

# PEDIATRIC PHARMACOTHERAPY

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## Glycopyrrolate Use in Children

Marcia L. Buck, Pharm.D., FCCP, FPPAG

**G**lycopyrrolate, a synthetic anticholinergic, was approved for use by the Food and Drug Administration (FDA) in 1961.<sup>1,2</sup> It is used primarily in the preoperative setting or during procedural sedation to reduce salivary, pharyngeal, and bronchial secretions, reduce the volume and acidity of gastric secretions, and block cardiac vagal inhibitory reflexes during induction and intubation. Glycopyrrolate is also used to antagonize the peripheral muscarinic effects (bronchospasm, bradycardia, and increased gastrointestinal motility) produced by acetylcholinesterases such as neostigmine when they are given postoperatively to reverse non-depolarizing neuromuscular blocking agents.

For many years, glycopyrrolate has been used off-label for the management of sialorrhea in children with cerebral palsy or other neurologic conditions and to reduce tracheobronchial secretions in children with tracheostomies.<sup>3</sup> On July 29, 2010, a new glycopyrrolate oral solution was approved by the FDA for the treatment of chronic severe sialorrhea caused by neurologic conditions in pediatric patients between 3 and 16 years of age.<sup>4</sup> This issue of *Pediatric Pharmacotherapy* will provide a brief review of the pharmacology of glycopyrrolate and an overview of recent case reports and studies related to its use in children.

### Mechanism of Action

Glycopyrrolate, 3[(cyclopentylhydroxyphenyl-acetyl)oxy]-1,1-dimethyl pyrrolidinium bromide, inhibits the action of acetylcholine on peripheral acetylcholine (muscarinic) receptors on smooth muscle, cardiac muscle, the sinoatrial and atrioventricular nodes, exocrine glands, and to a lesser degree, autonomic ganglia. It is a quaternary amine and is ionized at physiologic pH. Unlike other anticholinergics such as atropine and scopolamine, glycopyrrolate has only limited ability to cross lipid membranes such as the blood-brain barrier.<sup>1,2,4</sup>

### Pharmacokinetics and Pharmacodynamics

In pharmacokinetic studies conducted in children and adults, glycopyrrolate has been shown to be poorly absorbed after oral administration, with a range of bioavailability from 1-20%. There is considerable variation in absorption among patients. Administration with a high fat meal further reduces absorption of glycopyrrolate oral solution by approximately 74%. Glycopyrrolate is widely distributed in children, with an average volume of distribution of 1.3-1.8 L/kg, significantly greater than that reported in adults (0.42 L/kg).<sup>1,2,4,5</sup>

Approximately 65-80% of a glycopyrrolate dose is recovered in the urine as unchanged drug. The remaining portion is believed to be metabolized and excreted in the bile. The clearance of glycopyrrolate appears to be more rapid in children. In two pediatric studies using intravenous glycopyrrolate, the average clearance was 1-1.4 L/kg/hr, with a range of 0.3-2.2 L/kg/hr. In adults, the average rate of clearance is 0.54 L/kg/hr. The clearance of glycopyrrolate in patients with renal dysfunction is significantly delayed.<sup>1,2,4</sup>

In adults, the peak effects of glycopyrrolate occur approximately 30-45 minutes after IM administration. The vagal blocking effects last for 2-3 hours, while the antisialogogue effects continue for up to 7 hours. Pharmacodynamic studies have not yet been conducted in children.<sup>1,2</sup>

### Clinical Experience

#### **Adjunctive Therapy for Anesthesia**

Anticholinergics are frequently used to reduce the increase in oral secretions and bradycardia produced by anesthetic agents. While widely accepted as beneficial by clinicians, controlled studies evaluating their efficacy have produced mixed results. In a 2005 study of 45 children between 1 and 36 months of age who were

undergoing cardiac catheterization with sevoflurane-remifentanyl anesthesia, IV glycopyrrolate doses of 0.006 or 0.012 mg/kg effectively prevented bradycardia.<sup>6</sup> In contrast, the placebo group had a reduction in heart rate from  $117 \pm 20$  bpm at baseline to  $99 \pm 16$  bpm at 45 minutes. While the 0.006 mg/kg dose maintained a stable heart rate, the 0.012 mg/kg dose often produced temporary mild tachycardia. The authors concluded that glycopyrrolate 0.006 mg/kg was an effective adjunctive therapy to prevent bradycardia, and that higher doses were not necessary.

Another 2005 paper compared the efficacy of glycopyrrolate and atropine in 90 children between 1 month and 12 years of age undergoing surgery.<sup>7</sup> After induction with halothane and succinylcholine, the children were randomized to receive either 0.005 mg/kg glycopyrrolate or 0.01 mg/kg atropine given IV. None of the patients developed bradycardia. Tachycardia was more common in the atropine-treated patients. Those in the atropine group had an average 35.7% rise in heart rate from baseline, compared to 22.5% in the glycopyrrolate group ( $p = 0.001$ ). However, hypoxia was reported more frequently in the glycopyrrolate group (11.1% versus 2.2% in the atropine group). In both studies, the authors concluded that glycopyrrolate improved cardiovascular stability at the time of induction of anesthesia in children.

The ability of glycopyrrolate to reduce secretion-related adverse respiratory effects was studied by Tait and colleagues in 2007.<sup>8</sup> The authors randomized 130 children between 1 month and 18 years of age to receive 0.01 mg/kg IV glycopyrrolate or placebo prior to elective surgery. To better define efficacy, the authors enrolled only children who presented for their surgery with an upper respiratory tract infection. The incidence of secretion-related adverse effects was no different between the groups (45.2% in the glycopyrrolate group versus 37.5% in the controls). The glycopyrrolate group, however, had a shorter time to discharge (83.9 min versus 111.4 min,  $p = 0.024$ ) and less postoperative nausea and vomiting (10.7% versus 33.3%,  $p = 0.005$ ).

Earlier this year, Green and colleagues evaluated the efficacy of glycopyrrolate and atropine in controlling secretions in patients given ketamine.<sup>9</sup> The authors used a database developed from 32 previously published studies which included the records of 8,282 pediatric Emergency Department patients. A total of 3,881 children received atropine, 1,799 received glycopyrrolate, and 2,602 were not pretreated with an anticholinergic. The most frequently

reported doses were 0.01 mg/kg atropine, up to a maximum of 0.5 mg, and 0.005 mg/kg glycopyrrolate, up to a maximum of 0.25 mg, given IV or IM. Patients who received atropine experienced less vomiting than those who received glycopyrrolate or no treatment (5.3% compared to 10.7% and 11.4%, respectively,  $p < 0.001$ ). There were also more adverse respiratory adverse events in the glycopyrrolate group compared to the atropine group or those who received no treatment (6.4% compared to 3.3% and 3%,  $p < 0.001$ ). There were no differences in the incidence of laryngospasm or apnea. The authors concluded that atropine may be a more advantageous agent for reducing ketamine-related adverse effects.

### Treatment of Sialorrhea

Clinical studies of glycopyrrolate in the treatment of sialorrhea have demonstrated response rates of 70-90%.<sup>3</sup> In 1996, Blasco and Stansbury conducted an open-label study of oral glycopyrrolate in 40 children and adults.<sup>10</sup> Thirty-six (90%) of the patients had a reduction in drooling, two patients did not respond and two could not be assessed. In 2000, Mier and colleagues conducted a small double-blind, placebo-controlled crossover study in 39 children with sialorrhea associated with developmental disabilities.<sup>11</sup> The authors found that an oral glycopyrrolate dose of 0.1 mg/kg was effective in controlling sialorrhea, but that 20% of children developed adverse effects severe enough to require discontinuation.

The FDA approval of the new glycopyrrolate oral solution was based upon the results of a multicenter, randomized, double-blind, placebo-controlled study conducted by the manufacturer in children with chronic sialorrhea associated with an underlying neurologic condition.<sup>4</sup> A total of 38 patients between the ages of 3 and 23 years were enrolled into the 8-week study. Patients received either glycopyrrolate at a dose of 0.02 mg/kg or placebo three times daily. The dose was titrated by increments of 0.02 mg/kg every 5 to 7 days based on clinical responses. The maximum dose was 0.1 mg/kg or 3 mg given three times daily.

Patients were evaluated with the Modified Teacher's Drooling Scale (mTDS), a nine-point scale ranging from dry to frequent profuse drooling which wets clothing, hands, and objects. Patients were considered responders if there was at least a 3-point reduction in mean daily mTDS score from baseline to week 8. At week 8, 15/20 (75%) of the children given glycopyrrolate were considered responders, compared to only 2/18 (11%) of the patients in the placebo group.<sup>4</sup>

Glycopyrrolate has also been shown to be effective in managing sialorrhea associated with clozapine, an atypical antipsychotic. Clozapine has been reported to cause sialorrhea in 60-90% of patients. In 2008, Robb and colleagues reported effective control of drooling with oral glycopyrrolate in three adolescent girls between 13 and 16 years of age.<sup>12</sup> The patients were being treated with clozapine (120-500 mg daily) in an inpatient facility. Glycopyrrolate dosing as initiated at 2 mg twice daily in the first two patients and 1 mg three times daily in the third. The dose was titrated based on response, up to maximum of 8 mg/day. One patient developed constipation and one experienced dry mouth, but neither patient required discontinuation of treatment. The authors suggest that glycopyrrolate may be a useful adjunctive therapy for adolescents requiring treatment with clozapine.

#### Contraindications and Precautions

Glycopyrrolate is contraindicated in patients with glaucoma, gastrointestinal obstruction, paralytic ileus, ulcerative colitis, obstructive uropathy, and myasthenia gravis. It should be used with caution in patients with cardiac or coronary artery disease, hyperthyroidism, autonomic neuropathy, hepatic or renal disease. The injectable form of glycopyrrolate contains 0.9% benzyl alcohol as a preservative. Excessive amounts of benzyl alcohol have been associated with hypotension and metabolic acidosis in neonates, with rare reports of fatalities. It should not be used in neonates, and should be used with caution in older infants.<sup>1,2,4</sup>

The use of anticholinergic agents such as glycopyrrolate may produce blurred vision, intestinal obstruction, or decreased sweating. In patients with fever or in the presence of high temperatures or with exercise, anticholinergics may produce heat prostration.<sup>1,2,4</sup>

#### Adverse Effects

In the pediatric clinical trials conducted with glycopyrrolate oral solution, the most common adverse reactions included dry mouth (in 40% of patients), vomiting (40%), constipation (35%), flushing (30%), nasal congestion (30%), headache (15%), sinusitis (15%), signs of an upper respiratory tract infection (15%), and urinary retention (15%). This adverse effect profile is similar to that previously reported in adult clinical trials. Previous pediatric studies have reported that 30-60% of families discontinue treatment because of these adverse effects.<sup>3,4</sup>

Patients who develop diarrhea after being treated with glycopyrrolate may be experiencing

incomplete intestinal obstruction and should immediately be seen by their health care provider. Hypersensitivity reactions to glycopyrrolate may include rash, pruritus, anaphylactic or anaphylactoid reactions. Other rare, but serious reactions to glycopyrrolate include arrhythmias, hypotension, hypertension, seizures, and respiratory arrest. Following an overdose, penetration of glycopyrrolate into the central nervous system may result in agitation, restlessness, or psychotic behavior.<sup>1,2,4</sup>

#### Drug Interactions

Administration of IM or IV glycopyrrolate with cyclopropane anesthesia can increase the risk for ventricular arrhythmias. If the combination is necessary, the glycopyrrolate dose should be divided and given in small incremental doses.<sup>1,2</sup>

The effects of glycopyrrolate may be intensified by administration with other anticholinergics, including amantadine, phenothiazines, or tricyclic antidepressants. The slower gastrointestinal time produced by glycopyrrolate may increase the risk for hyperkalemia from sustained-release potassium chloride products and reduce the effectiveness of digoxin. Glycopyrrolate may increase plasma levels of atenolol or metformin if given concomitantly with these agents. Administration with glycopyrrolate may reduce plasma levels of haloperidol or levodopa.<sup>1,2,4</sup>

#### Dosing Recommendations

The manufacturer-recommended preanesthetic dose of glycopyrrolate in infants and children is 0.004 mg/kg given IM 30 to 60 minutes prior to induction.<sup>1,2</sup> Most of the clinical studies and case series published to date have used a range of 0.004 mg/kg to 0.006 mg/kg, but some authors have used doses as high as 0.01 mg/kg.<sup>7</sup> Additional doses, up to a maximum of 0.1 mg, may be given IV during surgery every 2-3 minutes as needed.<sup>2</sup>

To reverse non-depolarizing neuromuscular blockade, the recommended pediatric dose is 0.2 mg given IV for every 1 mg of neostigmine or 5 mg of pyridostigmine to be given. Glycopyrrolate may be mixed in the same syringe as the anticholinesterase to allow for simultaneous administration.<sup>2</sup>

For management of sialorrhea, the manufacturer of the oral solution recommends initiating therapy at a dose of 0.02 mg/kg given enterally three times daily. Based on patient response, the dose may be increased by increments of 0.02 mg/kg every 5-7 days. The maximum recommended dose for children is 0.1 mg/kg (not to exceed 3 mg) three times daily.<sup>4</sup> For

adolescents and adults, oral glycopyrrolate may be initiated at a dose of 1-3 mg two or three times daily and titrated up to a maximum daily dose of 8 mg.<sup>1,2</sup> Glycopyrrolate should be given on an empty stomach, 1 hour before or 2 hours after a meal.<sup>1,2,4</sup>

#### Availability

Glycopyrrolate is available in a 0.2 mg/mL injectable form (Robinul<sup>®</sup> and others), as well as 1 and 2 mg tablets (Robinul<sup>®</sup>, Robinul-Forte<sup>®</sup>, and others). The new pediatric oral preparation is a 0.2 mg/mL cherry-flavored solution (Cuvposa<sup>®</sup>).<sup>2,4</sup>

#### Summary

Glycopyrrolate serves a useful role in both the perioperative setting and in the management of chronic sialorrhea in children. Although several studies have demonstrated its efficacy, the adverse effects associated with glycopyrrolate often limit its use. A new oral solution may make glycopyrrolate easier to administer to children with sialorrhea, but additional research is needed to determine its long-term benefit.

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adolescents. *J Child Adolesc Psychopharmacol* 2008;18:99-107.

#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 11/19/10:

1. Dronedarone (Multaq<sup>®</sup>), an oral antiarrhythmic used in the management of patients with paroxysmal or persistent atrial fibrillation or atrial flutter, was added to the Formulary. It is restricted to use by Cardiology and Electrophysiology divisions.

2. Mycophenolate sodium (Myfortic<sup>®</sup>) was added for patients who cannot tolerate mycophenolate mofetil or for inpatients that have been maintained on mycophenolate sodium at home. This product is enteric coated and cannot be crushed, chewed, or cut.

3. Sildenafil injection (Revatio<sup>®</sup>) was added to the Formulary for patients with pulmonary hypertension who are unable to take the medication orally.

4. Cabazitaxel (Jevtana<sup>®</sup>) was also added. This agent is used in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer who were previously treated with a docetaxel-containing regimen.

5. Plerixafor (Mozobil<sup>®</sup>) was added for use in combination with G-CSF to mobilize hematopoietic stem cells prior to blood collection for autologous transplantation in patients with non-Hodgkin's lymphoma or multiple myeloma.

6. Sargramostim (Leukine), recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF), was added for induction chemotherapy in acute myelogenous leukemia, for mobilization and following transplantation of autologous peripheral blood progenitor cells, in myeloid reconstitution after autologous or allogeneic bone marrow transplantation, or in the management of bone marrow transplant failure or engraftment delay.

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