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Hyponatremia is common in preterm infants. The causes are usually related to the inability of the premature kidneys to excrete a given water load, excessive sodium losses, or inadequate sodium intake. Here, we present a case of severe hyponatremia in an extreme preterm infant, associated with the use of aminophylline. Aminophylline was administered intravenously on day 1 for the treatment of apnea of prematurity. On day 3, the patient developed hyponatremia which was not responsive to sodium replacement and fluid restriction. Due to concerns of aminophylline-induced hyponatremia, aminophylline was discontinued on day 6, and within 48 h of discontinuation, serum sodium normalized without the need for sodium supplementation. The purpose of the case report is to present a rare complication associated with aminophylline use and to shed light on potential deleterious effects associated with drug shortages.

**Keywords:** Aminophylline, apnea of prematurity, caffeine, drug shortages, hyponatremia

**Case Report**

We present a 26 week gestational age male, born to a 32-year-old G2P1 mother with birthweight of 1085 g, who was transferred to our Neonatal Intensive Care Unit from an outside hospital for the management of respiratory distress syndrome secondary to prematurity. Apgar scores were 7 and 8 at 1 and 5 minutes. The patient was intubated for 12 h and subsequently extubated to noninvasive ventilation with FiO2 of 0.21. Due to a caffeine shortage, aminophylline 8 mg/kg IV followed by 2.5 mg/kg IV every 12 h was initiated on day 1 to treat AOP. He was reintubated on day 8 due to worsening respiratory distress.

Daily basic metabolic panels were obtained for the first 9 days of life. On day 3, serum sodium decreased from 137 mEq/L to 132 mEq/L. Fluid rate was not advanced any further at this point due to mechanical ventilation due to apnea and decreases extubation failure. For a brief period of time, our institution utilized intravenous (IV) aminophylline for facilitation of extubation after our institution exhausted our supply of IV caffeine due to a nationwide IV caffeine citrate shortage in 2015. We present a case of severe hyponatremia in a very low birth weight (VLBW) infant associated with the use of aminophylline. The purpose of the case report is to present a rare complication from aminophylline use and to shed light on potential deleterious effect associated with drug shortage.
to the concern of dilutional hyponatremia. On day 4, serum sodium further decreased to 129 mEq/L. Fluids at this time were advanced to 120 mL/kg/day as the baby’s weight was down 15% from birthweight, and sodium supplementation in the total parenteral nutrition (TPN) was increased to 6 mEq/kg/day. On day 5, serum sodium further decreased to 124 mEq/L, and sodium supplementation in the TPN was further increased. The use of enteral sodium supplementation was limited by the small volume of feeds. Despite increasing sodium content in the TPN to 10 mEq/kg/day (approximately 0.45% NaCl), serum sodium decreased to 122 mEq/L on day 6. Due to concerns of aminophylline-induced hyponatremia, aminophylline was discontinued and within 48 h, serum sodium corrected to 130 mEq/L and sodium supplementation was reduced [Table 1].

The patient did not receive any diuretics or other medications that could either cause or exacerbate hyponatremia. At the lowest sodium level (serum sodium 122 mEq/L), serum glucose was 90 mg/dL (5 mmol/L), ruling out pseudohyponatremia as a cause for the observed hyponatremia. Neither nephrology nor endocrinology were consulted for the hyponatremia since the serum sodium improved after stopping the aminophylline.

**DISCUSSION**

Hyponatremia defined as serum sodium of <130 mmol/L occurs in around 30% of VLBW infants in the 1st week of life and between 25% and 65% after the 1st week of life.[6] The general mechanisms for hyponatremia include the inability to excrete a given water load leading to volume overload and dilution of serum sodium levels, excessive gastrointestinal or renal sodium losses, and inadequate sodium intake. Other less common etiologies include acute renal injury, inherited tubulopathies such as Bartter’s syndrome, congenital adrenal hyperplasia, pseudohypoaldosteronism, and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[6] This is our center’s first experience with significant hyponatremia in a premature neonate receiving aminophylline. Our protocol for aminophylline during the IV caffeine citrate shortage was to provide a loading dose of 8 mg/kg, followed by a maintenance dose of 2.5 mg/kg IV every 12 h based on previously published pharmacokinetic data.[7] On day 5, theophylline level was obtained approximately 2 h postdose and resulted at 9.2 mcg/mL, within therapeutic range of 6–12 mcg/mL. In this patient, our unit’s procedure for fluid requirements was followed, starting at 80 mL/kg/day, and titrated as appropriate based on daily electrolytes, urine output, and weight.

Hyponatremia associated with aminophylline has been described earlier. In a study published at the University of Zambia, premature neonates were given an IV loading dose of 5 mg/kg, followed by 2.5 mg/kg IV every 12 h.[8] Baseline (soon after birth) and 12 h basic metabolic panels were obtained, in which they noticed an average drop in serum sodium from 134.5 mEq/L to 128.7 mEq/L.[8] One caveat of the study is that it did not describe fluid management in the 1st day of life, which may be a contributor for the drop in serum sodium during those 12 h. Srinivasan et al. reported hyponatremia in a neonate who received theophylline, chlorothiazide, and spironolactone.[9] While it is difficult to determine exactly what impact aminophylline had on serum sodium in their case, it was likely multifactorial due to numerous natriuretic-inducing medications being administered. The mechanism behind aminophylline-induced hyponatremia is thought to be related to A1 adenosine antagonism, which has been demonstrated to promote diuresis and natriuresis.[10] In both, our case and the case reported by Srinivasan et al., serum osmolarity was calculated below normal range at 256 mmol/L and 204 mmol/L, respectively, indicating an SIADH-like picture.

Our case displays a relatively common challenge facing health care drug shortages. Drug shortages and supply

### Table 1: Age in days, fluids, serum electrolytes, and aminophylline dosing

<table>
<thead>
<tr>
<th>Day of life</th>
<th>Weight (g)</th>
<th>Fluids (mL/kg)</th>
<th>Serum sodium (mEq/L)</th>
<th>Sodium replacement (mEq/kg)</th>
<th>Aminophylline dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1085</td>
<td>80</td>
<td>139</td>
<td>0</td>
<td>8 mg/kg IV×1 followed by 2.5 mg IV q 12 h</td>
</tr>
<tr>
<td>1</td>
<td>1035</td>
<td>100</td>
<td>139</td>
<td>2</td>
<td>2.5 mg/kg IV q 12 h</td>
</tr>
<tr>
<td>2</td>
<td>1010</td>
<td>110</td>
<td>137</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>950</td>
<td>110</td>
<td>132</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>925</td>
<td>120</td>
<td>129</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>950</td>
<td>120</td>
<td>124</td>
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<td>6</td>
<td>970</td>
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<td>7</td>
<td>995</td>
<td>140</td>
<td>125</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1055</td>
<td>120</td>
<td>130</td>
<td>Discontinued</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1130</td>
<td>140</td>
<td>135</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

IV – Intravenous
disruptions affect how a pharmacy dispenses a drug that influences patient care by forcing prescribers to use an alternative agent. It has caused serious complications to patients such as prolonging disease course and increasing adverse events including death.[11-13] In this case, the use of the alternative to caffeine, aminophylline, resulted in hyponatremia. Preliminary studies have alluded to an association between hyponatremia and adverse long-term neurological outcomes.[6,14] Some neurotoxic effects such as tremors and seizures could be related to the inhibition of pyridoxal kinase in the brain by theophylline. Such mechanism has particular implication in preterm infants because pyridoxine which is usually supplemented in parenteral nutrition cannot be utilized.[15,16] Conversely, the methylation of caffeine is thought to be neuroprotective.[15,16] Aminophylline continues to be used in preterm infants in developing countries due to either lack of availability or cost of caffeine.[17-19]

**CONCLUSION**

We reported a preterm neonate with severe hyponatremia receiving IV aminophylline therapy. Given that aminophylline is hydrolyzed to its active form (theophylline) in the bloodstream, it is reasonable to suspect aminophylline as the cause for hyponatremia in this neonate. In a clinical setting, where caffeine is not available, careful electrolyte monitoring is warranted for premature neonates receiving aminophylline. There has to be a permanent solution to the ever recurring drug shortages which seem to plague the healthcare system and jeopardize patient safety.[20]

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**