Hyperprostaglandin E syndrome: use of indomethacin and steroid, and death due to necrotizing enterocolitis and sepsis

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SUMMARY: Çetinkaya M, Köksal N, Özkan H, Dönmez O, Sağlam H, Kırıştıoğlu İ. Hyperprostaglandin E syndrome: use of indomethacin and steroid, and death due to necrotizing enterocolitis and sepsis. Turk J Pediatr 2008; 50: 386-390.

Hyperprostaglandin E syndrome (HPS) is the antenatal variant of Bartter syndrome and characterized by polyhydramnios and preterm delivery in the antenatal period and salt-wasting, isosthenuric or hyposthenuric polyuria, hypercalciuria and nephrocalcinosis in the postnatal period. We report a one-month-old infant with HPS with a 15-year-old sister with Bartter syndrome. The infant's birth weight was 2750 g and she had severe dehydration on the 2nd day of life. She had hypercalcemia, hyponatremia, hypokalemia, metabolic alkalosis and elevated plasma renin and aldosterone levels. We instituted indomethacin therapy accompanied by steroid therapy for hypercalcemia. However, the patient developed abdominal distention on the 30th day, which was due to diffuse pneumatosis in sigmoid colon revealed by a subsequent surgical intervention. Following surgery, the patient developed fever, electrolyte abnormalities and subsequently sepsis. The patient died due to sepsis 10 days after surgery. We conclude that indomethacin and steroid therapy must be used cautiously in infants with HPS.

Key words: hyperprostaglandin E syndrome, antenatal Bartter syndrome, indomethacin, steroid, necrotizing enterocolitis, death.

Hyperprostaglandin E syndrome (HPS) is the antenatal variant of Bartter syndrome (BS); hence, it is also called "antenatal Bartter syndrome". HPS is an autosomal recessively inherited syndrome with an incidence of 1 in every 50,000-100,000 newborn infants[1]. Excessive saluresis and polyuria that occur in the fetal period lead to polyhydramnios and preterm delivery between 24 and 36 weeks of gestation[2]. HPS can be identified in utero by detection of elevated chloride levels with normal sodium, potassium and prostaglandin levels in amniotic fluid analysis[3]. After birth, infants with HPS have impaired tubular reabsorption in the thick ascending limb of Henle's loop, which leads to salt-wasting isosthenuric or hyposthenuric polyuria, rapid weight loss, hypercalciuria, osteopenia, nephrocalcinosis, and failure to thrive[3,4].

Characteristic laboratory findings, which include hypokalemic hypochloremic metabolic alkalosis, isosthenuria and high urinary sodium, chloride, calcium and normal potassium levels, occur in the first week of life. Urinary potassium excretion increases after 1-3 weeks while urinary sodium excretion is reduced compared to the measurements during the first week of life[3]. Urinary and blood prostaglandin levels, as well as serum renin and aldosterone levels, are increased[5]. Treatment of HPS patients with indomethacin, the prostaglandin synthesis inhibitor, improves both renal and systemic symptoms[6].

We report an infant with HPS who developed necrotizing enterocolitis and sepsis after indomethacin and steroid treatment and died 10 days after surgery due to sepsis. We are not aware of a similar report in the literature.

Case Report

A female infant was born by cesarean section to a 40-year-old mother at 35 weeks of gestation due to severe polyhydramnios. Her birth weight was 2250 g (10th percentile), length was 50 cm (50-90th percentile) and head circumference was 35 cm (50-90th percentile). She was referred to us on the second day of life because of petechia and thrombocytopenia (platelet: 80,000/mm3). Physical examination revealed an alert child weighing 2000 g with moderate dehydration (estimated at 10% body weight loss) and fever. In her blood biochemistry, serum urea, creatinine, sodium, potassium and calcium levels were 58 mg/dl, 1.2 mg/dl, 145 mEq/L, 4.1 mEq/L and 10.5 mg/dl, respectively. She was put on intravenous fluid for dehydration and antibiotic treatment for sepsis and was given 2 g intravenous immunoglobulin for thrombocytopenia. Despite intravenous fluids, on the 7th day, she was again noted to have polyuria (10 ml/kg per hour) and dehydration. Her renal and electrolyte profile revealed: serum urea 72 mg/dl, creatinine 1.2 mg/dl, sodium 125 mEq/L, potassium 2.5 mEq/L, chloride 88 mEq/L, and calcium 11.9 mg/dl. Her blood gas analysis showed metabolic alkalosis (pH 7.65) with bicarbonate levels of 28.5 mmol/L and PCO_2 of 26.4 mmHg. Her first renal ultrasonography was normal. Serum aldosterone and renin were elevated at 2.42 ng/ml/h and 43 ng/dl, respectively. Her urinary sodium was 14.6 mEq/24 h, chloride was 202.1 mEq/24 h, and potassium was7.1 mEq/24 h. Her urinary calcium excretion was high at 13 mg/kg/24 h. Her parathyroid hormone (PTH) level was 60.6 ng/L (range: 12-70 ng/L). These biochemical abnormalities were corrected with proper fluid and electrolyte management, but hypercalcemia persisted despite fluid and furosemide therapy. Indomethacin therapy was instituted to manage HPS on the 12th day of life at a dose of 1 mg/kg/day orally and increased progressively up to 3 mg/kg/day by the 20th day. Indomethacin was accompanied by steroid therapy with a dose of 1 mg/kg/day to reverse hypercalcemia. Table I shows the data about her serum calcium levels and therapies used in hypercalcemia management. Therapy resulted in a prompt reduction in urine output from 12 ml/kg per hour to 4 ml/kg per hour and the patient's calcium was found to be 9 mg/dl. Nephrocalcinosis was detected in the patient's second renal ultrasonography that was performed three weeks after the first. However, on the 30th day of hospitalization, she developed abdominal distention. Urgent surgical intervention was performed upon detection of abdominal free air on X-ray of the abdomen. In the course of surgery, diffuse pneumatosis and widespread necrotizing enterocolitis involving the entire colon were observed and a colostomy was performed. Necrotizing enterocolitis required cessation of indomethacin and steroid therapies. The patient was put on antibiotic therapy with meropenem, amikacin, clindamycin, and fluconazole. Despite these therapies, she developed septicemia within the first week of the surgery and died despite supportive therapy and resuscitation efforts. In her blood culture, Klebsiella pneumoniae was determined.

Pathology report revealed moderate chronic inflammation and necrotizing enterocolitis upon detection of lymphocytes, neutrophils, congestion, and edema in all sections of the surgical specimen.

Family history revealed similar characteristics for the third pregnancy, which was associated with polyhydramnios and concluded with delivery of a dead fetus. The mother's fourth

Table I. Serum Calcium Levels and Treatments During Hospitalization of the Patient

Day	Serum Calcium (mg/dl)	Treatment
1	10.5	Intravenous fluid
3	10.7	Intravenous fluid + furosemide (1 mg/kg/day)
7	11.9	Intravenous fluid + furosemide (1 mg/kg/day)
10	11.2	Intravenous fluid + furosemide (1 mg/kg/day)
12	11.9	Indomethacin (1 mg/kg/day)
15	11.5	Indomethacin (2 mg/kg/day)
20	11.8	Indomethacin (3 mg/kg/day) + steroid (1 mg/kg/day)
25	9	Indomethacin (3 mg/kg/day) + steroid (1 mg/kg/day)

pregnancy had also been complicated by severe polyhydramnios. A female infant with polyuria and failure to thrive was delivered who was later diagnosed with Bartter syndrome and given indomethacin therapy. Indomethacin was stopped after her findings returned to normal. She is now 15 years old and healthy.

Discussion

Hyperprostaglandin E syndrome is characterized by endogenous prostaglandin E_2 (PGE2) synthesis, which is thought to be responsible for the aggravation of clinical symptoms. Postnatal management of newborns with HPS includes prevention of fluid and electrolyte imbalances. Since treatment with the prostaglandin synthesis inhibitor indomethacin improves the systemic and renal symptoms, it has been suggested that formation of prostaglandins is responsible for deterioration in this disease[6].

As mentioned previously, HPS is a hereditary salt-losing tubulopathy characterized by highly elevated synthesis of PGE2. Expression of cyclooxygenase (COX)-2 in distal tubular epithelial cells at and adjacent to the macula densa was observed in the renal biopsies of children with HPS. It has been suggested that COX-2-dependent PGE2 formation is a crucial step in the pathogenesis of HPS[7]. Urinary and blood prostaglandin levels, serum renin and aldosterone levels are also increased[5]. We confirmed HPS diagnosis by finding significantly high renin and aldosterone levels in the patient's serum. However, failing to analyze eicosanoids including urine prostaglandin metabolites was our limitation in this case report.

Recently, mutations in the luminal Na-k-2Cl co-transporter (NKCC2) and in the luminal potassium channel (ROMK) have been identified in patients with HPS indicating the genetic heterogeneity of this disease[8]. Also, a mutation in a novel protein (barttin) responsible for CLC-Kb activation has been described in patients with Bartter syndrome with congenital sensorineural deafness, and this form is reported to cause a more severe antenatal type leading to chronic renal insufficiency[9]. Genetic diagnosis of fetal HPS and subsequent prenatal indomethacin therapy may have a beneficial effect on the prognosis of HPS. With the identification of the genetic basis of HPS, molecular analysis should be performed in all affected families[4].

Since the expression of COX-2 in macula densa of patients with HPS has been demonstrated and a major part of the clinical symptoms can be explained by hyper-PGE2 secretion, prostaglandin formation is suggested to have a potential role in the pathogenesis of HPS[10]. Indomethacin blocks prostaglandin formation by inhibiting cyclooxygenase enzyme. The enzyme has two isoforms known as COX-1 and COX-2. Indomethacin inhibits both isoforms as it is a non-selective COX inhibitor with a wide range of side effects. Inhibition of the COX-1-dependent formation of PGE2 in gastric mucosa can cause gastrointestinal damage[11]. Gastrointestinal side effects are frequently observed in patients with neonatal BS as a consequence of long-term treatment with indomethacin[12]. More recently, newer and more selective, specific COX-2 inhibitors have become available. COX-1 has been proposed to be the general cellular cyclooxygenase in all organs, whereas COX-2 is only expressed under specific conditions such as stress, infections, inflammation or specific cellular dysfunction. In contrast to most other tissues, the kidney expresses COX-2. Patients affected by HPS also show expression of COX-2 in the macula densa. Therefore, the use of selective COX-2 inhibitor seems logical[10]. Haas et al.[10] reported that a selective COX-2 inhibitor rofecoxib might control the clinical symptoms of severe HPS after ineffective indomethacin therapy. Reinalter et al.[7] also used rofecoxib in six HPS cases with no adverse effects. As a result, rofecoxib may be used in severe HPS cases when indomethacin treatment is unsuccessful. There have been few reports of indomethacin use in HPS due to the concern of adverse effects of indomethacin in this age group. The recommended dose of indomethacin is 1 mg/kg/day in two or three divided doses, which must be titrated carefully due to the increased risks of acute renal failure and necrotizing enterocolitis. Therefore, indomethacin use is recommended only after 4-6 weeks of age, but not in premature infants. Various studies reported necrotizing enterocolitis in babies who were given indomethacin for the treatment of patent ductus arteriosus[13]. In one study, 8% of 36 preterm neonates who were given indomethacin for patent ductus arteriosus developed major gastrointestinal complications such as necrotizing enterocolitis and bowel

perforation. However, all of these babies were smaller than 29 gestational weeks[14]. In another study, Fujii et al.[12] reported that indomethacin administration for patent ductus arteriosus increased the risk of necrotizing enterocolitis in extremely premature infants. All of these reports included premature infants. Also, in one study, Deschenes et al.[15] reported six antenatal BS cases, all of whom were preterm infants, and one of them died at one month of age due to necrotizing enteropathy. Kömhoff et al.[16] recently reported a preterm neonate with HPS who was treated with indomethacin successfully. They had started indomethacin therapy with a dose of 0.05 mg/kg/d and increased this dosage to 1.5 mg/kg/day. No adverse effects were observed with this therapy. Although our patient was not extremely premature, she developed necrotizing enterocolitis. The dose of indomethacin used in our case was similar to the recommended dose in the literature, but it was higher than the dose suggested by Kömhoff et al.[16]. We also had started steroid therapy for severe hypercalcemia.

Although our patient was not a very low birth weight (VLBW) premature infant, she seemed to have mild intrauterine-growth retardation (IUGR) because her birth weight was at 10th percentile. IUGR can adversely affect the maturation of the immune system. Chatrath et al.[17] reported that both T and B lymphocytes as well as total lymphocyte count and lymphocyte percentage decreased in small for gestational age (SGA) infants compared with appropriate for gestational age (AGA) infants. These authors also concluded that depressed immune status in SGA infants might be responsible for the increased predisposition of these infants to infections.

Hypercalciuria, osteopenia and nephrocalcinosis are the most evident features of HPS. The mechanism of hypercalciuria in HPS has not been clearly explained. It has been suggested that the primary tubular defect in HPS is associated with excessive PGE2 formation. This PGE2 affects tubular calcium handling and stimulates renal 1-α hydroxylase. These events result in increased renal calcium leak. Negative calcium balance due to urinary losses would result in elevated serum PTH and $1, 25\text{-}(OH)_2D$ levels[18]. However, Restrepo de Rovetto et al.[19] reported six children with BS, all of whom had hypercalciuria with normal serum PTH but

increased $1,25\text{-}(OH)_2D$ levels. McCredie et al.[20] reported four children with BS, three of whom had positive calcium balance, and they suggested that primary renal calcium leak was not found in their patients. It is suggested that indomethacin treatment decreases renal calcium wasting but does not normalize urinary calcium excretion in all of the patients[18]. In the literature, total serum calcium has also been reported to be high due to hemoconcentration in these patients[3]. As a result, the relationship between increased PGE2 formation and calcium homeostasis has not been completely elucidated. Hypercalcemia is a fairly common metabolic emergency but is very uncommon in the newborn period. However, its sequelae, particularly renal outcome, are serious, hence these infants must be treated urgently. The treatment of hypercalcemia includes adequate hydration, loop diuretics, corticosteroids, bisphosphonates, calcitonin and dialysis. High-dose glucocorticoids reduce the absorption of calcium in the gut and may decrease bone resorption. Our patient had resistant hypercalcemia, which did not respond to hydration and furosemide therapies. Therefore, we started methylprednisolone treatment at a dose of 1 mg/kg/day in addition to indomethacin therapy. Long-term use of glucocorticoids is not recommended because of their side effects[21]. They also have short-term side effects such as hyperglycemia, hypertension and gastrointestinal problems of bleeding and perforation. In a meta-analysis, it was found that gastrointestinal events and nosocomial infections were similar in the patients who received steroids and in the control group[22]. It was also concluded in the Cochrane Database that late corticosteroid therapy did not increase the risk of infection, necrotizing enterocolitis, or gastrointestinal bleeding[23]. Although postnatal steroid did not decrease necrotizing enterocolitis incidence effectively, it was suggested that it improved the clinical outcome[24]. In contrast, it was found in another study that postnatal low-dose dexamethasone for 10 days increased spontaneous gastrointestinal perforation[25]. In addition, dexamethasone therapy was found to increase the infection risk in VLBW infants compared with placebo[26].

Our patient used indomethacin and steroid therapy together for 10 days for BS and for hypercalcemia. Postoperatively, she developed sepsis and died. As a result, indomethacin

should be used cautiously with steroids even in term infants because of its side effects such as necrotizing enterocolitis. The deranged immune status of the infants with IUGR and prematurity must be considered as well. Newer alternative therapies such as rofecoxib must be considered in infants who are susceptible to gastrointestinal adverse effects and sepsis, in view of the increasing number of studies reporting their effectiveness and safety in patients with HPS.

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