Use of Physostigmine for Cyclopentolate Overdose in an Infant

abstract

Topical application of eye drops may cause mild or severe adverse ocular or systemic effects. Children, particularly infants, are more prone to systemic adverse effects of topical eye drops because of their lower body mass and blood volume, immature metabolism, and immaturity of excretory, nervous, and cardiovascular systems. Early recognition of signs and symptoms of systemic toxicity is very important. Most of the signs and symptoms can resolve spontaneously; however, in severe cases, physostigmine treatment may be required. Respiratory distress is a rare adverse effect of cyclopentolate. We report an infant who developed respiratory distress after ocular instillation of cyclopentolate and was successfully treated with physostigmine. The benefit of physostigmine use with close follow-up should be borne in mind in cases with a life-threatening cyclopentolate adverse effect. *Pediatrics* 2012;130:e703–e705
Cyclopentolate eye drops are commonly used for mydriasis during screening for retinopathy of prematurity (ROP). Topical application of these eye drops may cause severe adverse ocular or systemic adverse effects. Some of these effects can be life-threatening and require immediate treatment. We report an infant who developed respiratory distress after ocular instillation of cyclopentolate eye drops and was successfully treated with physostigmine.

CASE REPORT
The patient was born at 28 weeks' gestation to a 20-year-old primiparous woman. She was born 1000 g by caesarean delivery as a twin spouse. Apgar score was obscure. Her neonatal problems included minimal lung disease that required 1 month of mechanical ventilation. At 90 days of age (corrected postterm age of 12 days), she was transferred to our hospital for cyclopentolate examination. One drop 1% cyclopentolate was instilled 6 times in each eye at 5-minute intervals in our ophthalmology department. Approximately 30 minutes later, she developed vomiting, cyanosis, and respiratory distress and was referred to our pediatric emergency department (PED).

In the PED, physical examination revealed mild cyanosis, abdominal distention, and respiratory distress without flushing and rash. Her respiration was irregular. Her abdomen was distended. Neurologic examination revealed no pathologic finding except mydriasis. Her vital signs were as follows: fever, 39°C; respiratory rate, 65 breaths per minute; heart rate, 210 beats per minute; blood pressure, 70/15 mm Hg; and oxygen saturation, 90%. While in the PICU she was still intubated and mechanically ventilated. Physostigmine infusion with a dose of 0.02 mg/kg over 10 minutes was given at the ninth hour of her hospital admission. Before physostigmine, her electrocardiography was normal. The clinical symptoms resolved immediately after administration of physostigmine. The child awoke, opened her eyes at the end of the infusion, and her abdominal distention resolved completely on the following days. Her heart and respiratory rates decreased and her respiration became regular. Finally, she was extubated at the second day of PICU follow-up. She was discharged 8 days after admission to hospital.

DISCUSSION
Topical application of eye drops may cause serious ocular or systemic adverse effects. Systemic absorption of these drugs occurs primarily via nasal mucosa and conjunctiva, nasolacrimal duct, oropharynx, digestive system, and skin. The toxicity is dose-related. Early recognition of systemic toxicity after eye drop instillation is important. Neonates are more susceptible than adults to the effects of systemic absorption because of their lower body mass and blood volume, and their immature metabolic, excretion, and cardiovascular systems. Cyclopentolate is an anticholinergic agent whose topical administration to eyes causes mydriasis and cycloplegia. Its recommended maximum dose in an infant is 1 drop per day per eye of 0.5% solution. Because of its atropinelike actions via blocking acetylcholine receptors at postganglionic neuron, systemic adverse effects of cyclopentolate are similar to atropine. Dryness of the skin and mouth, dermal flushing, fever, irritability, abdominal distention, urinary retention, feeding intolerance, psychosis, ataxia, hallucinations, convulsion, coma, tachycardia with normal blood pressure, arrhythmia, and death can be observed after multiple instillations of the eye drop or accidental ingestion by infants, children, and patients with neurologic disorders (particularly Down syndrome). Most common adverse effects are cerebellar dysfunction, hallucinations, psychosis, seizure, hypersensitivity, and anaphylactic reaction and transient paralytic ileus. These effects can be reduced by preventive interventions, such as administering cyclopentolate at the lowest effective dose and/or pharmaceutical dilution of ophthalmic agent and/or applying digital pressure to the punctum for 1 to 2 minutes after drop administration. We observed respiratory distress in our patient as well; however, we were not sure whether this adverse effect was secondary to the direct or indirect act of cyclopentolate. Cyclopentolate can cause vomiting and abdominal distention, which may lead to respiratory distress by aspiration of gastric contents. The underlying factors that precipitated the cyclopentolate adverse effect in our case were the use of a 1% solution, which is the only available form in Turkey, and administration of cyclopentolate over the recommended dose for an infant.
Although eye drop–related systemic toxicity and preventive interventions have been well documented, there is very little information in the literature about treatment of systemic toxicity. Systemic adverse effects generally improve spontaneously without sequelae at the end of 2 hours in adults and 4 to 6 hours in infants/children; however, severe toxicity should be treated with physostigmine. In our country, some antidotes, such as physostigmine, are not available in hospitals. In case of emergency, the Turkish Minister of Health is the only source for supplementation of this drug to hospitals. Therefore, our case was treated with physostigmine with a 9-hour delay after her admission. Eye drops–induced adverse effects usually resolve within a few hours and antidote use is not generally required. Our patient’s clinical status did not improve until the time that we obtained the antidote; hence, she was treated with physostigmine. To our knowledge, our case is the youngest one in literature who was treated with physostigmine for a cyclopentolate-related overdose. Physostigmine is a short-acting acetylcholinesterase inhibitor, which acts as an antidote of anticholinergic poisoning. It slows the synaptic degradation of acetylcholine, thus increasing its synaptic concentration and overcoming the postsynaptic blockade of anticholinergic agents. The chemical properties of the physostigmine facilitate its passing into the central nervous system and thus leads to recovery of all central and peripheral anticholinergic symptoms. Physostigmine infusion with a dose of 0.02 mg/kg (maximum of 0.5 mg/dose) over 3 minutes is recommended in infants/children. Importantly, before infusion, conduction abnormalities (eg, PR, QRS, or QTc interval prolongation) should be checked on ECG.

Cyclopentolate may cause respiratory distress because of its either direct or indirect effect in cases undergoing ROP examination. Therefore, physicians should be aware of its possible systemic adverse effects and can safely use physostigmine in severe cases and in infants, with close follow-up. In our opinion, availability of physostigmine should be sustained in ophthalmology clinics and PEDs.

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