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ORIGINAL ARTICLE

Accidental poisoning with brimonidine eye drops in a 9-day-old infant

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Summary Brimonidine is a selective alpha-2-adrenergic agonist used to treat glaucoma. We report a case of a 9-day-old female who developed, 90 minutes after accidental ingestion of 3 eye drops of 0.2% brimonidine, coma, apnea, hyperglycemia and miosis requiring intubation and mechanical ventilation. Plasma concentration, 3 hours after intake, was 11.7 ng/mL. Normal consciousness was reached after 27 hours. Apnea recovered slowly, normal breath was reached 47 hours after accidental intake. This report adds to the existing evidence that brimonidine has serious systemic effects in newborns and can require fast and supportive management in intensive care unit.

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Introduction

Brimonidine is a selective alpha-2-adrenergic agonist that lowers intraocular pressure by decreasing aqueous humor production and increasing uveoscleral outflow. Alphagan® eye drops (Allergan Pharmaceuticals, Ireland) contain 0,2% brimonidine. We report the case of a neonate who has developed a serious intoxication following oral administration of 3 eye drops of this drug. The distinctive features of this case are the low age of the patient (nine days), the intensity and the duration of coma and respiratory depression following ingestion of only three eye drops and the brimonidine plasma assay.

Case report

Following her childbirth, at time of discharge, a mother went to the pharmacy with a medical prescription of cholecalciferol (Zyma D*). The pharmacist provided brimonidine 0,2% (Alphagan®), instead of cholecalciferol (ZymaD®) and gave advices to the mother to give orally three drops per day. Thus, the mother, illiterate, followed the instruction of the pharmacist.

At home, one hour after administration, the neonate was drowsy and Angers Poison Control Center was called and recommended prompt transfer to the Pediatric Emergency Center.

The origin of the mismatch was discovered by checking medication administered before the first clinical sign: instead of cholecalciferol (ZymaD®), brimonidine 0,2% (Alphagan®) ophthalmic solution has been provided by the pharmacy and subsequently administered (three eye drops)

At emergency center admission, 90 minutes after ingestion, the 9-day-old female infant, born at 41 weeks weighting 3,34 kg, suddenly displayed respiratory depression. She was comatose (Glasgow Coma Scale [GCS] = 3/15: no eye opening, no verbal response, and no motor response). Physical examination revealed an apnea, a body temperature 35.1 °C, a bilateral miosis reactive to light, a 105-bpm heart rate, a 92/69 mmHg blood pressure (systolic/diastolic). She was immediately intubated and admitted to an intensive care unit (ICU) for respiratory failure requiring mechanical ventilation.

Comprehensive metabolic panel was normal except: glucose 12,5 mmol/L (reference range: 2,5—4,5 mmol/L). Arterial blood gas did not revealed acidosis; A blood sample was remove in order to perform a comprehensive toxicology testing benzodiazepines, ethanol and acetaminophen were undetectable, toxicological laboratory investigations are detailed below.

Ten hours after administration of brimonidine, accidental extubation occurred. The newborn displayed a GCS at 8 and she was still apneic, thus she required a new intubation and sedation by midazolam.

Forty-seven hours after ingestion, she was extubated with full recovery of consciousness and normal respiratory function. Hospital stay in ICU lasted three days. Neurological examination was normal at exit. A long-term psychomotor follow-up was scheduled in order to detect eventual neurological lesions which could be unapparent so young.

Fig. 1 shows the evolution of glycemia and GCS. The maximal glycemia level (19,5 mmol/L) was reached 5 hours after the accidental intoxication. Twenty-five hours after brimonidine ingestion, baseline level was not ever achieved. The evolution of Glasgow Coma Scale is the following: score of 3 persisted 7,5 hours after intake and reached 5 (Abnormal (spastic) flexion, decorticate posture) after 10.5 hours. During the 12 following hours, eye-opening response was spontaneous; GCS reached 8. Normal consciousness was reached after 27 hours post ingestion. Apnea recovered slowly, normal breathing was only reached 47 hours after accidental ingestion.

Toxicological laboratory investigations

Our analytical methods were made using a LC-MS/MS system consisted of a 3200 Q TRAP® triple-quadrupole linear ion trap mass spectrometer fitted with a TurboIonSpray interface (Applied Biosystems/MDS Sciex, Darmstadt, Germany) and an Agilent HPLC system.

Our approach is a multi-target screening (MTS): a multiple reaction monitoring (MRM) as survey scan and an enhanced product ion (EPI) scan as dependent scan were performed in an information-dependent acquisition (IDA) experiment. The MS/MS spectra obtained by the IDA controlled enhanced product ion (EPI) scans are compared with the spectra of our electrospray ionization—MS/MS library [1]. No other drug was detected.

As we knew that she had ingested brimonidine, thus we decided to first identify it and then to quantify it in blood sample.

The identification step was performed as follow: MRM transitions of our MTS method described above were removed and replaced by brimonidine MRM transition (292.1—212.2). The acquired MS/MS spectra was compared to those of a brimonidine spiked blood. Retention times and spectra were superposable and identical (Fig. 2).

After this identification step, brimonidine plasma level was measured using a specific MRM method. Briefly, brimonidine was extracted from plasma by liquid-liquid extraction with 1-chlorobutane as organic solvent in alkaline condition (pH = 9). Glafenine was used as internal standard chromatographic separation was achieved with a C18 column using water/acetonitrile gradients, spectrometry detections were MRM for quantification. Brimonidine concentration was 11.7 ng/mL.

Discussion

Although previously reports of brimonidine poisoning in children have been published [2—6], according to our knowledge, no other report of such rapid, profound and long association of apnea, coma, documented hyperglycemia, miosis and low temperature. In literature, the circumstances of child intoxication are the following: unintentional ingestion of brimonidine eyes drops [6] and systemic effect of topical administration [7].

Brimonidine is a α_2 adrenergic agonist such as clonidine. Central and peripheral effects can be attributed to this drug.

Coma, respiratory depression and miosis are central effects mediated by α_2 receptor stimulation. Even if