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Generalised oedema in an extremely low birthweight infant during treatment with dexamethasone for chronic lung disease

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A 585 g male infant was born at 22 weeks gestation. Immediately after birth, he was placed on a ventilator and became ventilator-dependent. He required sodium supplementation starting on day 22 for late hyponatraemia. His respiratory condition deteriorated at 3 weeks after birth. Chronic lung disease was diagnosed based on the infant being oxygen-dependent beyond 28 days of life and chest x-ray findings. A 12 day course of dexamethasone was initiated on day 39 of life. Within one day after initiation of dexamethasone treatment, his respiratory state improved. The next day, however, generalised oedema developed and gradually worsened, and his weight increased by 126 g over the next 8 days. Laboratory studies revealed progression of hypernatraemia. After the dexamethasone treatment was completed and fluid and sodium intake was restricted, the oedema gradually improved. Generalised oedema may have been caused by the mineralocorticoid property of steroids, which has been noted after administration of high doses of dexamethasone, and fluid and sodium intake may have contributed to its progression. This complication of treatment with steroids has not been previously described in preterm infants.

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Introduction

Dexamethasone, a corticosteroid with predominantly glucocorticoid activity, has been reported to improve the lung function and pulmonary outcome of very low birthweight infants with chronic lung disease (CLD)[1]. However, potentially serious short-term and long-term adverse effects of dexamethasone limit its usefulness. Short-term adverse effects include hyperglycaemia, hypertension, hypertrophic cardiomyopathy, gastrointestinal bleeding and gastrointestinal perforation[2]. Long-term problems include growth failure and significant adverse neurological effects including cerebral palsy and developmental delay[2-5]. In this paper, we report generalised oedema and hypernatraemia as rare adverse effects of dexamethasone therapy in a low birthweight infant with CLD.

Case report

A male infant was born at a gestational age of 22 weeks and 6 days with a birth weight of 585 g, due to premature rupture of the membranes and premature labour. The Apgar

scores at 1 and 5 minutes were 1 and 2, respectively, and the infant was intubated immediately after birth and placed on a ventilator. He was treated with exogenous surfactant immediately after the initiation of mechanical ventilation for respiratory distress syndrome. Although his respiratory state improved after treatment with exogenous surfactant, it remained unstable and he continued to be ventilator- and oxygen-dependent. Chest X-rays showed a bilateral diffuse hazy shadow and emphysema from day 7 of life.

As he gradually became tolerant of enteral feedings and his intravenous infusion was weaned his nutritional status improved. On day 15, his serum sodium level started to gradually decrease and it was 120 mmol/l on day 22. Sodium chloride supplementation was started by enteral administration at a dose of 3 mmol/kg/day on day 22, and the amount of sodium administered was gradually increased to 10 mmol/kg/day on day 26 (Figure 1).

His respiratory status was worsening day by day and he required increased inspired oxygen concentration beyond 28 days of life, confirming the diagnosis of CLD. On day 39, he required mechanical ventilation with a mean airway pressure of 11 cm H_2O as well as inspired oxygen concentration of 40-50% to maintain an arterial oxygen saturation of greater than 90%. A 12 day course of intravenous dexamethasone therapy (500 microg/kg for 3 days followed by 300 microg/kg for 3 days, 200 microg/kg for

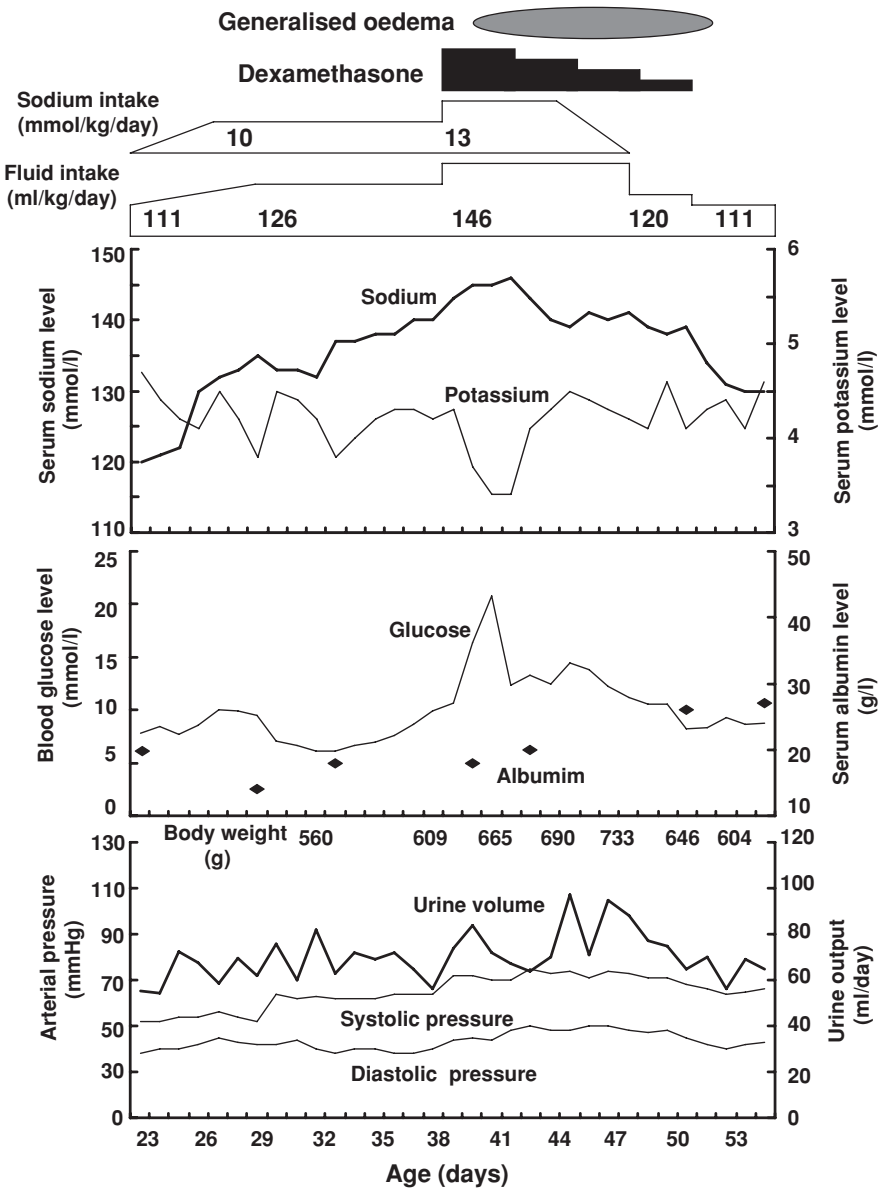

Figure 1 Changes in the fluid and sodium intake, laboratory findings, and circulatory conditions before and after initiation of dexamethasone therapy for chronic lung disease in a very premature infant. The fluid intake includes the fluids in the supplemented sodium chloride, enteral feedings, and intravenous saline infusion. The sodium intake includes the sodium in the supplemented sodium chloride and intravenous saline infusion.

3 days, and 100 microg/kg for 3 days) was initiated on day 39. At the time of initiation of dexamethasone therapy, intravenous sodium chloride 0.9% solution was started at an infusion rate of 0.5 ml/h (equivalent to 3 mmol/kg/day) as the peripheral route for drug administration.

Within 24 h of starting the dexamethasone, his respiratory state improved. However, on the second day of dexamethasone therapy, the patient developed generalised oedema. The oedema worsened and was followed by an unstable respiratory state. There was no evidence of cardiac failure on chest X-ray or echocardiography, and no other cause of oedema could be identified. The patient also developed hypertension (systolic pressure > 70 mmHg) on the second day of dexamethasone therapy.

The laboratory findings in the blood sample obtained three days after initiation of dexamethasone therapy were as follows: white blood cell count, 20.4 × 10^9/l; haemoglobin, 9.4 g/dl; haematocrit, 30.2%; platelets, 31.9 × 10^9/l; urea, 1.4 mmol/l; creatinine, 37 μmol/l; total protein, 40 g/l; albumin, 18 g/l; sodium, 145 mmol/l; potassium, 3.4 mmol/l; chloride, 119 mmol/l; total calcium, 2.2 mmol/l; and C-reactive protein (CRP), 0.1 mg/dl. The serum sodium level was elevated, and the serum potassium and albumin levels were reduced compared with the normal ranges. The plasma glucose level reached 20.8 mmol/l on day 41, and insulin was administered for one day. We decided not to utilise a urine collecting bag since the infant had previously had recurrent dermatitis; therefore, urinary electrolytes were not measured.

The scheduled tapering of dexamethasone improved the hyperglycaemia, but the generalised oedema and elevated serum sodium level persisted. His weight increased by 126 g (from 607 g to 733 g) over 8 days. The enteral feedings were reduced on day 47 of life, and sodium supplementation was tapered on day 44 of life and discontinued on day 51 of life. The serum sodium level gradually returned to the normal range and the oedema and hypertension improved.

Dexamethasone was discontinued after completion of the 12 day treatment on day 51, and the oedema disappeared on day 53 of life. After dexamethasone was discontinued, the serum sodium level initially decreased to 128 mmol/l but it returned to the normal range in the following ten days without sodium supplementation. Thereafter, the patient had a good clinical course and was discharged from the hospital at 191 days of age.

Discussion

Fluid and electrolyte imbalance associated with corticosteroid administration is rare in premature neonates. Since dexamethasone is thought to have insignificant mineralocorticoid activity, the question arises as to how treatment with dexamethasone caused hypertension, hypernatraemia and oedema formation in this case. The dose of dexamethasone or other factors may have been related to the pathophysiology. As the glucocorticoid potency of dexamethasone is 25 – 30 times stronger than that of hydrocortisone, the dose of dexamethasone administered in the present case is similar to the initial dose in replacement therapy in patients with primary adrenal insufficiency.

Our patient was born at 22 weeks gestation, and was 27 weeks postconceptional age and weighed 607 g at the time of initiation of dexamethasone therapy. Our institution has adopted the protocol of a 12 day course of dexamethasone therapy for the treatment of CLD in premature infants based on the protocol reported by Avery et al.[6]. In our very premature infant, however, the initial dose of dexamethasone therapy (500 microg/kg/day) may have been high. The significant hyperglycaemia observed in our patient may have been related to excessive glucocorticoid activity.

Neonatal mononuclear cells are reported to be much more sensitive to dexamethasone than adult cells[7]. As infants who develop CLD often have reduced production of endogenous steroid hormones, it is speculated that these infants are more sensitive to dexamethasone. Several authors have described glucocorticoid-dependent enhancement of Na–K-ATPase activity in the distal segment of kidney tubules[8]. It is possible that a high concentration of dexamethasone induces a mineralocorticoid-like response that is not mediated by the mineralocorticoid receptor pathway[8]. Dexamethasone, which is a synthetic glucocorticoid receptor agonist, also binds to the mineralocorticoid receptor, albeit with lower affinity[9]. It is also possible that when administered at high doses, dexamethasone directly binds to mineralocorticoid receptors and shows mineralocorticoid activity.

As for the aetiology of oedema, excess glucocorticoid replacement may theoretically induce oedema formation by directly affecting vascular tone, altering capillary permeability, and/or influencing other factors such as the level of atrial natriuretic peptide. For example, oedema is a common clinical feature of Cushing's syndrome[10]. As for other factors, excessive fluid and sodium intake may have contributed to oedema

formation. During the first few weeks of life, premature infants often suffer from late hyponatraemia as a result of renal salt wasting due to deficient proximal and distal tubular reabsorption of sodium[11].

Our patient had late hyponatraemia and required sodium supplementation. The dose of sodium administered enterally was gradually increased to 10 mmol/kg/day, in addition to enteral feeding. When intravenous sodium chloride 0.9% solution was started at the time of initiation of dexamethasone therapy, fluid intake increased by 20 ml/kg/day and sodium intake increased by 3 mmol/kg/day. The very small infusion volume may have greatly increased the fluid and sodium load in this extremely small neonate.

Excessive sodium intake increases the extracellular fluid volume and results in oedema formation because the neonatal kidneys have limited capacity of sodium regulation[12]. However, it is thought that excessive fluid and sodium intake was not the sole cause of the oedema because the urine volume did not significantly increase as fluid intake increased. On the other hand, after dexamethasone therapy was initiated, the serum potassium level decreased as the serum sodium level increased. After dexamethasone was discontinued, the serum potassium level increased as the serum sodium level decreased. These electrolyte changes may have been due to the mineralocorticoid properties of the corticosteroid. Unfortunately, we were unable to monitor urinary electrolytes. Therefore, it is speculated that administration of high-dose dexamethasone, which has a mineralocorticoid-like property, in addition to excessive fluid and sodium intake caused water and sodium retention and hypertension, and that excessive glucocorticoid activity caused generalised oedema. Moreover, in this patient, it is speculated that latently decreased colloid osmotic pressure due to persistent hypoalbuminaemia may have caused the development of capillary leak and contributed to oedema formation when the intravascular fluid volume increased due to the presence of dexamethasone and excessive fluid and sodium.

The European Association of Perinatal Medicine issued a warning about postnatal corticosteroid therapy, and the American Academy of Pediatrics and the Canadian Pediatric Society do not recommend routine use of dexamethasone for prevention or treatment of CLD, because recent reports raised concerns that postnatal steroids may cause significant neurodevelopmental impairment in preterm infants[13,14]. However, extremely premature infants born at 22 or 23 weeks gestation often require steroid administration because the majority develop severe CLD that requires high concentrations of oxygen and high ventilator settings. Recent studies have suggested that some preterm infants may require early physiological replacement of cortisol to prevent the development of CLD, because their adrenal response may be immature and, in the face of stress, they may be in a state of adrenal insufficiency[15]. The pharmacological dose of dexamethasone used for CLD in preterm infants may be higher than physiologically necessary, although the physiological level of cortisol in these infants has not been well-defined. If dexamethasone is to be administered to very premature infants, lower dosages that may have fewer adverse side effects should be considered. It is important to monitor fluid, weight and electrolyte balance in preterm neonates during dexamethasone therapy even after the acute period of the first four weeks of life.

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