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Apnea in preterm neonate following administration of cyclomydril eye drops. Case report

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Abstract

Context: Apnea is a prolonged cessation of respiration which is a common presentation in a pediatric emergency department in neonates and premature babies which can be caused by direct depression of CNS control of respiration (hypoglycemia, meningitis, intracranial hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (obstruction of the airway, pneumonia, muscle weakness) and can be caused by some drugs.

Objective: We report a case of a premature infant presented to the ophthalmology clinic for the regular screening of ROP, and pupils were dilated with Cyclomydril eyedrops. Approximately a few minutes after giving the drops, the baby was unresponsive, apneic, Cyanotic.

Patient: The patient came to the ED at 37 weeks' corrected gestational age when he received Cyclomydril eyedrops to dilate the pupils during his screening for ROP. Approximately a few minutes after giving the drops, the baby was found unresponsive, apnic, cyanotic; the patient was taken by his mother to a pediatric emergency. Upon arrival, the boy was apnic, cyanosed and unresponsive.

Conclusions and Outcome: Although very rare, Cyclomydril eye drops have been known to cause apnea, and even hypoxic arrest, in outpatient ophthalmology clinics at routine screening for retinopathy of prematurity. Adverse events such as apneas and bradycardias have been documented to occur up to 24 hours following the instillation of the eye drops. After clinical assessment and investigations, we conclude that these eye drop side effects should be considered a cause of apnea in neonates and premature babies. So, the pediatric ophthalmologists should be equipped to handle this type of emergency, either personally or with ancillary services that are immediately available.

Keywords: apnea, retinopathy of prematurity, preterm neonate, cyclomydril

Introduction

Apnea is defined as an "episode of a stop of breathing for 20 seconds or more, or less than 20 seconds when associated with bradycardia, cyanosis, pallor, or marked hypotonia." Apnea is more common in preterm infants [1]. It is well known that premature neonates have immature respiratory control that may result in apnea, with or without bradycardia [2]. Preterm births are a significant public health problem. These infants are at increased risk for medical and developmental complications at birth [2]. One common complication of preterm birth is Retinopathy of prematurity (ROP), a disease of the developing blood vessels on the retina that may lead to vision impairment or blindness. The American Academy of Pediatrics (AAP) has published guidelines for ROP screening examinations that start at 4–6 weeks of age, focusing on infants born at less than 30 weeks gestational age or weighing less than 1500 g [2]. These examinations require the administration of mydriatic ophthalmic drops to dilate the pupils and sometimes involve physical manipulation of the eye. Ocular administration of cyclopentolate alone or in combination with phenylephrine is the preferred drug to induce pupil dilation in infants [2]. Cyclomydril, a mydriatic containing both cyclopentolate (0.2%) and phenylephrine (1%), was used in the present study. Cyclopentolate/phenylephrine (Cyclomydril) is a combination of Adrenergic Agonist Agent with an anticholinergic agent, which is a commonly used medication topically as an eye drops in ophthalmology clinics before the retinal examination to produce mydriasis in both adults and pediatrics as well as in premature infants for screening of Retinopathy of prematurity [3]. Side effects of this medication were reported locally as blurred vision, burning sensation in the eye, sensitivity to light, reactive hyperthermia, transient keratitis, a transient elevation in intraocular pressure, as well as systemic side effects related to systemic absorption as tachycardia, increased blood pressure ataxia, hyperactivity, restlessness, seizures, oxygen desaturation, delayed gastric emptying. One of the rarely reported side effects is apnea [4]. We report a case of a premature infant presented with apnea following eye examination using cyclopentolate/phenylephrine drops.

Case report

Preterm neonate born at 26 weeks gestational age weighing 720 g was a product of emergency cesarean section to a primigravida mother due to abruption placenta with extreme low birth weight admitted to neonatal intensive care unit (NICU) for two months, was intubated, diagnosed as extreme preterm with respiratory distress syndrome, indirect hyperbilirubinemia and ROP stage II. The patient presented at an ophthalmology clinic in King Saud Medical City (KSMC) for follow-up retinopathy of prematurity (ROP)

screening examination at 37 weeks of corrected gestational age, ten days after discharge. The patient had received Cyclomydril drops as part of routine ROP screening at 30 weeks' corrected gestational age and regularly as protocol during hospitalization. At each of these examinations, the patient had received Cyclomydril (cyclopentolate hydrochloride 0.2%, phenylephrine hydrochloride 1%) without complications. At his outpatient retinopathy of prematurity screening, the pupils were dilated with Cyclomydril eyedrops. Approximately a few minutes after giving the drops, the baby was found to be unresponsive, apneic, and cyanotic. The patient was taken to the emergency department by his mother to a pediatric emergency. Upon arrival, the boy was apnic, cyanosed, and unresponsive with BP 65/47 mmHg, pulse 120 b/m, T 37 C. Resuscitation started with oxygen bagging; the patient returned to consciousness after 1-2 minutes started crying. His color returned to pink and regular pulses with no need for CPR, then was maintained O2 saturation by BiPAP. By examination, the chest was similar bilateral air entry with transmitted sounds. A chest x-ray was done and reported no significant findings of infiltration or aspiration (figure 1).

Initial laboratory findings showed WBCS 8.15, HGB 9.6, HCT 29.7, PLT 447.

Serum chemistry showed ALT 21, AST 37.3, ALP 560, Direct bilirubin 3.9, Total bilirubin 7.1, Urea 3.1, Creatinine 31, Ca 2.43 mmol/L, Na 139 mmol/L, K 5.28 mmol/L. Venous blood gas showed Ph 7.20, Pco2 72, Hco3 17

After one hour of resuscitation, he was shifted to a nasal cannula for close observation to the NICU. Did blood and urine cultures, and the patient was started on cefotaxime and caffeine citrate; two days later, stopped antibiotics as the culture results came negative. The patient was discharged home after six days with no further episodes or complications.

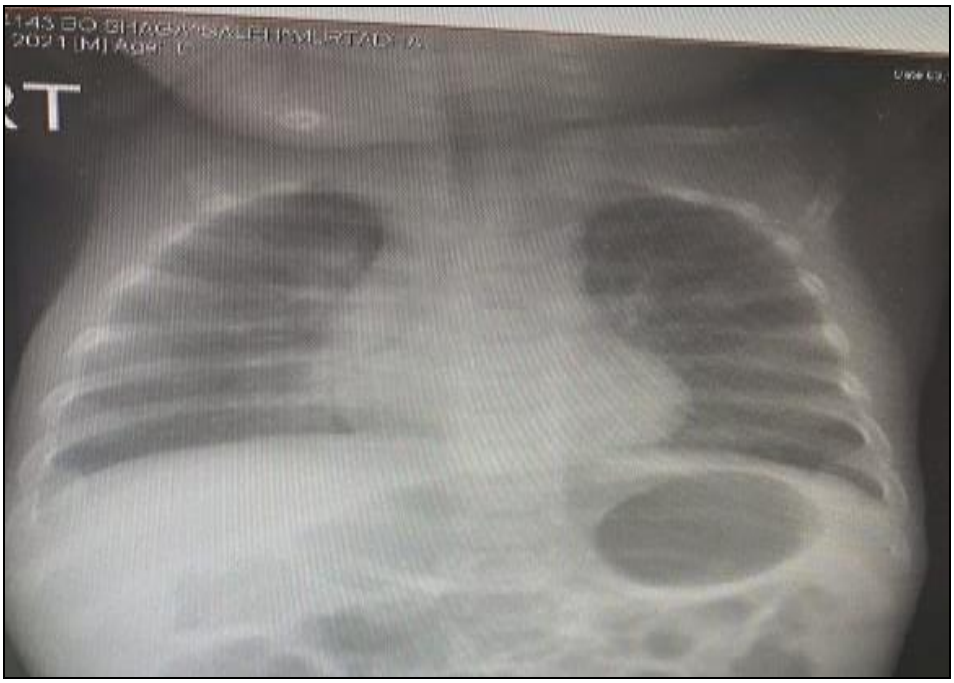

Fig 1

Discussion

Cyclomydril eye drops contain cyclopentolate, an anticholinergic, and phenylephrine, an adrenergic drug, frequently used for premature infants' mydriasis for ROP screening examinations [5]. The Cyclomydril produces mydriasis of short duration that is superior to that of either drug alone with little or no cycloplegia [5]. The dose is one drop in both eyes, every 5-10 minutes, not to exceed three drops per eye. When instilling the drops, it is recommended that it compress the lacrimal sac to minimize systemic absorption [5]. Systemic absorption of topical ophthalmic medications has been known to produce side effects by the "first pass" effect [3]. Topical ophthalmic agents drain through the nasolacrimal duct system. Up to 80% of the drug is absorbed through the nasal mucosa and passes directly into the systemic circulation without hepatic filtering [3]. In infants, low body mass and immature cardiovascular and nervous systems can increase the risk of toxicity [3]. Adverse effects related to systemic absorption of mydriatic eyedrops are well documented. A temporary rise in systolic and diastolic blood pressures and bradycardia have been noted with systemic absorption of phenylephrine [3]. The side effects of cyclopentolate include oxygen desaturation, apnea, feeding intolerance, delayed gastric emptying, transient paralytic ileus, tachycardia, seizures, and psychosis [4]. Premature infants are susceptible to neurological and cardiopulmonary side-effects of cyclopentolate due to their immature neurological and cardiovascular systems and their immature metabolic pathways [5]. Although very rare, Cyclomydril eye drops have been known to produce apnea, and hypoxic arrest, in ophthalmology clinics at the routine examination for retinopathy of prematurity. Adverse events such as apneas and bradycardias have been documented to occur up to 24 hours following the instillation of the eye drops [5]. To our information, our case is one of the first cases reported with apnea following administration of Cyclomydril Eye drops.

The case reported by Lee *et al*. exhibited 41 weeks old, extreme preterm with cardiopulmonary arrest occurred before the ROP examination and only after administration of the eye drops. Suggests that the Cyclomydril caused the

cardiopulmonary arrest [3]. One of the cases reported by Pfister, C., & Timmerman, K. 2019 exhibited An ex-premature baby 39 presented for a laparotomy for necrotizing enterocolitis (NEC) at 39 weeks postconceptual age. Planned ophthalmologic procedure to follow the laparotomy under a general anesthetic. Postoperatively the neonate remained apnic, and the anesthetists could not extubate her. She required mechanical ventilation in the intensive care unit (ICU) overnight. After considering all causes of postoperative apnoea in this neonate, an overdose of Cyclomydril eye drops was thought to be a significant factor [5]. So, our case is one of the first cases reported with apnea following administration of Cyclomydril Eye drops. So, the preterm infants presenting for retinopathy of prematurity screening requiring Cyclomydril eye drops should have the drops instilled by an ophthalmologist, not receive a dose exceeding the recommended dose of three drops per eye administered five to ten minutes apart, receive appropriate postoperative placement ensuring apnea monitoring and the infants are in a carefully controlled and monitored environment with extensive support personnel. So, pediatric ophthalmologists should be prepared to handle this type of emergency, either personally or with ancillary services that are immediately available [5].

Abbreviations
ROP: Retinopathy of Prematurity
KSMC: King Saud Medical City
ED: Emergency Department
NICU: Neonatal Intensive Care Unit
ICU: Intensive Care Unit

Funding
None

Conflict of Interest
None declared

Disclosure
Abdullah M. Kamel is a Pediatric Emergency Consultant. King Saud Medical City, Riyadh; he received and managed the patient in ED, and reviewing patients' files..

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