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An unreported complication of intravenously administered ibuprofen: gastrointestinal bleeding

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Abstract. – Ibuprofen is used for the closure of ductus arteriosus either intravenously or enterally. Although intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, transient renal failure, oliguria, hyponatremia and thrombocytopenia are reported complications during or after ibuprofen treatment, gastrointestinal bleeding, to our knowledge, has not been reported previously. We herein report a premature newborn, in whom ibuprofen was used intravenously for the closure of ductus arteriosus and gastrointestinal bleeding developed as a complication, and aim to discuss this rare adverse effect. In conclusion, we emphasize the importance of close follow-up of premature newborns during intravenous ibuprofen treatment considering also the other rare systemic side effects reported in the literature.

Key Words:

Ibuprofen, Gastrointestinal bleeding, Premature, Ductus arteriosus

Introduction

Patent ductus arteriosus (PDA), is a cardiac pathology frequently observed in premature newborns and has negative effects on morbidity and mortality. Of the pharmacological agents used in the closure of PDA, indomethacin and ibuprofen prevent the synthesis of PGE_2 inhibiting cyclooxygenase[1].

Ibuprofen is used for the closure of PDA either intravenously or enterally. Ibuprofen lysin and ibuprofen-tromethamine are present as intravenous drugs[2,3]. Side effects such as intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, transient renal failure, oliguria, hyponatremia and thrombocytopenia have been reported during or after enteral and/or intravenous ibuprofen treatment[4,5] although there are less acidotic side effects with ibuprofen-tromethamine. Cases of intestinal perforation due to intravenous and enteral ibuprofen treatments have also been reported[6]. However, gastrointestinal hemorrhage, to our knowledge, has not been reported as a complication during or after ibuprofen treatment previously.

In this article we report a premature newborn, in whom ibuprofen was used for the closure of ductus arteriosus and gastrointestinal bleeding developed as a complication, and aim to discuss the rare side effects developing due to intravenously administered ibuprofen.

Case Report

A male newborn infant who was born to a G_2P_2 25-year-old mother with a birth weight of 1350 g at the 31th week of gestation was transferred to the neonatal intensive care unit (ICU) with the diagnosis of prematurity and respiratory distress syndrome (RDS). The patient was intubated and surfactant treatment was administered because of the need for respiratory support and respiratory distress syndrome. The mother was being followed up with the diagnosis of preeclampsia, and the baby was delivered because of the progressing hypertension, proteinuria and thrombocytopenia. On the second day of life the patient's situation deteriorated, and the need for oxygen and ventilatory support increased, and an echocardiogram was performed which showed a PDA with a diameter of 3 mm. Intravenous ibuprofen protocol with respective doses of 10 mg/kg, 5 mg/kg and 5 mg/kg with 24-hour intervals was started. At that time the patient was receiving ampicillin, netilmicin, flu-

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conasole and calcium replacement. Prominent pallor, hypotonia and tachycardia developed 14 hours after the second dose of ibuprofen. In orogastric aspiration 7 ml of fresh blood was detected, and repeating episodes of hematocesia and melena-like rectal bleeding occurred on the same day. The laboratory investigation was as follows: hemoglobin 6.6 g/dL, white blood cell 7100/mm^3, platelet 199,000/mm^3, pH 7.30, PCO_2 44 mmHg, PO_2 68.5 mmHg, HCO_3^- 21.2 mmol/L. An upright abdominal X-ray showed no free fluid-air levels, and the diagnosis of intestinal perforation was excluded. The last dose of ibuprofen was not given, gastric lavage and decompression was performed, and the treatments of sucralfat and ranitidine were started. A packed red blood cell with a dose of 20 ml/kg was transfused. After the control of active bleeding, transcranial and abdominal ultrasonography was performed as further investigations to search for other possible bleeding foci. However, those revealed no pathology. The patient was extubated on the 4th day of life and left on free oxygen. A control echocardiogram showed the closed PDA on the 17th day of life. The patient was discharged on full enteral feeding with a weight of 1880 g on the 27th day of life.

Discussion

Ductus arteriosus is spontaneously closed in most of the healthy term newborns in the first 4 days of life. Closure of the ductus arteriosus, on the other hand, may be delayed for various reasons in preterm newborns[7]. It has been reported that intravenous ibuprofen is as efficacious as other treatment modalities in either prophylactic closure or curative treatment of PDA in preterm newborns, has significantly less renal side effects, and also decreases the appearance of intraventricular hemorrhage, which tends to occur much more frequently in these patients[8,9]. In various metaanalyses comparing the effectiveness of indomethacin and ibuprofen in the treatment of PDA, no difference has been reported between these two agents. There have been no increases in the frequency of side effects such as intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and volume overload after intravenous ibuprofen treatment when compared to indomethacin treatment, and intravenous ibuprofen is currently considered as a safe and effective agent in the pharmacologic treatment of PDA[2-5,8,10].

To our knowledge, gastrointestinal hemorrhage we observed after intravenous ibuprofen treatment in our patient has not been reported before. Tatli et al[11] have used only penrose drainage in two cases with spontaneous intestinal perforation developing due to enteral ibuprofen and without the findings of necrotizing enterocolitis. Our case also did not have the findings of necrotizing enterocolitis. Fujii et al[12] have reported intestinal perforation developing with the findings of necrotizing enterocolitis in 20% of the 30 preterm newborns with a gestational age of <27 weeks who were administered prophylactic indomethacin treatment in the first 48 hours of life. In our case we excluded the diagnosis of intestinal perforation as there were no air-fluid levels on upright abdominal X-ray, and bleeding was controlled with orogastric decompression, gastric lavage, and sucralfat and ranitidine treatments.

Conclusions

In our case we observed that intravenous ibuprofen we used for the treatment of PDA caused gastrointestinal hemorrhage. Gastrointestinal hemorrhage may develop due to intravenous ibuprofen used in the treatment of PDA, and newborns who are treated with this drug should be closely monitored with respect to this side effect.

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