Treatment of non-oliguric hyperkalaemia with inhaled salbutamol in premature infants with severe respiratory distress syndrome

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ABSTRACT

Non-oliguric hyperkalaemia (NOHK) in neonates is defined as a plasma potassium level > 6.5 mmol/L in the presence of urine output ≥ 1 mL/kg/h during the first 72 hours of life. It is characterized by a rapid rise of serum potassium to excessively high values, a high risk of cardiac arrhythmias and no occurrence after 72 hours of birth. NOHK commonly occurs in premature neonates, especially in those with a gestational age <28 weeks, with only a few reports of this entity in moderate or late preterm neonates. The effectiveness and safety of different treatments for NOHK is uncertain and currently there is no firm treatment recommendation. We describe the case of a moderately premature neonate (32+2 weeks gestation), with severe neonatal respiratory distress syndrome, who developed NOHK that was treated with inhaled salbutamol. When salbutamol is used for the treatment of NOHK, an initial paradoxical rise in potassium levels should always be taken into account to avoid cardiac arrhythmias. Key words: non-oliguric hyperkalaemia, premature, infants, salbutamol, hyperkalaemia

INTRODUCTION

Non-oliguric hyperkalaemia (NOHK) is a common and serious complication in premature neonates, especially in those with very low birth weight (<1500g) and/or very preterm (≤28 weeks gestational age). (1,2) The reported incidence of NOHK is 11% to 52%. (3-5) With increased survival of premature neonates, NOHK is becoming more common. (5) Reversible hyperkalaemia in premature neonates was first reported in 1959 by Usher. (6) Characteristics of NOHK as we know it today were described by Perkkio and Räihä (7) in 1977. NOHK is defined as a serum potassium ≥ 6.5 mmol/L during the first 72 hours of life in a non-haemolysed arterial or venous blood sample in the presence of urine output ≥ 1 mL/kg/h. (2) It is characterized by a rapid rise in serum potassium to excessively high values after birth in premature neonates, a high risk of cardiac arrhythmias and no occurrence after 72 hours of birth. The pathophysiology of NOHK is not completely understood. Current evidence suggests that it is mainly due to a shift in potassium from the intra- to the extracellular spaces because of immaturity of the Na+/K+ ATPase in premature neonates. (5,8-10) More than 80% of neonates with NOHK are extremely low birth weight (ELBW) infants with gestational age below 28 weeks. (4) Few cases have been reported in moderate to late preterm neonates. (1,4) The effectiveness and safety of different treatment options for NOHK is uncertain and currently there is no firm treatment recommendation. (2) We describe a case of a moderately premature neonate (32+2 weeks gestation) with severe neonatal respiratory distress syndrome, who developed NOHK that was treated with inhaled salbutamol.

CASE REPORT

A premature girl was admitted to the interdisciplinary neonatal and paediatric intensive care unit (ICU) of the Department of Paediatric Surgery and Intensive Care, University Medical Centre Ljubljana, Slovenia because of respiratory distress. Due to incipient premature labour, the mother received a course of antenatal steroids (betamethasone) 16 days before delivery. The girl was delivered at 32 weeks and 2 days gestational age at the regional maternity hospital by caesarean section after minor antepartum haemorrhage because of placenta praevia and persistent foetal tachycardia. The girl weighed 1900 g and appeared vigorous, with spontaneous respirations; the 1-minute and 5-minute Apgar scores were 8 and 9, respectively. Haemoglobin level at birth was 126 g/L, which was an indicator that she suffered some blood loss because of placenta praevia. Shortly after birth she developed tachypnoea with shallow respirations and retractions. Features of severe hyaline membrane disease were found on chest X-ray. Endotracheal intubation was performed and assisted...
Despite rather low pH values (Table 1, normal range for the first 36 hours of life, rum concentrations (K+) were in the lower birth (Table 1). Potassium seft checked a developmental status at postnatal age of 6 months. Her neuromaternal hyperglycaemia she received an insulin infusion for 7 h during saemia. Due to early hyperglycaemia she was receiving only po the insulin infusion, glucose levels were be- after the dose was repeated every 4 hours for another 12 hours. The potassium level slightly increased after the first inhalation of salbutamol (figure 1), but declined rapidly thereafter and reached 6.0 mmol/L within 6 hours following the first inhalation. Changes in heart rate and blood pressure after salbutamol inhalation are shown in table 2.

**DISCUSSION**

Even though NOHK is most common in ELBW infants with a gestational age < 28 weeks (4) and there are only a few reports of this entity in late preterm infants, (1,4) our report emphasizes that NOHK can oc-
cur in more mature preterm infants. The characteristic feature of NOHK is a rapid rise in serum K+ to high values during the first 72 h of life. (5) In our infant, as seen in Figure 1, K+ increased steeply between 42 and 52 hours of age. Low to normal K+ levels during the first 36 h of life in our report underscores the importance of regular electrolyte checks in preterm infants during the first days of life.

Antenatal steroid therapy may reduce hyperkalaemia. (8,11) In our report NOHK developed despite antenatal steroids. However, the peak K+ level might have been higher in the absence of antenatal steroids. (8) Current evidence suggests NOHK is associated with increased K+ intake and decreased K+ excretion, but these are not causes of NOHK (2) and were ruled out in the case described. Our patient was infused potassium-free solutions. The theoretical possibility of increased potassium load by red cell transfusion is very unlikely as transfusion was administered at 12 h of life and transfusion as a cause of NOHK has been ruled out by several authors. (10,13-15) NOHK is not associated with decreased diuresis, reflecting diminished glomerular filtration and polyuria, as was seen in our case. (3,13,16) NOHK has been shown to be unrelated to leakage of K+ from cell disruption associated with bruising, intracranial haemorrhage, or haemolysis. (5,13,17) NOHK is associated with a high risk of cardiac arrhythmias, (5,8) especially with K+ levels higher than 7 mmol/L. (5,6) Tall peaked T waves developed in our patient when the K+ level reached 7.8 mmol/L; the ECG quickly normalized after calcium administration. As mortality related to NOHK is reported to be 12% and in the report by Szychlowy et al. only one in seven infants with cardiac arrhythmias secondary to NOHK survived, (18) NOHK represents an emergency situation requiring prompt therapy. The high incidence of cardiac arrhythmias is probably related to the common occurrence of hyperkalaemia in preterm infants, with lowest values of Ca++ occurring at a time when NOHK sets in. (14,19)

Several treatment approaches are used in NOHK, all adapted from the treatment of hyperkalaemia due to renal failure in infants. However, hyperkalaemia in NOHK has a different pathogenesis. In view of the limited information from small studies, the effectiveness and safety of different treatment options for NOHK is uncertain and currently no treatment guidelines can be recommended. (2) Administration of intravenous calcium is supported when ECG changes occur to counteract the arrhythmogenicity of hyperkalaemia. (5,14,19) The effect of salbutamol on transmembrane K+ flux has been studied in neonatal red blood cells under hyperkalaemic conditions and resulted in a 50% increase in net transmembrane K+ flux. No such increase occurred in adult red blood cells. (20) Salbutamol inhalation or infusion is effective in lowering serum potassium concentrations in adults and children beyond the neonatal period. (5) Salbutamol treatment has only anecdotally been reported for the treatment of hyperkalaemia in neonates, usually as an infusion. (21) Singh et al. reported on the efficacy and safety of inhaled albuterol for the treatment of NOHK in premature neonates. (22) Our report is one of only a few that describes salbutamol inhalation for the treatment of NOHK and underscores the effectiveness of this treatment approach.

In our case, salbutamol was given by nebulization every 2 hours until the K+ level fell below 5 mmol/L, thereafter the dose was repeated every 4 hours for another 12 hours. The K+ decreased from a peak level to 6 mmol/L over the course of 6 h. There are some safety concerns about salbutamol use in hyperkalaemia. (5) Firstly, salbutamol increases heart rate and blood pressure by stimulating β1 adrenoceptors. In our case (table 2), the mean arterial pressure and heart rate increased significantly after salbutamol inhalation, but this adrenergic stimulation was not excessive and

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<th>Blood pressure (mmHg)</th>
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Median 50 55 137 146 135 142 134 139 146 146

IQR 4 7 11 13

p-value 0.0653 0.0028
clinically relevant. Secondly, a slight initial rise in K+ (≈0.1 mmol/L) has been reported between 1 and 3 minutes after salbutamol administration, before the hypokalaemic effect takes place. (23) We noticed the same slight transient increase in K+ (0.1 mmol/L) after the first dose of salbutamol followed by a significant decrease in K+. The early paradoxical increase in K+ may be the result of K+ release from skeletal muscle after β2 adrenoceptor stimulation. Whether this increase in K+ in already hypokalaemic infants may provoke cardiac arrhythmias, especially as salbutamol also facilitates cardiac excitability through β1 adrenoceptor stimulation, is unknown. To conclude, this report underscores the need to recognize the possibility of NOHK in moderately and late preterm infants as well as in very preterm infants. Even in the face of low or normal K+ during the first 24 h of life, K+ should be checked every six hours during the first days of life as K+ can quickly rise and lead to rhythm disturbances. As seen in our case, salbutamol inhalation can effectively and rapidly lower K+ in NOHK, but the paradoxical increase in K+ during the first minutes following administration needs to be taken into account. It seems reasonable to administer calcium first to stabilize the myocardium and then commence salbutamol inhalation. With no absolute treatment recommendation, and in view of the limited information from small studies, the effectiveness of potentially beneficial interventions should be tested in further studies.

REFERENCES