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Is metoclopramide safe for the premature infant?

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Abstract. – BACKGROUND: Gastroesophageal reflux disease (GERD) may occur with poor weight gain, esophagitis, hematemesis and respiratory problems in an infant. Common treatment strategies include positioning, feeding thickeness, histamine$_2$ receptor antagonists, antiacids, and prokinetics. Metoclopramide is a prokinetic drug used to treat GERD and it has been reported to be a most commonly prescribed medication in neonatal intensive care unit (NICU). This research involves a patient that was born at 30 weeks' gestation age and on the twentieth day of his admission, vomiting and gastric residuals were observed. All diseases which are related these symptoms were excluded. With no improvement observed following non-pharmacological interventions and metoclopramide was started with a dosage of 0.1 mg/kg, per dose 12 hours. After the second dose of metoclopramide, dystonic reactions occured. The premature infant was evaluated for differential diagnosis of the abnormal movements. No abnormal findings were reported. The dystonic reactions didn't recur after metoclopramide was stopped.

CONCLUSIONS: The observed adverse effects of metoclopramide in the preterm infant might be due to an excessive serum concentration of the drug as a result of its prolonged plasma clearance in this age group. Attention is drawn to the serious adverse effects of metoclopramide in the neonate, particularly premature infant.

Key Words:
Gastro-eosophageal reflux, Metoclopramide, Premature infant, Dystonic reaction.

Introduction

Gastroesophageal reflux (GER), described as the retrograde movement of stomach contents into the esophagus, is the most common esophageal disorder in the neonatal period. Gastroesophageal 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[1]. While the infants who have physiological GER usually do not require treatment, the infants with respiratory symptoms and signs of GERD undoubtedly needs treatment.

Metoclopramide is a prokinetic drug used to treat GERD in neonates and infants[2-4]. Like all the other pharmacologic agents recommended for the treatment of GERD, the safety, efficacyand appropriate dosing for metoclopramide remains uncertain in these populations[5]. In spite of it's popularity and usage there are also growing concern about metoclopramide toxicity. The case presented in this report is a preterm neonate who exhibited extrapyramidal signs following metoclopramide therapy.

Case Report

The patient was born by caesarean section at 30 weeks' gestation age to a 26-year-old mother and was referred to Zekai Tahir Burak Maternity Teaching Hospital, neonatal intensive care unit (NICU) because of it 's prematurity and respiratory distress. He was treated for respiratory distress syndrome and enteral feeding with breast milk was initiated using an orogastric tube. But on the twentieth day of his admission, vomiting and gastric residuals were observed. The physical examination did not reveal any abnormalities. The differential diagnosis of his signs and symptoms, such as sepsis, metabolic diseases, necrotizing enterocolitis and structural abnormalities of brain were investigated using appropriate laboratory studies and none of them was documented. Risk factors for GERD, such as anatomic malformations and congenital foregut anomalies were also evaluated and ruled out. As GERD and delayed gastric emptying were thought to be the causes of vomiting, the patient was placed prone with an inclination of approximately 30-degrees, with his head higher than his feet. He was fed more frequently with smaller volumes. As no im-

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provement was observed following interventions, metoclopramide therapy was started with a dosage of 0.1 mg/kg, repeated twice daily. After the second dose of metoclopramide, dystonic reactions occurred (twisting, stiffening of his extremities with abnormal posturing) and with increased frequency in the following hours. Laboratory and radiological studies were performed for differential diagnosis of the abnormal movements. Cranial ultrasonography, blood glucose, serum electrolytes including calcium and magnesium, 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. Then after the withdrawal of metoclopramide, dystonic reactions dissappeared in 48 hours. The patient was discharged on the forty-fifth day of his admission without any reoccuring problems.

Discussion

GERD is usually associated with delayed gastric emptying and feeding intolerance commonly seen in premature infants[6]. Although the effects of GERD in premature infants are largely undefined and poorly understood, it typically occurs with continual regurgitation, vomiting, and feeding intolerants[4]. Current radiographic tools used for neonates, such as upper gastrointestinal radiography, ultrasonography, and radionucleotide studies are inadequate for diagnosing GER because of the episodic nature of the condition. Furthermore, information on the best strategies for diagnosis and treatment of GERD in premature infants are mainly extrapolated from studies of term infants and older children[6]. Common treatment strategies includes positioning, feeding thickeness, histamine$_2$ receptor antagonists, antiacids, and prokinetics. Although studies have been unable to show the short-term benefits of antireflux medications in preterm infants, H_2 receptor blocker therapy was shown to be used commonly for preterm infants and also metoclopramide was reported to be medication prescribed most commonly in NICUs[7]. Malcom et al[8] demostrated that use of antireflux medications at the time of discharge seems to be common for extremely low birth weight infants (24.8% were discharged with medications), especially those discharged at postmenstrual age of 42 weeks. Metoclopramide is a central and peripheral acting dopamine antagonist which has been used for treatment of a variety of gastrointestinal symptoms over the last thirty years. It also stimulates motility in the upper gastrointestinal tract and increases lower esophageal sphincter pressure. Craig et al[3] suggested that metoclopramide may have some benefit in comparison to placebo in the symptomatic treatment for GER, but that must be weighed against possible side effects. Parkman et al[8] drew attention reiterating that, the FDA issued a black box warning regarding long-term or high-dose usage of this medication because of the risk of developing tardive dyskinesia. The meta-analyses showed that risk of tardive dyskinesia from metoclopramide usage is likely to be < 1%, much less than the estimated 1-10% risk previously suggested in the US guidelines[9]. The study by Blumenthal and Costalos[9] included 15 infants and reported that metoclopramide does not promote gastric emptying in the newborn period. Meadow et al[11] demostrated that metoclopramide improved symptoms, and did not show harmful side effects such as extrapyramidal symptoms, hepatic disfunction. A similar study by Sankaran et al[4] found that metoclopramide administered to preterm infants led to a good response and withdrawal of the drug led to recurrence of all ssigns and symptoms. These three reports, are non-randomized, non-controlled, non-blinded natüren as well as, their very small sample size. Therefore, their conclusions have great limits. In contrast, two well-designed studies showed that metoclopramide does not improve symptoms in preterm infants with GERD[12,13]. Although no significant side effects of metoclopramide were identified in this study, the sample size precludes any conclusions regarding the safety of metoclopramide in preterm infants with gastric residuals. Thus, current literatures are insufficient either to support or to oppose the use of metoclopramide for GER disease in infants.

Furthermore, multiple adverse effects of metoclopramide usage in infants have been reported, including apnea, irritability, and acute extrapyramidal reaction like as dystonia or dyskinesia. Acute dystonias (including oculogyric crisis and opisthotonus), the most common adverse effect associated with metoclopramide usage, occur approximately in 25% of children[14,15]. Many reports have described these adverse effects in children[14,16,17]. The pharmacokinetics and pharmacodynamics of metoclopramide in the newborn period is not fully understood. Kearns

et al[18] studied pharmacokinetics of metoclopramide in neonates and found a prolonged plasma clearance in 30%. In this case report, dystonic reactions were observed in a preterm newborn after starting metoclopramide therapy. The drug used according to the recommendations in the literature. The observed adverse effects of metoclopramide in the preterm infant might be due to an excessive serum concentration of the drug as a result of its prolonged plasma clearance in this age group.

Conclusions

Clinician must be observed closely for its adverse affects, particullary in preterm infant. Also, large, prospective, controlled and blinded clinical trials are also required to determine the efficacy and safety of metoclopramide in the neonatal period.

Conflict of Interest

None to declare.

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