Unintentional Pediatric Ophthalmic Tetrahydrozoline Ingestion: Case Files of the Medical Toxicology Fellowship at the University of California, San Francisco

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Case Presentation

An 18-month-old child was brought to the emergency department (ED) by his mother for evaluation of diarrhea, vomiting, and somnolence. He was lethargic, with “pinpoint” pupils. Blood pressure was 125/77 mmHg, heart rate was 70/min, temperature was 36.5 °C, respiratory rate was 25/min, and pulse oximetry saturation (SpO₂) was 99 % on room air. Blood glucose was 101 mg/dL. Other initial laboratory investigation was unremarkable. Ethanol, acetaminophen, and aspirin were below detection limits. Urine drug screening was negative for amphetamine, methamphetamine, MDMA, barbiturates, benzodiazepines, cocaine, methadone, oxycodone, and opiates. Initial ECG done 3 h after ED arrival showed bradycardia with first-degree heart block. There was no response to 1 mg IV naloxone.

What Is the Differential Diagnosis of His Presenting Clinical Features?

Drowsiness with miotic pupils should always raise the suspicion for opioid intoxication. Response to naloxone may be inadequate or incomplete, such that repeated, increasing doses may be needed [1, 2]. Up to 4 mg of naloxone has been given in some cases involving propoxyphene or codeine [3, 4]. Some sources advise giving 0.1 mg/kg or as much as 10–20 mg if there was no response to the initial dose [3, 5]. Higher

doses of naloxone or even continuous infusions have been reported in symptomatic pediatric buprenorphine exposure [6]. Although screening for methadone and oxycodone was included in addition to the opiate urine immunoassay, other synthetic or semisynthetic opioids could have been involved, which might remain undetected. Other drugs that can cause drowsiness and small pupils include benzodiazepines, barbiturates, antipsychotics, other CNS depressants, clonidine, and other imidazoline derivatives [7–11].

Case Continued

On further questioning, it was discovered the child ingested milk that had been adulterated by tetrahydrozoline eye drops (Visine® Original; Johnson & Johnson Healthcare Products, New Brunswick, NJ) and maliciously intended for another family member. Toxicology lab analysis revealed a tetrahydrozoline concentration in the child’s urine sample of 2,430 ng/mL and a serum tetrahydrozoline level of 21.56 ng/mL. The concentration of tetrahydrozoline in the milk sample was 2,995.4 ng/mL. According to the subsequent investigation, the tetrahydrozoline (approximately 15 mL of 0.05 % solution) was added to a half gallon (1.89 L) of milk, and the child drank an unknown amount of it.

What Are the Common Scenarios for Imidazoline Toxicity?

The most common reported cases of toxicity involve accidental pediatric ingestions of tetrahydrozoline (THZ) 0.05 and 0.1 % solutions [12–15]. Other topical imidazolines such as naphazoline and xylometazoline (0.1 % or more) have also been reported to cause toxicity in children [16–18]. Some cases involved adulteration of drinks with THZ as a prank,

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believing it would cause diarrhea [19]. One case involved naphazoline that was mis-prepared at a compounding pharmacy as 4 % instead of 0.05 % [17]. Other case reports have described the use of imidazolines in drug-facilitated sexual assault [20, 21]. Imidazoline derivatives include clonidine, tetrahydrozoline (THZ), tizanidine, naphazoline, and xylometazoline, and ingestion by children can present with similar clinical features of CNS depression and miotic pupils [11–13, 16, 18, 22].

What Is the Mechanism of Toxicity of Imidazoline Derivatives?

Most of the imidazolines are designed as decongestants with direct activity on peripheral alpha-1 adrenoreceptors, which explains the transient initial hypertension sometimes seen after oral overdose, as seen in this child initially [23]. Their more conventional antihypertensive effects result from activation of presynaptic alpha-2 adrenoreceptors, which decrease sympathetic output centrally and peripherally, and possibly by increasing vagal activity or activating specific imidazoline receptors in the medulla which cause the hypotension and bradycardia seen later [23–27].

What Are the Common Reported Signs and Symptoms of Imidazoline Toxicity?

Altered mental status and bradycardia are the most common reported signs [14]. Respiratory depression, hypotension, miosis, and hypothermia have been reported with variable frequency [14]. Vomiting has been reported as well [18, 28, 29]. Convulsion-like episodes have been reported in two case reports [17, 30]. Transient hypertension is not uncommon [14, 31, 32]. Hypertensive crisis and myocardial infarction were reported in one adult patient with clonidine toxicity [33]. One child had hypoglycemia and hypothermia, which were attributed to poor oral intake and blunted central sympathetic response to cold and hypoglycemia [12].

What Other Drugs can Cause Bradycardia?

Drugs that can cause bradycardia with hypertension include phenylpropanolamine (PPA) [34], phenylephrine [35], and sometimes pseudoephedrine [10]. The mechanism is probably vagally mediated reflex bradycardia due to systemic hypertension. First- and second-degree heart blocks have also been reported [36, 37].

Bradycardia accompanied by hypotension should prompt suspicion of intoxication by beta-adrenergic blockers, calcium

channel blockers, and digoxin in addition to the imidazoline derivatives [38–40].

What Is the Expected Onset and Duration of Imidazoline Toxicity?

Multiple studies showed that onset of symptoms are rapid and usually within 2 h, and most of the children showed complete resolution of symptoms within 24 h [41–43]. Prolonged hypothermia up to 24 h has been reported [44]. Sinoatrial node block lasting up to 20 h has been also reported [20]. A prolonged cardiovascular effect up to 36 h was reported after ingestion of THZ [45].

How Did the Analytical Toxicology Results of the Tetrahydrozoline Concentrations in This Case Compare to Reported Therapeutic and Toxic Levels in the Literature?

Laboratory analysis revealed a urine tetrahydrozoline concentration of 2,430 ng/mL and a serum level of 21.56 ng/mL. The concentration in the adulterated milk sample was 2,995.4 ng/mL. Studies in healthy volunteers after therapeutic instillation of THZ 0.05 % eye drops showed maximum serum concentrations ranging from 0.068 to 0.380 ng/mL and maximum urine concentrations ranged from 44.0 to 400.0 ng/mL [46]. Previous authors reported three cases of pediatric THZ ingestion with plasma concentrations ranging from 23.6 to 41.4 ng/mL and urine concentrations of 9.2 to 49.5 µg/mL (9,200–49,500 ng/mL) [47]. A forensic case report showed that THZ may not be detected in blood after 16–22 h, and checking urine may be better in late presentations [29].

What Is the Recommended Management for Imidazoline Derivative Toxicity?

Treatment of imidazoline derivative toxicity is mainly supportive by assisting ventilation and airway protection for patients with severe central nervous system depression [12] and support of blood pressure and heart rate when needed. Close observation of neurological and hemodynamic status of the patients for at least 24 h and supporting their hemodynamics are done if needed with intravascular fluid in cases of hypotension and atropine if significant bradycardia and hypotension occur [16]. If the initial transient hypertension is severe, it should be treated with a short-acting vasodilator like nitroprusside or phentolamine [32, 48].

What Is the Role of Naloxone in Treatment of Imidazoline Toxicity?

There are some case reports suggesting response after naloxone administration in THZ and clonidine overdose, although concomitant opioid exposure was not adequately excluded by toxicological testing [11, 49–51]. The purported mechanism of naloxone effect was reversal of clonidine-enhanced endogenous opiate release, but animal studies have not confirmed this [52, 53]. There are several reports of failure of naloxone to reverse clonidine [54, 55] and toxicity from THZ and other imidazoline derivatives [12, 16, 44]. Of course, it is reasonable to try naloxone in a patient presenting with neurological and respiratory depression and miotic pupils, because of the possibility of unrecognized opioid toxicity [56]. Although worsened hypertension has been reported in a case series after naloxone treatment for pediatric clonidine poisoning, hypertension in these cases occurred following multiple treatments including atropine, making the causative role of naloxone unclear [57].

Case Conclusion

The child was admitted for observation. After 20 h, he had a heart rate of 90/min and a blood pressure of 90/50 mmHg. His mental status was back to baseline. No treatment was given. Child protective services and the police department were involved in the investigation of the circumstances surrounding the child's exposure.

Conflict of Interest None of the authors have any conflicts of interest.

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