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Case Report

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Plasma Exchange as a Treatment for Hyperbilirubinemia in 2 Foals with Neonatal Isoerythrolysis

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Bilirubin can cross the blood-brain barrier, especially when plasma concentrations are high and in neonates. Bilirubin is toxic and can lead to irreversible brain damage, signs of neurologic disease, and coma, which is called "kernicterus."

The most important cause of clinical icterus in equine neonates is neonatal isoerythrolysis (NI), an alloimmune disease characterized by immune-mediated hemolytic anemia and, consequently hyperbilirubinemia and hypoxia. Prognosis generally is guarded to good, but when NI leads to kernicterus, chances for survival are low.[1] Treatment of NI consists of supportive care and blood transfusions, but none of these lower plasma bilirubin concentration. In human medicine, therapeutic plasma exchange has been successfully used in cases of hyperbilirubinemia.[2–4]

This case report describes 2 foals that were examined because of severe anemia and hyperbilirubinemia because of NI. Despite treatment, bilirubin concentrations continued to rise in the first 48 hours. Because of the risk of the development of kernicterus, plasma exchange treatment was performed with a commercial plasmapheresis device. Both foals had an immediate decrease (44 and 57%) in plasma bilirubin concentration and fully recovered.

Abbreviations:

BBB	blood-brain barrier
CB	conjugated bilirubin
NI	neonatal isoerythrolysis
PCV	packed cell volume
RBC	red blood cells
UB	unconjugated bilirubin

Case Presentation

A 2-day-old warmblood colt was presented with complaints of icterus, weakness, and hemoglobinuria. The foal was born healthy and nursed well for the first 2 days. IgG concentrations 24 hours after birth were more than 8 g/L. On the morning before arrival, the foal was found to be lethargic and reluctant to drink, and his condition quickly deteriorated during that day. Upon arrival at the University hospital, the foal was in lateral recumbency. There was no reaction to external stimuli. Skin turgor and capillary refill time were severely lethargic. Mucous membranes were yellow and dry. Laboratory abnormalities included severe anemia (PCV 9%, normal values 30–45%), moderate metabolic acidosis, and hyperbilirubinemia (total bilirubin 365 μmol/L, normal values 0–80 μmol/L). The presumptive diagnosis was NI. The foal received 3 L of blood from a donor gelding at arrival; no cross match tests were performed before transfusion. After the transfusion, the foal regained consciousness, the sucking reflex returned, and he was able to stand and walk. PCV was 18% but bilirubin concentration had not changed. The foal was further treated with Ringer's lactate (4 mL/kg/h IV), oxygen (6 L/min), broad spectrum antibiotics (Cefquinome,[a] 2 mg/kg q12h), and vitamin E and selenium supplements. He was separated from the mare and received milk replacer every hour. Six hours after the transfusion, the foal's condition started to slowly deteriorate and 12 hours after the transfusion, the foal again was very weak and unable to rise. PCV had dropped to 10%. The foal received 2 L of washed red blood cells from the mare and after this 2nd transfusion, his behavior markedly improved. He regained activity, was alert, and able to rise and suckle. Total bilirubin plasma concentrations however continued to rise, reaching 466 μmol/L 2 days after arrival at the clinic. To reduce the risk of the development of kernicterus, plasma exchange treatment was performed with a commercial plasmapheresis device and 3 L of donor plasma. Plasma exchange resulted in an immediate decrease in total plasma bilirubin from 466 μmol/L to 261 μmol/L (Table 2). Neurologic signs did not develop and the foal fully recovered. Ten days after their arrival at the clinic, foal and mare could return home.

The 2nd foal, a 5-day-old warmblood filly, was examined because of icterus and weakness. The foal was born healthy and immediately nursed well. Five days after birth, she was found icteric and reluctant to rise.

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Upon arrival at the clinic, the foal was standing, but lethargic and weak. Mucous membranes were yellow and dry, skin turgor and capillary refill time diminished. Blood examination revealed severe anemia (PVC 10%), severe acidosis (pH: 7.08, BE: −15, bicarbonate: 13.2 mmol/L), hyperbilirubinemia (total bilirubin 398 μmol/L), moderate hypoglycemia, and leukocytosis. The presumptive diagnosis was NI. The foal received 2 L of blood from a donor gelding. After the transfusion, the foal's general condition improved, she was active and alert and able to suckle from the mare. Treatment was continued with Ringer's lactate (4 mL/kg/h IV), glucose (4 mg/kg/h), and broad spectrum antibiotics (Cefquinome,[a] 2 mg/kg q12h). The following day, total plasma bilirubin concentration had increased to 445 μmol/L and plasma exchange treatment was performed to reduce the risk for development of kernicterus. Three liters of plasma were replaced with plasma from a donor horse. The day after the procedure, total bilirubin concentration had decreased to 191 μmol/L. The foal was alert and nursing, nervous signs did not develop. After 5 days, foal and mare left the clinic in good health.

Materials and Methods

In both horses, a 16-gauge catheter was aseptically inserted in the left jugular vein. This catheter was connected to a commercial plasmapheresis device (Baxter Fenwall, model 200). This device, commonly used in human medicine, withdraws blood from the patient and automatically separates plasma from red blood cells (RBC) by filtration. Approximately, 300 mL of blood at a time is withdrawn over a time period of 3 minutes, anticoagulant (anticoagulant citrate dextrose solution,[b] 3 mg/mL) is automatically added and plasma and RBC are separated. After separation, RBC are returned to the patient, plasma is collected in separate bags, and the cycle recommences. One cycle takes between 10 and 15 minutes. In both foals, a pediatric long-term catheter (Certofix Mono, Braun[c,d]) was already present in the right jugular vein for the administration of fluids and antibiotics. This catheter was also used to administer donor plasma during the plasma exchange procedure. In both foals, a total of 3,000 mL plasma was removed and simultaneously the same amount of plasma from a donor horse was administered. The first 300 mL of donor plasma was given slowly over 45 minutes, with close monitoring of the foal's vital signs. If no signs of transfusion reaction occurred, the remaining plasma was given at a rate of approximately 1,000 mL/h. The total plasma exchange procedure lasted approximately 4 hours, whereby the foals were kept in lateral recumbency. Both foals were calm and cooperative and no sedatives were used. After the procedure, the short-term catheter from the left vein was removed and a cotton bandage placed to avoid bleeding and swelling of the catheter entrance site. The right catheter was left in place to be used for further intravenous treatments.

Discussion

In horses, 1 study showed that foals with a total bilirubin concentration above 461.7 μmol were 17 times more likely to develop kernicterus than foals with a lower total bilirubin.[1] Although not all foals with total bilirubin concentrations above 461.7 μmol/L will develop kernicterus, benefits of plasma exchange may outweigh the risk of the procedure, if total bilirubin concentrations approach this cut-off value. Because total bilirubin concentrations of both our foals approached the cut-off value and bilirubin concentrations continued to increase, we decided to perform a plasma exchange procedure. However, it is unknown whether kernicterus would have developed if this technique would not have been used.

In humane medicine, plasmapheresis is used to lower bilirubin concentrations in the blood of patients at risk of developing kernicterus. Its use has been described in neonatal babies as well as in adults with extreme hyperbilirubinemia.[2–4] Plasmapheresis refers to the extracorporeal filtration of blood, to remove plasma from, and return RBC to the circulation. If the removed plasma is replaced with plasma from a donor, the technique is called plasma exchange. In human medicine, plasmapheresis and plasma exchange are routinely used for the removal of toxic substances from the circulation. Next to auto-immune disorders, where the rapid removal of disease-causing autoantibodies from the circulation is required, plasmapheresis or plasma exchange is used for a variety of other disorders, such as hyperviscosity syndrome, hemolytic uremic syndrome, and intoxications.[5] In horses, the use of plasma exchange has not been studied. Although our cases showed a clear decrease in plasma bilirubin concentrations after plasma exchange, more controlled studies are necessary to assess the benefit of this treatment in foals.

Three different techniques for plasmapheresis exist: continuous flow centrifugation, discontinuous flow centrifugation, and plasma filtration.[5] In our cases, discontinuous flow centrifugation was used. With this technique, blood is intermittently withdrawn and RBC intermittently returned via the same catheter. A 300-mL batch of blood is removed at a time and centrifuged, and in human medicine such large quantity hampers the use of this technique in babies. In a 50-kg warmblood foal, withdrawal of 300 mL of blood was not expected to result in an important cardiovascular compromise. In small foals or when the withdrawal of 300 mL blood is expected to cause cardiovascular problems, a plasma filtration technique should be used. This technique, especially designed for babies, uses 2 venous lines and only removes 50 mL of blood at a time from the body.

Although plasmapheresis and plasma exchange are considered safe techniques, complications have been reported. Most common complications involve the placement of a catheter (bleeding, infection) and subclinical to clinical hypocalcemia. When patient blood is outside of the body passing through the plasmapheresis machine, the blood has a tendency to clot. To reduce this tendency, citrate is infused while the blood is running through the circuit. Citrate binds to calcium, an important factor in blood coagulation. Citrate is very effective in preventing blood from clotting, but can lead to life-threatening hypocalcemia, an important complication of plasmapheresis and plasma exchange in 6% of human patients.[5,7,8] Monitoring and treating hypocalcemia is therefore important during the procedure. Neither of our cases developed hypocalcemia dur-

ing or after the plasma exchange procedure. Other complications include hypotension, immune suppression, and clot formation.[5,7] In 3 studies evaluating plasmapheresis in horses, no adverse effects were noted.[6–8] Plasma exchange requires the use of donor plasma and as such, the additional risks of adverse reactions or of transmitting an infectious disease. Ideally, plasma donors should be kept in isolation and thoroughly tested for infectious diseases. Alternatively, commercially available plasma can be used. To minimize the risk of transfusion reactions, compatibility testing can be done before performing plasma transfer. In our case, no compatibility tests were performed. The first 300 mL of plasma was given slowly while the foals were closely monitored for signs of incompatibility. Fresh frozen plasma of gelding donors was used to reduce the risk for transfusion reactions. As plasma exchange takes time, it requires restraint of the foal to avoid dislodgement of the tubings. Our foals were kept in lateral recumbency by manual restraint throughout the procedure. As they tolerated this procedure well, we chose not to administer sedatives. Alternatively, low-dose sedatives could be used or the foals could be placed in a small box next to the machine to limit movement. Neither of the 2 foals showed a change in behavior during or after the procedure. Of plasma, 3,000 mL was exchanged with an immediate decrease in more than 50% in plasma bilirubin concentration. Kernicterus did not develop and both foals recovered completely.

Footnotes

[a] Cobactan 4,5%, MSD Animal Health BVBA, Lynx Binnenhof 5, 1200 Brussel, Belgium

[b] ACD-A, anticoagulant citrate dextrose solution 500 mL, Fenwal Europe sprl, Rue Edouard Belin 2-4, 1435 Mont Saint Guibert, Belgium

[c] Certofix Mono V320 16G, B. Braun Melsungen, Carl Braun Strase 1, 34209 Melsungen, Germany

[d] SNAP Foal IgG test, IDEXX Europe B.V., Scorpius 60 Building F, Hoofddorp, 2132LR, The Netherlands

Acknowledgment

Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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