

Executive Summary

The Use of Antimuscarinics for the Control of Drooling in Children with Cerebral Palsy and other Neurologic Deficits

1. Introduction

The Food and Drug Administration (FDA) has long appreciated the importance of information that can support the safe and effective use of medicines in children as well as in adults. Congress has enacted law and the FDA has developed regulations to encourage the appropriate study of drugs in children. The large population of children with cerebral palsy and other neurodevelopmental diseases is one group that can benefit from medications to help control the manifestations of these illnesses.

Drooling is a major problem in children with neurodevelopmental diseases, such as cerebral palsy. The literature often refers to this drooling as "sialorrhoea," which is defined as excess secretion of saliva. In truth, the problem has nothing to do with excessive salivation; rather it is caused by difficulty swallowing because of poor motor control.

Drooling may lead to aspiration, maceration of surrounding skin, and secondary fungal and bacterial infections. It can also interfere with the education of these children and can affect patient placement. For these reasons, various methods are employed to control the drooling, including pharmacologic control. There are currently no drugs that are approved and labeled for this indication, though several drugs are widely used. It would clearly be desirable to study medications used to control drooling in children.

While the design of these studies would address the usual questions about formulations appropriate for children, pharmacokinetics, dose ranging, and efficacy and safety, these studies would also have to address other issues. A significant issue in the study of these drugs is how the subjects, who may be significantly impaired, will express their desires for treatment, and how adverse events will be elicited.

2. Non-pharmacologic Control of Drooling

The most conservative methods of control are behavioral modification and oral-motor therapy. These methods involve working with a speech pathologist to learn how to consciously swallow. However, the severity of the disability frequently militates against the development of "normal" motor control. Patients who fail behavioral and/or pharmacologic control may be candidates for surgery to ligate and transpose the salivary ducts, or nerve resections to stop the stimulus to salivate.

3. Medications Used to Control Drooling

The most widely used method to control drooling is pharmacologic, using antimuscarinics to inhibit salivation. The medications used include benztropine, glycopyrrolate, scopolamine, and trihexyphenidyl. The drugs inhibit the action of acetylcholine on structures innervated by postganglionic muscarinic receptors and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia.

Because there are muscarinic receptors on end organs throughout the body, the effects of these medications are predictably widespread. Small doses depress salivary and bronchial secretion and sweating, at larger doses the eyes dilate and accommodation is inhibited, the vagal tone on the heart is depressed, and the heart rate increases. Larger doses can lead to inhibition of urination and gut motility, and in some of the medications, neurologic effects such as headache, drowsiness, disorientation, nervousness and depression may be seen.

The FDA has approved the use of these drugs in adults for various indications (see table 2.1), but none of the medications have been approved for the chronic control of drooling in children. They are however, widely used in children, though without benefit of dosing information or other data from clinical studies. Furthermore, because there is no approved liquid formulation, these are locally compounded resulting in a variety of formulations.

Table 2.1: Approved Indications for Antimuscarinics.

Medications	Approved Indications
Benzotropine	Adjunct in the therapy of all forms of Parkinsonism Control of extrapyramidal disorders due to neuroleptic drugs
Glycopyrrolate	Peptic ulcer disease Premedication to reduce secretions for anesthesia
Scopolamine	Prevention of nausea and vomiting due to motion sickness and recovery from anesthesia and surgery
Trihexyphenidyl	Adjunct therapy of all forms of Parkinsonism

4. Difficulties in Conducting Studies in Impaired Patients

There are ethical and strategic problems inherent to the study of patients with cerebral palsy and other neurodevelopmental defects. These problems include selection of study subjects, obtaining consent, and measurement of outcomes.

Some of these patients may be institutionalized or wards of the courts, raising questions regarding who can legally give consent, and whether it is fair to deny patients the opportunity to participate in a trial that may benefit them because of custody issues.

The efficacy of the antimuscarinic drugs in reducing drooling is predictable and relatively easy to observe. There are several scales already used (Teacher's Drooling Scale) to assess efficacy, though these scales must rely on subjective third party caregivers.

The assessment of safety in this very vulnerable population is more problematic. Pain and discomfort are difficult to measure in severely impaired patients. Also, while several tools exist for measuring the behavioral and physiologic changes that may signal an unwanted side effect, it is frequently difficult to identify the origin of the specific pain or discomfort.

5. Conclusion

While it is clear that drooling is a problem in cerebral palsy patients, and that the medications used to reduce drooling are effective, there is a large knowledge deficit regarding dosing of these medications as well as measuring adverse events that result from their use. Optimal dosing should balance the desirable and undesirable antimuscarinic effects, and since response may vary from child to child, a controlled dose titration regimen should be characterized. The marketed formulation should allow such a gradual dose titration.

The FDA would like to stimulate discussion about questions of study design, endpoints, and particularly about the ethical issues that impact on the study of this vulnerable patient population. The goal is to foster humane, well-designed studies that respect the needs and rights of patients and result in the development of pediatric formulations and labeling for these antimuscarinics.