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Exogenous prostaglandin administration and pseudo-Bartter syndrome

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Abstract. Biological abnormalities simulating Bartter syndrome were observed in a preterm neonate with complex cyanotic congenital heart disease, for which ductus arteriosus was maintained open by high doses of prostaglandin (PG) until a Blalock shunt could be performed. These abnormalities spontaneously disappeared after cessation of PG administration. We postulate that the natriuretic effect of exogenous administered PG could further increase sodium wasting already induced by the cardiopathy thus leading to pseudo-Bartter syndrome.

Key words: Pseudo-Bartter syndrome – Prostaglandins – Ductus arteriosus – Cyanotic congenital heart disease

Introduction

Bartter syndrome is characterized by hypokalaemic alkalosis, increased plasma renin activity and aldosterone concentration, juxtaglomerular cell hyperplasia, renal potassium wasting and normal blood pressure [1]. It is caused by an impaired ability of the ascending loop of Henlé to reabsorb sodium and/or chloride [2, 9, 11]. A potassium-losing tubulopathy has been also proposed [3]. These defects result in a stimulation of the renin-angiotensin system which in turn enhances the production of prostaglandins (PG) [2]. That PG play a role in the pathophysiology of Bartter syndrome is also shown by the therapeutic effect of PG synthesis inhibitors [6, 10].

We describe a preterm neonate with cyanotic cardiac disease in whom PG administration provoked a Bartter-like syndrome which spontaneously resolved after withdrawal of the drug.

Case report

The patient, the second male infant of a healthy family, was born after 30 weeks of gestation. Birth weight was 1.470 g and Apgar score was 3 at 1 min and 7 at 5 min. The baby was immediately intubated because of respiratory distress and ventilation was necessary during the first days of life. A FIO_2 was ca. 1 during the first 3 days of life. Antibiotic therapy consisted of penicillin (150.000 U every 12 h) and netilmicin (3.5 mg every 18 h) administered during the first 10 days of life. The infant received several doses of thamacetate during the first 2 weeks of life. On day 5, a cardiac murmur became audible. Echocardiography showed a complex congenital heart disease with a patent ductus arteriosus. Cardiac catheterization and angiocardiography were performed on day 21 and confirmed the suspected congenital malformation, which consisted of a right ventricular hypoplasia without ventricular septal defect. A shunt was visualized through a large sinusoid channel connecting the right ventricle to the left coronary artery. Fluid restriction was initiated although cardiac failure was not present. The infant was extubated on day 25. On day 27, he abruptly deteriorated and had to be further ventilated. The cardiac murmur disappeared. Echocardiography showed an almost completely closed ductus arteriosus. IV PG E1 (Prostin R, Upjohn, Belgium) was administered at an initial dose of 0.1 µg/kg per min. Dramatic improvement followed, confirming the necessity to maintain a patent ductus arteriosus. The infant was again extubated on the 40th day. On day 56, oral administration of PG E2 (Upjohn, Belgium) was attempted. High doses (100 µg/kg per h) were needed to maintain acceptable transcutaneous oxygen pressures (40–45 Torr). Oral therapy appeared less effective despite high doses and IV PG E1 was reintroduced 3 weeks thereafter (day 82). Blalock shunt was performed on day 124, the baby weighing 3000 g. He was discharged on day 149. Plasma creatinine and creatinine clearance remained in the normal range throughout hospitalization [7]. After 10 days of PG infusion, symptoms of hypokalaemic alkalosis occurred (Fig. 1). Up to this point, the baby had received an adapted milk formula for preterm infants (average potassium content: 23 mmol/l). Digestive potassium wasting (vomiting and/or diarrhoea) and never been observed and diuretics had not been administered. Average diuresis during PG administration was between 3 and 4 ml/kg per h in spite of fluid restriction. He was supplemented with NaCl and KCl (mean: 3 mmol/kg per day and 4 mmol/kg per day respectively). In spite of additional electrolytes, the plasma potassium levels remained low and the baby had a persistent metabolic alkalosis (pCO_2 remaining in the normal range). During PG therapy, the fractional excretion of potassium, chloride and sodium was abnormally high while the pH varied between 7.38 and 7.48 (Fig. 2). On days 48 and 132, the plasma renin levels were 10 and 2 ng/h per ml respectively while aldosterone levels were high: 610 and 300 ng/dl on days 51 and 62 respectively. Thirteen days after stopping PG therapy (day 133), the plasma aldosterone concentration had returned to

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Abbreviation: PG = prostaglandin

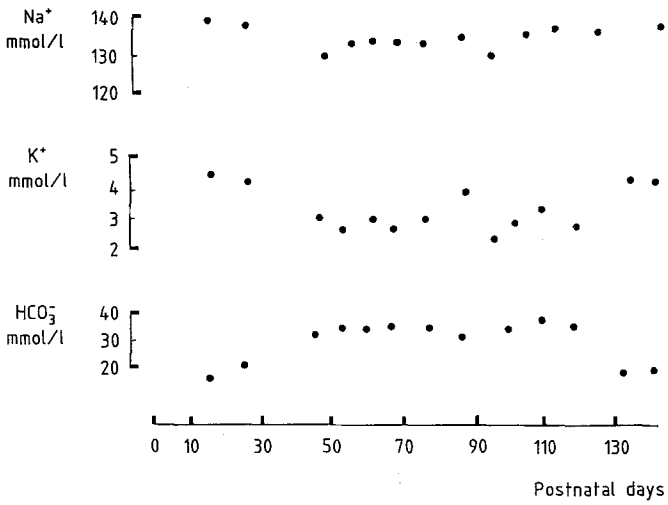

Fig. 1. Plasma levels of Na^+, K^+ and HCO_3^- before, during and after therapy with PG. Treatment began on day 27 and was stopped on day 120

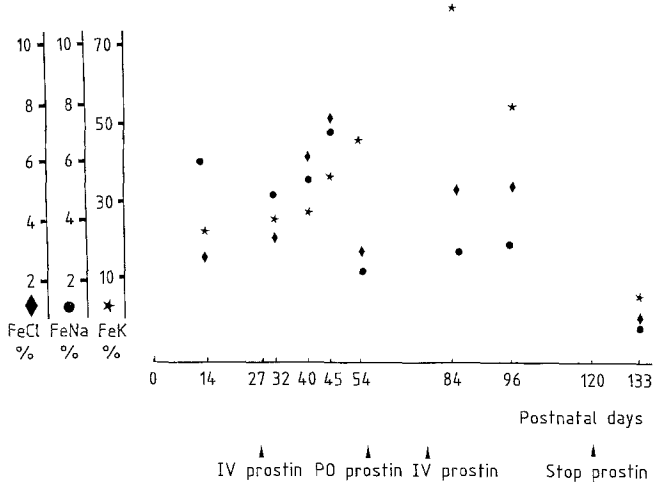

Fig. 2. Fractional excretion of Na^+, K^+ and Cl^- before, during and after PG therapy

50 ng/dl. Weight gain was poor during therapy (average 4 g/kg per day). All electrolytic abnormalities returned spontaneously to normal soon after cessation of PG treatment.

Discussion

The exact role of PG in the pathogenesis of Bartter syndrome remains unclear. Most authors agree that they play a role, although they may not be the causative agent [3]. PG are potent natriuretics and vasodilating agents, the latter effect explaining partly the normal blood pressure which is always seen in Bartter syndrome despite high renin and aldosterone production [6]. In our patient it is likely that pseudo-Bartter syndrome was initiated by the high dose of PG given to a preterm neonate with congenital heart disease. In such situations as well as in other stressed neonates, increased secretion of catecholamines has been reported [5, 12], and catecholamine-mediated prostaglandin synthesis could promote proximal tubular sodium loss, leading to increased distal sodium-potassium exchange [4]. The high doses of PG needed in the present case to keep the ductus arteriosus open, may have enhanced sodium wasting, thereby further increasing potassium and hydrogen secretion into the distal tubule, while the raised plasma aldosterone level also promoted urinary potassium excretion. In spite of the near normal plasma renin level, the biological abnormalities observed in our patient during PG administration are very similar to those observed in Bartter syndrome. Fractional excretion of sodium, potassium and chloride were normal for age before treatment and the observed biological abnormalities resolved spontaneously after PG were stopped. While several episodes of hypoxia were present during the early neonatal course, the transcutaneous oxygen pressure remained in an acceptable range during PG therapy and hypoxia could therefore probably not account for the tubulopathy. Similar observations of pseudo-Bartter syndrome have been reported after prolonged therapy with potassium-wasting diuretics [8]. However, our patient received no such diuretics.

Although, in this patient, the biological abnormalities are not exactly relevant to the same tubulopathy observed in Bartter syndrome, the role of PG is questionable. A prospective study may be of interest in assessing possible transient tubular dysfunction in such cases.

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