

Case Reports

Gaviscon and domperidon responsive apnea episodes associated with gastro-esophageal reflux disease in twins

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Background: The possible pathophysiology of the relationship between gastro-esophageal reflux disease and apnea of prematurity has been widely investigated. Various physiological protective reflex responses provide a plausible biological link between gastro-esophageal reflux and apnea of prematurity. It is uncertain whether or not there is a causal relationship between the two diseases. **Patient's Findings:** Twins were admitted to the neonatal intensive care unit due to feeding problems. Physical examination was normal except for reticulated, blue-violet skin changes. Short apneic attacks occurred on the first day in twin 1 and on the second day in twin 2, and these were initially treated by stimulation and increased ambient O₂ concentration. Then, we conducted methylxanthine and continuous positive airway pressure treatment. Laboratory and radiological analysis were normal. As gastro-esophageal reflux disease was thought to be the causes of the treatment-refractory apnea, therapy with gaviscon and domperidon was begun for both cases. Apneic attacks did not recur after gaviscon and domperidon therapy. **Conclusion:** Pharmacological therapy for gastro-esophageal reflux disease has not definitively been shown to be effective in improving symptoms and hence, should be reserved especially for infants with treatment refractory apnea episodes suspected as being gastro-esophageal reflux in premature infants.

Key Words: apnea, gastro esophageal reflux disease, premature, newborn, treatment

INTRODUCTION

During the first few days of life, premature infants encounter problems with temperature regulation, acquisition of oral feeding skills, and the normal control of respiration.¹ Resolution of apnea and establishment of a normal respiratory pattern is a major developmental milestone for many premature infants. Apnea of prematurity (AOP) is defined as a pause of breathing for more than 15-20 s, or accompanied by oxygen desaturation [transcutaneous oxygen saturation (SpO₂) ≤80% for ≥4 s] and bradycardia (heart rate <2/3 of baseline for ≥4 s), in infants born of less than 37 weeks of gestation.²

Gastro-esophageal reflux (GER), described as the retrograde movement of the stomach contents into the esophagus, is the most common esophageal disorder in the neonatal period. Gastro-esophageal reflux disease (GERD), which occurs as a consequence of GER, may be associated with poor weight gain, esophagitis, hematemesis, and respiratory problems, such as apnea, aspiration, recurrent pneumonia, or exacerbated bronchopulmonary dysplasia. While infants who have physiological GER usually do not require treatment, infants with respiratory symptoms and signs of GERD undoubtedly need treatment. The possible pathophysiology of the relationship between GER and AOP has been widely investigated.³ A recently study found a significant increase of the frequency of AOP in the period following the onset of GER, suggesting a causal relationship between GER and AOP.⁴

AOP treatment options are limited and include stimulation, methylxanthine therapy and nasal intermittent positive pressure ventilation or continuous positive airway

pressure (CPAP). Here, we report the resistance to management of CPAP and methylxanthine in the premature twins, treated with gaviscon and domperidon for GER presenting with apnea episodes.

CASE REPORT

The premature twins were born at 34⁺⁴ weeks of gestation by caesarean section to a 28-year-old healthy mother. The babies were admitted to the neonatal intensive care unit for feeding problems. The first twin birth weight was 2,450 g, length: 45 cm, head circumference: 33 cm and the Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. The second twin birth weight was 2,220 g, length: 42.5 cm, head circumference: 32 cm and the Apgar scores were 8 and 10 at 1 and 5 minutes, respectively.

Skin changes were observed shortly after birth, in the form of reticulated, blue-violet patches in both cases. The lesions were located on the trunk, the entire back, on the gluteal region and both legs and arms. They had no other systemic or dermatological disorders.

They were given breast milk using an orogastric tube on the first day, and then oral feeding was begun. Short apneic attacks occurred on the first day in twin 1 and

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were initially treated by stimulation and increased ambient O₂ concentration. Treatment with oral caffeine at 20 mg/kg loading dose and 5 mg/kg maintenance dose was begun on the 2nd day. Apneic attacks initially resolved by the 5th day, but were again present by the 7th day. This was followed by a further 2 days of CPAP.

We determined short apneic attacks on the second day in twin 2, which were initially treated by stimulation and increased ambient O₂ concentration. Treatment with CPAP was begun on the 5th day. CPAP therapy was discontinued on the 7th day. Since twin 1 was resistant to caffeine treatment, we did not start caffeine in twin 2.

Laboratory and radiological studies were performed for the differential diagnosis of apnea. The cranial ultrasonography, blood glucose, serum electrolytes, C-reactive protein, interleukin-6, urine and blood cultures were reported as being normal. Electroencephalography was performed to rule out any epileptic abnormality and was reported to be normal. The screening studies for inborn errors of metabolism were negative.

As GER was considered to be the cause of the treatment refractory apnea, therapy with Gaviscon and domperidone was started on the 8th day for both cases. Apneic attacks were not recorded after the 9th day. Feeding intolerance was not detected after gaviscon and domperidone treatment in the twins.

The twins were discharged on the eleventh day of their admission without any reoccurring problems. Based on the physical examination and laboratory analyses, they were diagnosed as GER presenting with apnea episodes. The twin babies were discharged in good condition.

DISCUSSION

Treatment of apnea of prematurity is instituted if apneic spells are frequent, prolonged or associated with bradycardia or desaturation. Management is a combination of the general measures that reduce the risk of apnea, nasal CPAP and methylxanthine therapy. Infants at risk for apnea should be started on cardiorespiratory monitoring. General measures are usually preventive in nature and are applied to all infants less than 35 weeks of gestation who are at risk for apnea. These interventions are directed towards eliminating the factors that increase the risk of apnea or reduce the prevalence of associated hypoxia. Infants are positioned to avoid extreme flexion or extension of the neck, which decrease the patency of the upper airway. Nasal patency is preserved by avoiding vigorous nasal suctioning or prolonged use of nasogastric tubes. Gentle tactile stimulation is often adequate therapy for mild and intermittent episodes. Nasal CPAP reduces the incidence of mixed and obstructive apnea, maintains functional residual capacity, and alters the timing of breathing in preterm infants.^{5,6} Methylxanthines cause stimulation of respiratory neural output presumably by inhibiting adenosine receptors. The two methylxanthines used in apnea of prematurity are caffeine and theophylline. Caffeine is the preferred agent because of its longer half-life, with a wide margin of safety and lower frequency of adverse effects. In our cases, apnea did not disappear despite caffeine therapy and nasal CPAP.

Various physiological protective reflex responses provide a plausible biological link between GER and AOP.⁷

It is uncertain whether there is a causal relationship between GER and AOP. Studies using multiple intraluminal impedance to detect non-acidic GER have failed to show a causal association of GER to apnea in preterm infants. Although the effects of GERD in premature infants are largely undefined and poorly understood, they usually occur with continuous regurgitation, vomiting, feeding intolerance and apnea. The diagnosis of GER is challenging in preterm infants because symptoms are non-specific and diagnostic testing is limited due to technical problems and difficulties in interpreting the results in the newborn. Thus, we defined GER presenting with apnea episodes in our cases based upon the history and physical examination without performing an extensive diagnostic evaluation.

The therapeutic management of GER is still debated. A non-pharmacological intervention such as body positioning, modification of feeding modalities or milk thickening, is currently considered a recommendable strategy to manage GER in preterm infants. Pharmacological therapy is reserved for infants who fail conservative management. Pharmacological therapy that has been used in preterm infants includes histamine H₂ receptor antagonists, proton pump inhibitors, antacid drugs and prokinetic agents.

The evidence currently available on the efficacy and safety of sodium alginate and domperidone in newborns is still limited. Alginate-based formulations are reported to be the most commonly prescribed antireflux medications in preterm infants symptomatic for GER. We used gaviscon and domperidone therapy for GERD presenting as apnea episodes. However, there are no similar comparative, randomized trials in preterm infants for GERD treatment. Pharmacological therapy for GERD has not been definitively shown to be effective in improving symptoms and hence, should be reserved, especially for infants with treatment of the refractory apnea episodes suspected to have GER.

AUTHOR DISCLOSURE

The authors do not have any conflict of interest to disclose. No financial assistance was received in support of the study.

ETHICAL CONDUCT OF RESEARCH

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Informed consent has been obtained from the parents of patients.

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双胞胎呼吸暂停发作对嘉胃斯康和多潘立酮的反应与胃食管反流病相关

背景：胃食管反流病和早产儿呼吸暂停之间可能的病理生理学机制已被广泛研究。多种生理保护性反射应答为胃食管反流和早产儿呼吸暂停提供了一个合理的生物学联系，但二者之间是否存在因果关系尚不确定。**患者的研究结果：**双胞胎因为喂养问题被送进新生儿重症监护病房，体格检查发现除了网状蓝紫色皮肤改变，其它正常。双胞胎 1 和双胞胎 2 分别在第一天和第二天发生了短暂的呼吸暂停。最初我们采用刺激和增加环境中氧气浓度来治疗，然后进行了甲基黄嘌呤和持续气道正压通气治疗。实验室和影像学分析均正常。因为胃食管反流被认为是难治性呼吸暂停的原因，开始用嘉胃斯康和多潘立酮治疗这两种情况，嘉胃斯康和多潘立酮治疗后没有再发生窒息。**结论：**胃食管反流病的药物治疗没有明确被证明能有效改善症状，因此，尤其在治疗难治性呼吸暂停疑似有胃食管反流的早产儿时应该谨慎。

关键词：呼吸暂停、胃食管反流病、早产、新生儿、治疗