Central Anticholinergic Syndrome Induced By Cyclopentolate Eye Drops In A 4 Year Old Child
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Citation

Abstract
Central anticholinergic syndrome (CAS) is a clinical entity which shows central and peripheral effects produced by over dosage or abnormal reaction to clinical dosage of anticholinergic drugs. Anxiety, delirium, disorientation, hallucinations, seizures, tachycardia, hyperpyrexia, mydriasis, vasodilatation, gastric and urinary retention can be observed during CAS. In this syndrome, it is common decreased salivary, sweating, bronchial, and nasopharyngeal secretions. Cyclopentolate is an anticholinergic drug and it was used in cycloplegic eye examinations for mydriasis.

A 4 year-old girl presented to ophthalmology clinic for refraction problems. Three drops of cyclopentolate 1% for each eye was used four times at 5-min intervals to dilate the pupil. Thirty minutes after drop instillation, she started to experience drowsiness, agitation, hallucinations, jerkily moving all extremities and making frequent high-pitched cries. She admitted to intensive care unit (ICU) diagnosed with CAS. After intravenous bolus (0.1 mg/kg) and infusion (0.05-0.4/mg/kg/h) of midazolam, the symptoms including agitation, hallucinations, and high-pitched crying of the patient was controlled. Six hours after starting therapy in the ICU, the patient was fully recovered and discharged at 10th h after admission.

Cyclopentolate eye drops can be absorbed to capillary circulation and reached to brain via deep cerebral veins and cavernous sinuses therefore, it may cause CAS.

INTRODUCTION
Central anticholinergic syndrome (CAS) was first described by Longo in 1966. The syndrome may consist of agitation, including seizures, restlessness, hallucinations and disorientation, or of signs of depression, such as stupor, coma, and respiratory depression. The estimated frequency of this syndrome varies between 1 and 11.2%. The syndrome may be induced by anticholinergic drugs such as atropine or scopolamine but has also been observed after administration of opiates, benzodiazepines, phenothiazines, ketamine, cimetidine, etomidate, propofol, nitrous oxide and volatile anesthetics.

Patients undergoing ophthalmoscopy in hospital for various reasons are given eye drops often for cycloplegia and mydriasis to facilitate examination of the retina. The agents commonly used are 10% phenylephrine eye drops to dilate the pupils and cyclopentolate in the form of 0.5% or 1% eye drops to paralyze the iris temporarily. Cyclopentolate is a muscarinic receptor antagonist similar to atropine. It shares certain rarely occurring side effects with atropine, which include the possibility of CAS.

We present a central anticholinergic syndrome due to cyclopentolate eye drop in a 4 year old girl.

CASE REPORT
A 4 year-old girl, whose weight was 16 kg, height was 95 cm, with no significant past medical history presented to ophthalmology clinic of our hospital. It was during this first visit to the ophthalmology clinic for refractive eye problems. Three drop of cyclopentolate 1% for each eye was ordered four times at 5-min intervals to dilate the pupil for cycloplegic eye examination. Thirty minutes after eye drops instillation; she started to experience drowsiness, agitation, hallucinations, jerkily moving all extremities and making frequent high-pitched cries. She admitted to intensive care unit (ICU) for diagnosis and treatment. Physical examination of patient during admission was included mild hyperthermia (37.8 °C skin temperature), tachycardia (160 beats per minute), and tachypnea (32 breaths min⁻¹). She had agitation and visual hallucinations. She was showing jerkily moving all extremities and making frequent high-pitched cries.

The child admitted to intensive care unit (ICU) for diagnosis and treatment. Physical examination of patient during admission was included mild hyperthermia (37.8 °C skin temperature), tachycardia (160 beats per minute), and tachypnea (32 breaths min⁻¹). She had agitation and visual hallucinations. She was showing jerkily moving all extremities and making frequent high-pitched cries.
extremities and making frequent high-pitched cries. Her mucous membranes and skin were dry. Abdominal examination was normal with no decreased bowel sounds. Laboratory studies consisted of a complete blood count, electrolytes, blood urea nitrogen, creatinine, hepatic enzymes and coagulation studies; all laboratory results were within normal levels. Transcutaneous oxygen saturation was measured as 94%.

Oxygen was delivered 2 L/min via a face mask. An intravenous access was established and lactated ringer infusion was started. Intravenous bolus of midazolam at the doses 0.1 mg/kg was administered to prevent agitation, hallucinations, and high-pitched crying. Midazolam infusion at the doses of 0.05-0.4/mg/kg/h was administered keeping the patient calm and sedated. Midazolam infusion was stopped at the fourth infusion hour. Six hours after admission to the ICU, the patient recovered, and was fully awake and orientation. Ten hours after admission to the ICU, the patient fully recovered and was discharged.

**DISCUSSION**

Acetylcholine and acetylcholine receptors are widely distributed in the brain. Acetylcholine is important in regulating many functions including the sleep-wake cycle, memory, alertness, orientation, and analgesia. An absolute or relative reduction in cholinergic activity in the central nervous system (CNS) can result in anticholinergic syndrome. Because of the ubiquitous presence and diverse functions of acetylcholine in the CNS, anticholinergic syndrome can manifest with a variety of signs and symptoms. Central manifestations can include CNS excitation or depression. These can include convulsions, excitation, hallucinations, disorientation, hyperpyrexia, hyperalgesia, ataxia, mental impairment, sedation, and coma.

Cyclopentolate has been widely used as a cycloplegic and mydriatic agent for over 30 years. It has gained widespread use as the cycloplegic drug of first choice for most children over the age of 1 year and allows many optometrists and ophthalmologists to carry out quick successful cycloplegic refractions with few complications. In our ophthalmology department cyclopentolate was used routinely for mydriasis and cycloplegia during cycloplegic refraction examinations. All eye drops in our ophthalmology department were applied by an experienced nurse under an ophthalmologist supervising.

Cyclopentolate is an anticholinergic, antimuscarinic tertiary amine with atropine-like actions. When instilled topically in the eye, it is well absorbed, both into the eye and systemically. This is because both the conjunctiva and nasal mucus membranes are good drug-absorbing surfaces and eye drops pass readily through the nasolacrimal duct into the nose. Systemic absorption also occurs through the conjunctiva, the nasolacrimal duct, the oropharynx, the digestive system and the skin. In our case, cyclopentolate eye drops can be absorbed by capillary and reached to brain via angulus venosus of deep cerebral veins and cavernous sinuses. This direct accessibility to brain may improve CAS in our case.

Some cases have been reported of agitation, visual hallucinations and other forms of anticholinergic toxicity after application of cyclopentolate eye drops. Adverse systemic effects of cyclopentolate that have been well documented, include tachycardia, generalized urticaria and seizures. Acute psychosis has also been reported after topical instillation, and it occurs more frequently in children with little weight. In our case this may have contributed to CAS developing via systemic adsorbed cyclopentolate. In view of the smaller body mass in children, the chances of toxicity are higher. They normally occur within 20-30 minutes of administration, and subside within 4-6 hours with no permanent sequel and the patients having no recollection of the hallucinations. Another possible reason for the hallucinations could be the similarity of cyclopentolate's amino-dimethyl group to the amino-methyl group found in LSD (a hallucinogenic agent). CNS toxicity is rare, though some studies have reported an incidence of psychosis as high as 4%.

The differential diagnosis for acute delirium in a 4-year old includes but is not limited to, infectious encephalitis, Reye syndrome, and closed head injury. As the patient was without signs of systemic illness, encephalitis was unlikely. Laboratory and other diagnostic procedures performed at ICU did not show any infections and closed injury. Acute agitation and hallucinations of our case was controlled by IV midazolam boluses and infusion. The findings of peripheral anticholinergic toxicity suggested that the patient’s neurological status was a manifestation of the CAS.

Physostigmine is the agent of choice in the treatment of CAS, and it competitively inhibits the action of acetylcholinesterase that normally degrades acetylcholine. Commonly used anticholinesterase inhibitors such as neostigmine, pyridostigmine, and edrophonium have...
Contained quaternary amines that prevent them from traversing the blood–brain barrier. Physostigmine, however, is a tertiary amine allowing rapid entry and activity in the CNS. We could not use physostigmine in current case due to unavailability of commercial preparation of the drug in our country.

Midazolam is a recently developed water-soluble benzodiazepine used widely as a pre-anesthetic medication. Preclinical and clinical analysis of this drug indicates that it shares anxiolytic, muscle relaxant, hypnotic, and anticonvulsant actions. We treated clinical signs of CAS, such as agitation and delirium with infusion of midazolam following a bolus dose. As to the author's knowledge, this is the first report that CAS treatment was accomplished without physostigmine administration.

As a result, this case demonstrated that CAS is possible in younger children when cyclopentolate eye drop are administered. Symptomatic and supportive treatment of the CAS was maintained successfully with keeping the balance of fluid-electrolyte and acid-base status of patient without using physostigmine.

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