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Case Report
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Bronchoconstriction following instillation of phenylephrine eye drops in premature infants with bronchopulmonary dysplasia
-two cases report-

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Premature infants requiring an ophthalmic examination or even surgery for retinopathy of prematurity (ROP) have a high prevalence of co-existing bronchopulmonary dysplasia (BPD). Reactive airway is one of the clinical presentations of BPD. We report two cases of bronchoconstriction following instillation of mydriatic eye drops. One occurred during induction of anesthesia for laser photocoagulation and the other before screening of ROP. The most likely cause in each case was phenylephrine eye drops. We recommend that the minimal dosage of phenylephrine needed to attain proper mydriasis should be instilled to infant patients, and the possibility of bronchoconstriction occurrence kept in mind, especially for infants with low body weight with BPD.

Key Words: Bronchopulmonary dysplasia, Bronchoconstriction, Phenylephrine, Retinopathy of prematurity.

Retinopathy of prematurity (ROP) is not an uncommon disease in premature infants. Surgical treatment is performed depending on the judgment of the ophthalmologist. At that time, anesthesiologists are challenged since these patients can have many coexisting diseases that require special concern. Mydriatic eye drops should be instilled in the target eye before the ophthalmic examination and operation to ensure the field of peripheral fundus. Mydriatics commonly used are classified in two groups: antimuscarinics and sympatominetics. Despite the necessity and common use of these mydriatics, various side effects after instillation of the drugs in pediatric patients have been reported [1-3]. We report two bronchospastic events after instillation of mydriatic eye drops in premature babies diagnosed with bronchopulmonary dysplasia (BPD). These events were likely side effects of the phenylephrine eye drops.

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Case Reports

Case 1

A 2-month-old boy weighing 2000 g was planned to undergo laser photocoagulation for ROP under general anesthesia. He was born at 28 weeks gestation, weighing 1190 g. His Apgar scores were 6 at 1 min and 7 at 5 min. He required 1 week of mechanical ventilation for respiratory distress syndrome and was ultimately diagnosed with moderate grade BPD, which required supplemental oxygen (O_2; 1 L/min via nasal cannula).

Patent ductus arteriosus (PDA) was detected and pharmacological closure was performed. He developed a grade II intraventricular hemorrhage and underwent an external ventricular drain operation due to post-hemorrhage hydrocephalus 1 week before ROP surgery. General anesthesia was established by inhalation anesthesia using sevoflurane; there were no associated adverse events.

Preoperative evaluation revealed fair patient condition with a blood pressure of 65/40 mmHg, heart rate of 130 beats/min, and SpO_2 of 95% under the aforementioned supplemental oxygen. Wheezing or rales were not heard on lung auscultation. Chest X-ray showed increased bilateral reticular markings in the lung fields. Fifteen minutes before the surgery, one drop of 1% tropicamide followed 30 s later by one drop of 2.5% phenylephrine was instilled in each eye twice at 5 min intervals. At the operation room, the patient's SpO_2 was 92% under O_2 (1 L/min via nasal cannula), systolic blood pressure 70 mmHg, and heart rate 125 beats/min. Anesthesia was induced by inhalation of sevoflurane. During manual ventilation using face mask with 100% O_2 and 6 vol% sevoflurane, SpO_2 did not increase above 92%. After tracheal intubation with a 3.0 mm internal diameter endotracheal tube, SpO_2 remained 90% under FIO_2 1.0 and scattered wheezing was detected in both lung fields. Under pressure-controlled ventilation, the tidal volume was only 7–8 ml at a pressure of 20 mmHg, end-tidal concentration of sevoflurane 3.8–3.9%, and end-tidal carbon dioxide 30 mmHg. Salbutamol nebulization was applied immediately and 5 min after the induction of anesthesia, SpO_2 increased gradually to 96% and the wheezing was resolved incompletely. Therefore, FIO_2 could be reduced to 0.3–0.5 to maintain the target SpO_2, 90–94%, during the surgery. The operation took 1 h, 20 min to perform. After discontinuing sevoflurane, spontaneous respiration was recovered and wheezing was barely audible. He was transferred to pediatric intensive care unit without extubation. There were no significant changes of findings on postoperative chest radiograph. Next morning, extubation was performed and supplemental O_2 (1 L/min) was continuously administered via nasal cannula. One week after the ROP surgery, he underwent ventriculoperitoneal shunt. The same anesthesiologist performed anesthesia, and there was no adverse event.

Case 2

A 1-month-old boy weighing 1700 g underwent ophthalmological screen for ROP. He was born at 25 weeks gestation and weighed 1000 g. His Apgar scores were 8 at 1 min and 9 at 5 min. His neonatal problems included PDA, which required pharmacological management. He required 3 weeks of nasal CPAP therapy for respiratory distress syndrome and was ultimately diagnosed with moderate grade BPD, which required supplemental oxygen. The nasal CPAP was discontinued 1 week before the examination. The chest radiograph demonstrated diffuse haziness in both the lungs. For mydriasis, one drop of 1% tropicamide followed 30 s later by one drop of 2.5% phenylephrine was instilled in each eye. At that time he was receiving O_2 (1 L/min via nasal cannula). Five minutes later, a second drop of both tropicamide and phynylephrine were instilled in each eye. About 10 min later, his saturation on pulse oximetry was slowly decreased from 94 to 88%, and mild wheezing was detected on both lung fields. Blood pressure was 75/40 mmHg and heart rate was 135 beats/min. During preparation of the nebulizer, he received O_2 at a rate of 8 L/min through a face mask, followed by inhaled salbutamol while positioned slightly head-up position with O_2 supplied continuously through the nasal cannula. The saturation was restored to 93–94% and the wheezing was resolved after 20 min. Follow-up chest radiograph revealed no interval changes. At the next eye review, only 1% tropicamide was used for mydriasis and there was no adverse event.

Discussion

The sudden occurrence of bronchospasm after anesthesia induction can originated from various factors including inadequate depth of anesthesia, endobronchial intubation, partially obstructed tube, and drug-induced anaphylactic reaction. The first case presented with a duration of 10 min and self-limited, bilateral wheezing, normal blood pressure, and heart rate without skin changes, hypotension, and angioedema. Desaturation developed during the manual mask ventilation under 6 vol% sevoflurane before tracheal intubation. Furthermore, this patient underwent general anesthesia 1 week before and 1 week after the surgery by the same anesthesiologist and through the same methods of inhalation anesthesia (VIMA). No bronchospastic events occurred. Considering this information, a main cause other than related with anesthesia was searched for. An alternative explanation for the desaturation event could be possible acute pulmonary congestion following pulmonary hypertension due to the abrupt increased left-to-right shunt in PDA patients. However, this hypothesis was not be supported by physical examination; he had definite wheezing, not crepitations.

The mydriatics used were tropicamide and phyenylephrine. Tropicamide is a paraysympathetic blocker that exhibits little effect on the cardiopulmonary system. Phenylephrine is a potent α-adrenergic agonist and exerts β-adrenergic stimulation in high dosage. Interestingly, we were briefed concerning some episodes of desaturation following instillation of mydriatics in premature infants at our pediatric intensive care unit; they had similar clinical presentations with Case 2. Therefore, associated relationships between the mydriatics and the co-existing diseases of premature infants were strongly suspected. There is no definite

guideline for dosage of phenylephrine ophthalmic solution and the historic recommendation for instillation of phenylephrine ophthalmic drops in infants is 1 drop of 2.5% solution in each eye every hour. However, clinicians' concern that is biased towards local mydriatic effect can lead to larger administration of ophthalmic drops, as in these cases and other reports relevant to adverse effects. Meanwhile, a question of the difference arises because there are many former infants with BPD who underwent ophthalmic examination in this institute who did not experience bronchoconstriction. We investigated the incidence of wheezing combined with desaturation, which is closely related temporally to the instillation of phenylephrine in patients with BPD of our neonatal intensive care unit during last 6 months. An incidence rate of 33% was found (3/9). Therefore, our clinicians are now paying particular attention to the dosage of the drug and conduct monitoring during ophthalmic examination of the infants with BPD, even though the causal relationship between BPD severity and the occurrence of bronchoconstriction remains unknown.

BPD, or chronic lung disease of infancy, occurs in 40% of very low-birth-weight infants and the development increases as the birth weight descends below 1500 g. The assessment of BPD is conducted at 28 days postnatally or 36 weeks postmenstrual age on the basis of O_2 requirement. The disorder is classified as mild, moderate, or severe following gestational age and the degree of O_2 requirement. The clinical features of BPD include tachypnea, intercostals retractions, increased airway resistance, wheezing or coarse crackle, and reactive airway [4,5]. Meanwhile, Mirmanesh et al. [4] have demonstrated bronchoprovocation in BPD infants using phenylephrine eye drops but not in control infants. The authors concluded that the α-adrenergic activity of phyenylephrine could exacerbate the bronchospastic component of BPD. Increased α-adrenergic activity has been suggested as a contributor to bronchoconstriction in asthmatic patients and α-receptor antagonists mitigates asthmatic symptoms. Phenylephrine reportedly tends to increased airway obstruction in sporadic asthma although it was not consistent in severe asthma [6].

The present cases appear to be bronchospasm in premature infants during anesthesia induction and ophthalmic examination. The most likely cause was phenylephrine eye drops. In Case 1, inappropriate depth of anesthesia may also have contributed by causing airway spasm. It seems to be the more reasonable interpretation that aggravated bronchospastic component of BPD infant might be induced by α-adrenergic eye drops worsened by the airway stimulation during tracheal intubation. This view supports the inference that desaturation did not occur at screening of ROP using one drop of phenylephrine.

The other reported side effects of phenylephrine are increased blood pressure [3], cardiac arrhythmia, renal failure [1], and pulmonary edema [2]. Shell [7] reported that 80% of the volume of eye drop passes down the nasolacrimal canal, which is highly vascular mucosa, where it can enter the systemic circulation. The estimated standard drop volume is about 35.4 μl [8] and this fixed volume is far less diluted by circulating blood in infants who have much smaller volume. Therefore, efforts to reduce the drop volume for minimalization of side effects have been performed [8]; other methods are punctuate pressure and eyelid closure. The present two patients had slight changes in blood pressures and heart rates during the events, but these were not serious. Phenylephrine plasma concentration after administration of a 2.5% solution to anesthetized adult patients was reported as 2–3 ng/ml after 10–20 min, with no serious cardiovascular side effects [9]. It is difficult to estimate the exact volume of administered phenylephrine into the eyes in this report because excess drugs flowed down out of the eyes when eyelids were closed after instillation. Therefore, the use of reduced volume of the drug [8] is more important in infant patients.

From the cases described above, phenylephrine can be a causative agent to initiate or aggravate bronchoconstriction in premature infants affected by BPD; although the causal relationship cannot be definitely concluded. We recommend that the minimal dosage of phenylephrine needed to attain proper mydriasis should be instilled to infant patients, and the possibility of bronchoconstriction occurrence could be kept in mind, especially in case of infants with lower body weights who are affected by BPD.

References

1. Shinomiya K, Kajima M, Tajika H, Shiota H, Nakagawa R, Saijyou T. Renal failure caused by eyedrops containing phenylephrine in a case of retinopathy of prematurity. J Med Invest 2003; 50: 203-6.
2. Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. Br J Anaesth 2002; 88: 440-2.
3. Greher M, Hartmann T, Winkler M, Zimpfer M, Crabnor CM. Hypertension and pulmonary edema associated with subconjunctival phenylephrine in a 2-month-old child during cataract extraction. Anesthesiology 1998; 88: 1394-6.
4. Mirmanesh SJ, Abbasi S, Bhutani VK. Alpha-adrenergic bronchoprovocation in neonates with bronchopulmonary dysplasia. J Pediatr 1992;

121: 622-5.
5. Kliegman R, Nelson WE. Nelson textbook of pediatrics. 19th ed. Philadelphia, Elsevier/Saunders. 2011, pp 587-90, 1516-e2.
6. Grandordy BM, Paiva de Carvalho J, Regnard J, Florentin D, de Lauture D, Marsac J, et al. The effect of intravenous phenylephrine on airway calibre in asthma. Eur Respir J 1995; 8: 624-31.
7. Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. Surv Ophthalmol 1982; 26: 207-18.
8. Elibol O, Alcelik T, Yuksel N, Caglar Y. The influence of drop size of cyclopentolate, phenylephrine and tropicamide on pupil dilatation and systemic side effects in infants. Acta Ophthalmol Scand 1997; 75: 178-80.
9. Kumar V, Schoenwald RD, Barcellos WA, Chien DS, Folk JC, Weingeist TA. Aqueous vs viscous phenylephrine. I. Systemic absorption and cardiovascular effects. Arch Ophthalmol 1986; 104: 1189-91.