranulas, and difficulty swallowing.⁶

Drug therapy is aimed at decreasing the volume of oral saliva without addressing impaired swallowing. Blockade of cholinergic muscarinic receptors reduces salivary volume, but lack of selectivity results in widespread and undesirable central and peripheral effects, including restlessness, irritability, drowsiness, constipation, urinary retention, and flushing. Scopolamine,⁷ benzotropine mesylate,⁸ benzhexol,⁹ and glycopyrrolate¹⁰⁻¹² have all been recently studied.

From the Shriners Hospital for Children, Lexington, Ky (Dr Mier, Mr Lakin, and Ms Barker), and the Alfred I. duPont Hospital for Children, Wilmington, Del (Drs Bachrach and Childs and Ms Moran).

PATIENTS AND METHODS

Thirty-nine children aged 4 years and older, with neurodevelopmental conditions and severe sialorrhea, were recruited from the Shriners Hospital for Children in Lexington, Ky, and the Alfred I. duPont Hospital for Children in Wilmington, Del, by word of mouth and by placing informational signs in examination rooms. This protocol was approved by human investigations committees at each site, and informed consent was obtained from each family.

Ages at enrollment ranged from 4 years 4 months to 19 years, with a mean age of 10 years 9 months.

Thirty-four children had cerebral palsy; 1 each had Smith-Lemli-Opitz syndrome, closed head injury, partial trisomy 22, congenital toxoplasmosis, and spinal muscular atrophy. Eleven children had additional medical conditions, most commonly a seizure disorder (6 children) but also including autism, fetal alcohol syndrome, hydrocephalus, congenital heart disease, hypothyroidism, and retinitis pigmentosa. Two children had tracheostomies, 1 of whom dropped out of the study because of excessively thick secretions. Five children had been previously treated for their drooling with medication, 3 of whom had taken glycopyrrolate but stopped because of adverse effects. Weights at enrollment ranged from 11.5 kg to 61.9 kg.

After an initial physical evaluation and a 1-week baseline medication-free observation period, each child was assigned randomly to either the drug or placebo treatment arm, each of which was 8 weeks long. At the end of the first arm, there was a 1-week washout period and a second week-long observation period, followed by the reciprocal arm, also 8 weeks in length.

Drooling was scored on a scale (**Table 1**) that ranged from 1 (never drools) to 9 (clothing, hands, and objects frequently become wet). A set of cartoon illustrations was used to educate parents about this scale and was provided to them for home use. Drooling scores were obtained during the baseline observation periods and through weekly telephone calls to the parents by a research assistant. All scores were obtained in the afternoon, 2 hours after a dose.

The parent was also questioned each week by telephone regarding the presence of any of 15 adverse effects (**Table 2**) as well as the presence of any that were not on the list. Adverse effects were recorded on a scale from 1 (not at all) to 4 (very much) and were considered significant if they were present "quite a bit" or "very much" and not present at baseline. A physical examination was performed at each visit, with particular attention to the presence of erythema, maceration or induration around the mouth, weight, and blood pressure.

Dosages were chosen based on the experiences of previous investigators¹⁰⁻¹² and were increased weekly for 4 weeks to a maximum dose, which was then continued for an additional 4 weeks. Doses were increased according to this schedule unless adverse effects occurred or unless desired dryness, as defined by the parent or caregiver, was obtained.

Two dosage regimens were used based on the weight category of the child: children weighing less than 30 kg began at 0.6 mg, increasing weekly to 1.2 mg, 1.8 mg, and 2.4 mg. Children weighing more than 30 kg began by taking 1.2 mg, increasing weekly to 1.8 mg, 2.4 mg, and 3.0 mg. Medication was given in the morning, early afternoon, and evening. Four children were given these same doses twice (rather than 3 times) daily in the morning and early afternoon, at parental request. No specific recommendations were given with regard to timing of medication and food.

Because placebo tablets identical to commercially available glycopyrrolate were not available to us, capsules were specially compounded by a pharmacist, who ground up commercially available glycopyrrolate tablets and placed the required amount of powder into gelatin capsules. If the child was not able to swallow the capsule, the parent was instructed to take the capsule apart and place the powdered contents in the child's food. Lactose powder or cellulose was used as the placebo control and was prepared similarly, using identical gelatin capsules.

Tests of statistical significance included the paired, 2-tailed *t* test and the unpaired *t* test.

Glycopyrrolate is a quaternary ammonium compound structurally related to atropine that is effective at reducing drooling in children with cerebral palsy in open-label trials.¹⁰⁻¹² Theoretically, it does not cross the blood-brain barrier in great amounts¹³ and exhibits a relatively long duration of action. However, dosages, frequency of dosing, and the number and severity of adverse effects have not been well studied in children. Glycopyrrolate is approved for use in adults as an adjunct to peptic ulcer treatment. In this context it is taken 3 times daily. Contraindications include glaucoma, obstructive uropathy, gastrointestinal obstruction, severe ulcerative colitis, and myasthenia gravis.

To define appropriate doses in a systematic and prospective manner and to assess semiquantitatively the resulting adverse effects in developmentally disabled children, we have undertaken a prospective, double-blind, crossover, randomized dose-ranging study of glycopyrrolate in 39 children with excessive drooling.

RESULTS

Thirty-nine children began the study, and 27 children (69%) completed it. Of the 12 children who did not complete the study, 8 dropped out because of adverse effects to medication, 1 of these while receiving placebo. Four children were dropped because of failure to comply with the protocol or because it was inconvenient for their families to continue. The 4-month study was completed by 18 boys and 9 girls (**Table 3**). Three of the 5 children in the study without a primary diagnosis of cerebral palsy did not finish it, and because of the small number of children involved, no inferences can be drawn regarding effectiveness or adverse effects for children with a diagnosis other than cerebral palsy.

The mean highest tolerated dose of glycopyrrolate among the 27 children who completed the study was 2.49 mg, with a range from 1.2 mg to 3.0 mg per dose. The mean highest tolerated dose of glycopyrrolate per kilo-

Table 1. Drooling Score Used in Glycopyrrolate Study

Score	Description
1	Dry, never drools
2	Mild; only the lips are wet occasionally
3	Mild; only the lips are wet, but frequently
4	Moderate; wet on the lips and chin occasionally
5	Moderate; wet on the lips and chin frequently
6	Severe; drools to the extent that clothing becomes damp occasionally
7	Severe; drools to the extent that clothing becomes damp frequently
8	Profuse; clothing, hands, and objects become wet occasionally
9	Profuse; clothing, hands, and objects become wet frequently

Table 2. List of Adverse Effects Queried of Parent or Caretaker on a Weekly Basis

Drowsy
 Restless, overactive, or short attention span
 Easily frustrated, irritable
 Rapid mood changes
 Temper outbursts, explosive behavior
 Overly sensitive, serious, sad, cries easily
 Fearful
 Worsening of coordination
 Facial flushing
 Nasal congestion
 Excessively dry mouth
 Vomiting
 Constipation
 Diarrhea
 Difficulty emptying bladder

gram of body weight was 0.11 mg/kg per dose, with a range from 0.04 mg/kg to 0.2 mg/kg per dose.

RESPONSE TO MEDICATION

All 27 children who completed the study demonstrated improvement in drooling. The mean baseline drooling score improved with glycopyrrolate from 7.52 to a maximum mean score of 1.85. A mean score of 1.85 corresponds to a description between “dry, never drools” and “mild drooling; only the lips are wet occasionally.” With placebo, the baseline score improved slightly from 7.44 to 6.33. Mean drooling score on glycopyrrolate (1.85) compared with placebo (6.33) is statistically different, with $P < .001$. Only 2 of the children failed to improve their drooling score by at least 4 points, and only 3 were left with a score of 4 (wet on lips and chin occasionally) or worse.

Drooling scores improved with increasing dose in a linear manner. The mean score for children finishing the study was 6.0 on their first dose level, 4.5 on the second dose level, 3.6 on the third dose level, 2.6 on the fourth dose level, and 2.3 after 4 weeks at their highest dose. Using an improvement-in-drooling score of 4 points or greater as a standard for significant clinical improvement, 12%, 38%, 54%, and 81% of study participants met this standard on the first, second, third, and fourth dosing levels, respectively (**Figure 1**).

Table 3. Glycopyrrolate Study Summary

Characteristic	
No. of patients enrolled	39
No. of patients completing study	27
No. of patients who withdrew because of adverse effects to glycopyrrolate	7
No. of patients who withdrew for other reasons	5*
Mean highest tolerated dose, mg/kg	0.11
Range of highest tolerated dose, mg/kg	0.04-0.20

*One patient dropped out because of adverse effects while receiving placebo; 4 patients were dropped because of problems keeping appointments or problems using study medication as prescribed.

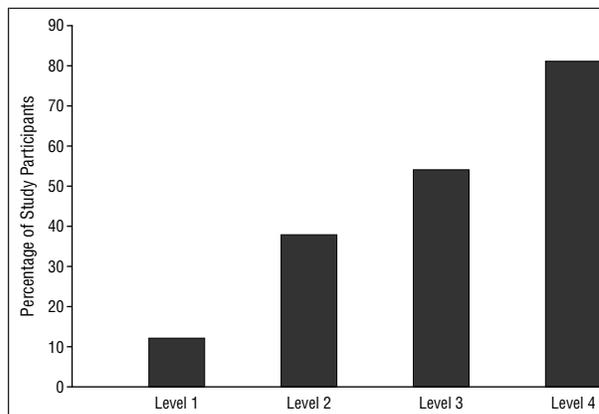


Figure 1. Percentage of study participants who improved drooling score by 4 points or more at each dosage level.

The children were maintained at their highest tolerated dose for 4 weeks to determine if drug effects changed during that period; the drooling score improved in 9 children, decreased in 9, and remained the same in 9.

Six (22%) of the 27 children who completed the study achieved their best drooling score while receiving doses lower than their fourth dosing level. Four of these 6 reached their best score 1 dosing level below their highest tolerated level. One child reached the best drooling score 2 dosing levels below the highest tolerated level, and another child reached the best score on the first dosing level.

Of the caretakers who responded, 15 (65%) of 23 reported that their child exhibited less drooling odor while receiving glycopyrrolate compared with the placebo, and 21 (87%) of 24 caretakers reported improved dryness of clothing compared with placebo.

ADVERSE EFFECTS

Adverse effects were common, affecting 25 (69%) of 36 children taking glycopyrrolate. Only 5 (17%) of 30 children described adverse effects during the placebo treatment arm. Eight children withdrew from the study because of adverse effects, 7 of whom did so while participating in the glycopyrrolate arm of the study. Unacceptable adverse effects resulting in withdrawal from the study included behavior changes such as hyperactivity and irritability, constipation, diarrhea, excessive oral

Table 4. Frequently Reported Adverse Effects Among 39 Children, With Percentage of Children Affected While Receiving Glycopyrrolate or Placebo

Adverse Effects	Percentage	
	Glycopyrrolate	Placebo
Behavioral changes*	23	3
Constipation	18	...
Excessive dryness of mouth or secretions	18	...
Urinary retention	13	...
Facial flushing	10	...
Nasal congestion	10	3
Vomiting	10	...
Diarrhea	10	3

*Includes drowsiness, restlessness, overactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behavior, excessive sensitivity, seriousness, sadness, frequent crying episodes, fearfulness. Ellipses indicate not applicable.

dryness, urinary retention, headache, drowsiness, dilated pupils, blurred vision, facial flushing, nasal congestion, vomiting, dizziness, dehydration, thickened secretions (in a child with a tracheostomy), urinary tract infection, fever, and rash.

Of the 7 children who dropped out because of adverse effects while receiving glycopyrrolate, 4 did so before the end of the first week while they were still receiving the lowest dosage level, a mean of 0.04 mg/kg per dose. The other 3 children dropped out from adverse effects at 10, 28, and 42 days while receiving a mean dose of 0.06 mg/kg per dose.

Adverse effects are listed in **Table 4**. The most frequently noted effects included behavioral changes (9 children), constipation (7), excessive dryness of the mouth or secretions (7), and urinary retention (5). One child with a history of seizures exhibited worsening symptoms while receiving glycopyrrolate, although the child did finish the study.

More children experienced adverse effects as doses increased. Whereas only 14% of study participants described at least 1 adverse effect while taking glycopyrrolate at the first dosing level, 30%, 26%, and 81% of children experienced at least 1 adverse effect while at the second through fourth dosing levels, respectively. There was a substantial increase as children were moved from the third to the fourth dosing level (**Figure 2**).

Although younger children tended to exhibit adverse effects more often than older children, this difference did not achieve statistical significance. The mean age of the 8 children who dropped out because of adverse effects was 8 years 7 months, whereas the mean age of the 27 children who completed the study was 10 years 11 months ($P=.15$).

COMMENT

Glycopyrrolate reduces salivary production and therefore inappropriate drooling. This has been well demonstrated by our data and by multiple open-label studies. Our goal with this controlled study was to systemati-

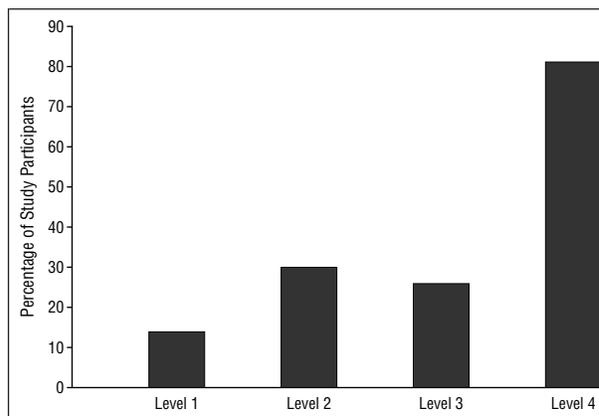


Figure 2. Percentage of study participants at each dosing level who experienced at least 1 significant adverse effect.

cally demonstrate at what dose glycopyrrolate could control drooling with a minimum of adverse effects. At what dose does the curve of reduced drooling cross the curve of increasing adverse effects?

Virtually all children who were able to tolerate the fourth or highest glycopyrrolate dose responded with dramatic improvement in their drooling, with 25 of 27 children who completed the study improving their drooling score by at least 4 points. In general, they needed the fourth, or highest, dosing level to accomplish maximum control of drooling, with only 6 of 27 children demonstrating their best score on a glycopyrrolate dose lower than the highest one.

Additionally, mean drooling scores improved at roughly equal increments from the first dosing level (drooling score, 6.0) to the second (4.6), the third (3.7), and the fourth (2.6).

Dosages per kilogram of body weight were relatively low for the 3 patients in the study who weighed more than 40 kg. Despite this fact, 2 of these responded well, and the third improved to a more modest degree. Assurances of safety for doses greater than 3 mg for patients weighing more than 30 kg, or greater than 2.4 mg for patients weighing less than 30 kg, cannot be made from our data.

Adverse effects were most frequently reported as the dose was increased. Five (26%) of 19 children reported at least 1 adverse effect at the third dosing level, and 21 (81%) of 26 reported at least 1 adverse effect at the fourth (highest) dosing level. This dramatic increase in the number of children with at least 1 adverse effect occurred between dosing levels corresponding to 0.08 mg/kg per dose (third level) and 0.11 mg/kg per dose (fourth level).

The dramatic reduction in drooling at the fourth dosing level in 81% of the children coupled with the presence of at least 1 adverse effect, also in 81% of the children at this same dosing level, functionally defines an upper dosing limit.

An occasional child responded optimally to lower doses of medication, with 2 of 27 obtaining maximal benefit while taking glycopyrrolate at the first or second dosing levels. Additionally, 4 children dropped out of the protocol because of adverse effects from medication while at their first dosing level. For these 6 children (15% of

the study population), initiating therapy at a low dose was important in identifying those who were either especially responsive to or unable to tolerate glycopyrrolate. This is a small but significant fraction of the children who began the study.

A major deficiency of this study relates to the possible subjectivity inherent in parent or caregiver evaluations of drooling improvement and adverse effects. We dealt with this subjectivity by providing the family with line drawings clearly defining the nature of drooling at each drooling score, through weekly reminders by study personnel, and by a blind, crossover protocol during which neither parent nor physician was aware of the contents of each capsule. Parent evaluation of drooling is supported by the similarities of mean baseline scores obtained during the week-long observation period preceding glycopyrrolate and placebo, 7.52 and 7.44, respectively.

Most parents professed to know when their child was receiving glycopyrrolate because of the dramatic improvement in drooling. One should keep in mind the possibility that observable drug effects biased the reporting of adverse effects in either direction. The opposite is also possible: the presence of adverse effects might have led parents to surmise greater improvements in drooling than existed in reality. However, when comparing glycopyrrolate and placebo treatment arms, the scale of the differences in reported drug and adverse effects make it unlikely that such bias is a major contributing factor.

CONCLUSIONS

Based on our data, several conclusions seem warranted. First, almost all children tolerating glycopyrrolate will demonstrate marked improvement in drooling at individual doses of about 0.1 mg/kg per dose. Individual doses of glycopyrrolate greater than 2.4 mg for children weighing less than 30 kg, and 3.0 mg for children weighing more than 30 kg, were not studied for safety but are not usually necessary. Second, the use of stepwise increases in dosing is prudent, beginning with individual doses of about 0.04 mg/kg per dose, with increases occurring no more frequently than once a week. Third, adverse effects, most commonly behavioral problems, constipation, excessive oral dryness, and urinary retention, cause 20% of developmentally delayed children to stop taking glycopyrrolate.

Although not demonstrated by our data, practical experience with our protocol patients led to the conclu-

sion that an evening dose was largely unnecessary because drooling at that time of day was not as much of a concern as daytime drooling. Two doses, given in the morning and midafternoon, usually suffice.

Accepted for publication July 24, 2000.

This research was supported in part by the Kosair Foundation, Louisville, Ky, and by the Nemours Foundation, Jacksonville, Fla.

Presented at the American Academy of Cerebral Palsy and Developmental Medicine, Washington, DC, September 15, 1999.

We very much appreciate the research coordination of Rebecca Ferguson and the statistical assistance of Christin Daniels.

Corresponding author and reprints: Richard J. Mier, MD, Shriners Hospital for Children, 1900 Richmond Rd, Lexington, KY 40502 (e-mail: rjmier@aol.com).

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