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CASE REPORT

Therapeutic plasma exchange to mitigate flunixin meglumine overdose in a cria

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Abstract

Objective: To describe the use of therapeutic plasma exchange (TPE) in the treatment of flunixin meglumine overdose in a cria.

Case Summary: A 3-day-old alpaca cria was diagnosed with ureteral obstruction and agenesis resulting in severe bilateral hydronephrosis. During hospitalization, the cria inadvertently received a flunixin meglumine overdose of >65 mg/kg. Here, we report the use of lipid emulsion and TPE to mitigate flunixin meglumine toxicosis. TPE appeared to prevent any flunixin-induced kidney or gastrointestinal injury, even in a patient with congenital defects of the urinary tract.

New Information Provided: This is the first report of the use of TPE in a cria.

KEYWORDS
alpaca, lipid emulsion, overdose, ureteral obstruction

1 | CASE SUMMARY

A male alpaca cria weighing 7.6 kg was presented to a university teaching hospital at 72 hours of age for straining presumed to be due to meconium impaction. Parturition was not witnessed, but the cria appeared normal after delivery and was nursing well. The 8-year-old hembra was clinically normal. Upon presentation, the cria was bright, alert, and responsive with normal vital parameters (heart rate, 144/min; respiratory rate, 62/min; temperature, 39.3°C [102.7°F]). Physical examination was consistent with a 72-hour-old term cria, with the exception of a slightly kyphotic appearance and a mass in the mid/caudal abdomen appreciated on palpation. Initial bloodwork revealed a leukocytosis (23.28 × 10^9/L [23.28k/μL]; reference interval [RI], 8–22 × 10^9/L [8k–22k/μL]), with an increased creatinine (176.8 μmol/L [2 mg/dL]; RI, 80–150 μmol/L [0.9–1.7 mg/dL]) and urea (15.7 mmol/L [44 mg/dL]; RI, 5–10 mmol/L [13–28 mg/dL]). The remainder of the CBC and serum biochemistry was unremarkable. The cria had adequate passive transfer of antibodies (immunoglobulin G = 11.25 g/L [1,125 mg/dL]).

Abdominal radiography revealed a right-sided, large, ovoid opaque soft tissue structure in the caudodorsal abdomen, which resulted in ventral displacement of the colon and cranial and left lateral displacement of the gastric compartments and spiral colon. To further investigate the abnormalities, abdominal ultrasonography was performed that revealed a markedly enlarged right kidney with severe hydronephrosis and a hydroureter. The left kidney also had severe hydronephrosis but retained more cortex than the contralateral side. Further assessment of structural defects using a computed tomography scan confirmed severe bilateral hydronephrosis and hydroureter that was worse on the right. Intravenously administered iodinated medium was not identified within the dilated right renal pelvis or within the right ureter; therefore, right kidney function was thought to be

Abbreviations: GFR, glomerular filtration rate; ILE, intravenous lipid emulsion; RI, reference interval; TPE, therapeutic plasma exchange

poor. A small volume of contrast medium pooled within the gravity-dependent aspect of the left renal pelvis and ureter. The primary differential diagnosis was partial left and complete right distal ureteral obstructions. A functional assessment of the urinary system showed normal fractional electrolyte excretions aside from potassium (sodium, 0.32%; potassium, 4.78%; chloride, 0.74%; phosphorus, 0.28%) and isosthenuric urine (urine-specific gravity, 1.013).

To further assess the function of both kidneys prior to considering surgical intervention, nuclear scintigraphy was performed using 3.5 miC of 99mTc-DTPA (IV) with dynamic acquisition of 1 frame per second for 5 minutes. The excretion phase was evaluated after administration of 1.5 mL furosemide IV with additional acquisition for over 3 minutes. Calculated global glomerular filtration rate (GFR) was 3.4 mL/kg/min; individual GFR of the right kidney was calculated at 1 mL/kg/min (30%), and the left kidney was calculated at 2.4 mL/kg/min (70%). The calculated GFRs, specifically the global GFR and right kidney GFR, were thought to be overestimated due to difficulty in delineating clear regions of interest given the severe hydronephrosis and secondary organ crowding. The GFR study concluded that the majority of kidney function (70%) was provided by the left kidney. The presumptive diagnosis based on imaging studies was left ureteral obstruction due to ectopia and right ureteral obstruction due to distal ureteral agenesis.

During the course of hospitalization, bilateral pyelocentesis was also performed under ultrasound guidance in order to reduce the size of the kidneys and ease pressure on the remaining parenchyma. The right yielded 310 mL and the left yielded 250 mL of urine. Analysis of the urine sample showed increased protein and RBCs (possibly from sampling), and a urine-specific gravity of 1.012. Culture yielded no growth.

On day 5 of hospitalization, the cria developed severe tachypnea and dyspnea with peracute respiratory distress after inadvertent IV flunixin meglumine[a] administration (500 mg; >65 mg/kg). Flow-by oxygen via a face mask was administered due to the initial respiratory distress. Arterial blood gas analysis performed on 100% oxygen within 10 minutes indicated metabolic acidosis with respiratory compensation, with an appropriate Pa_{O_2} (237.8 mm Hg), decreased Pa_{CO_2} (23.7 mm Hg), normal pH (7.455), low bicarbonate (16.8 mmol/L), and increased plasma lactate (6.5 mmol/L). Given the lipophilic nature of flunixin, IV lipid infusion therapy was initiated about 1 hour after the overdose. The cria was treated with 2 mL/kg of lipid emulsion[b] (IV) over 15 minutes, followed by a continuous rate infusion of 0.25 mL/kg/min over the subsequent 30 minutes. Therapeutic plasma exchange (TPE) was chosen to remove as much of the highly protein-bound drug as possible.

In addition to the 14-Ga jugular IV catheter[c] already present, a second jugular IV catheter (8-Fr × 10 cm)[d] was placed using a modified Seldinger technique after midazolam sedation to facilitate the prescribed plasma exchange. Placement of the dialysis catheter was confirmed with right lateral thoracic radiography. The plasma volume of the cria was calculated to be approximately 387 mL based on an approximated total plasma volume for a cria to be total blood volume 70 mL/kg × 1 – HCT (0.7), with the goal to exchange at least 1.5 plasma volumes, which should result in a removal of 78% of the toxin, or more, if tolerated by the cria.

TPE was initiated about 4 hours after overdose and performed using an extracorporeal membrane-based device.[e] A TPE 2000 cartridge[f] was employed. This polypropylene filter has a surface area of 0.35 M^2 and a priming volume of 125 mL and a plasma filter volume of 41 mL. This resulted in an extracorporeal circuit volume of 166 mL. The plasma was exchanged with a replacement fluid consisting of 1 unit (500 mL) of 3% hydroxyethyl starch[g] dilute with 0.9% saline and 2 units (approximately 600 mL) of hyperimmune *Lama glama* plasma.[h] Midazolam was given intermittently IV and titrated to effect to keep the cria amenable to the procedure. Over the course of treatment, activated coagulation time and venous blood gases were measured to monitor heparin administration and electrolytes, respectively. Pre- and post-TPE blood samples were drawn and frozen, and serum samples subsequently sent for toxicology analysis.[i] Because this was a neonate, and an expected large amount of antibodies from passive transfer would possibly be removed and only one third of colloid administered at the start of exchange is typically present at the end of the session, we elected to provide 500 mL of hetastarch first and follow with 2 units of hyperimmune plasma. In total, 1,064 mL of replacement fluid was provided (2.5 plasma volumes exchanged) to remove an estimated 92% of the flunixin (equating to removal of about 60 mg/kg, leaving 5 mg/kg flunixin).

After TPE, the cria was returned to his hembra and maintained on 2 mL/kg/h Plasmalyte-A[j] (IV) with intermittent doses of furosemide to encourage urine production. Other medications administered included 2.2 mg/kg ceftiofur sodium[k] (IV) every 12 hours due to having multiple IV catheters placed, and 1 mg/kg pantoprazole (IV) every 24 hours to prevent third compartment ulcers secondary to flunixin toxicity. Serial hematology and biochemistry profiles were performed during hospitalization. Coagulation assessment (clotting times, platelet count, thromboelastography) was unremarkable apart from a slightly prolonged activated partial thromboplastin time (25.9 s [RI, 8–22 s]). Using BUN, creatinine, potassium, and sodium plasma concentrations as indicators of kidney function, no change was attributed to flunixin meglumine toxicosis after overdose (Figure 1). In addition, no signs of gastrointestinal ulceration became apparent, with the cria continuing to nurse well from the dam throughout. The cria was discharged 7 days post-flunixin overdose with stable kidney function, albeit compromised due to ureteral stenosis and agenesis, as clients wanted more time to consider surgery. Although lost to follow-up by the hospital, 3 months after discharge the cria was reported to have not undergone surgery and appeared to be clinically well.

Toxicology analysis[h] was performed using a liquid–liquid extraction of sample at pH 3.3 with a 1:1:1 mixture of hexane, diethyl ether, and dichloromethane. The sample was evaporated to dryness and reconstituted in 50 μL ethyl acetate, then analyzed via gas chromatography–mass spectrometry with the flunixin peak area plotted against a prespiked standard curve prepared in equine plasma. This confirmed flunixin overdose as the presence of pre-TPE flunixin was found, although the exact concentration was unable to be obtained due to insufficient sample; however, it was estimated to be about 13 times higher than post-TPE flunixin concentration, which was 4.8 μg/mL. Per the manufacturer, administering 3–5 times the recommended dosage of flunixin meglumine (1 mg/kg) did not result in any apparent adverse

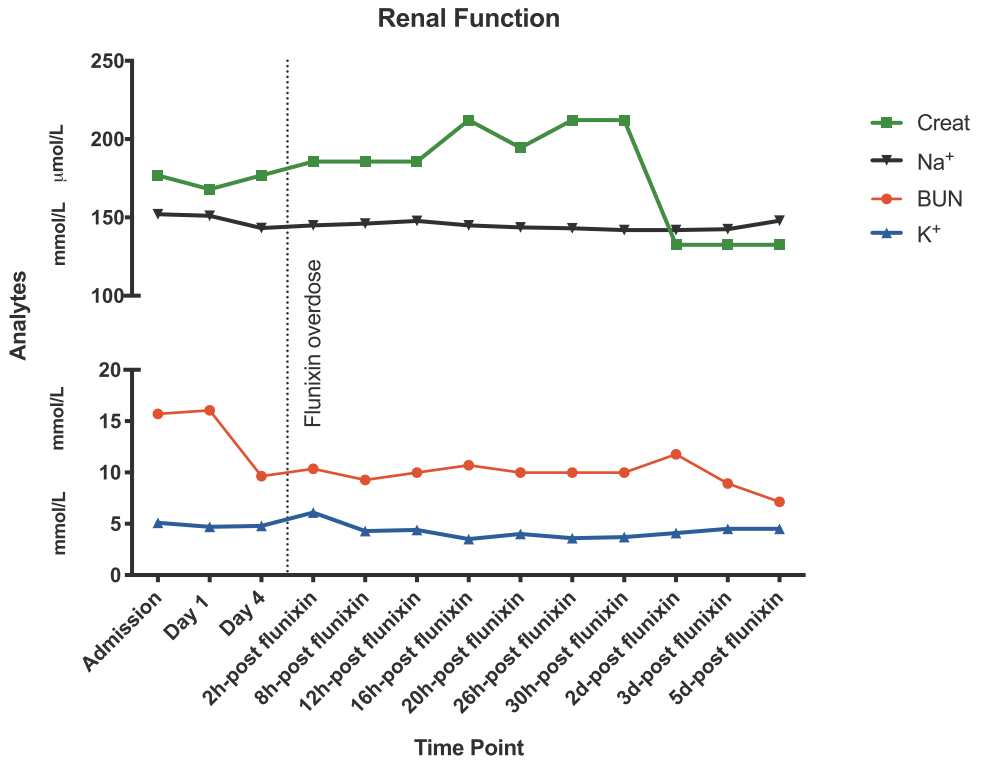

FIGURE 1 Renal function assessed by sodium (Na^+), BUN, potassium (K^+), and creatinine (Creat) concentrations in plasma in a cria before and after flunixin meglumine overdose

effects in adult horses or cattle (Banamine product insert). However, flunixin-induced renal crest necrosis has been reported in an adult horse, even at the recommended dosage.[1] Neonatal foals receiving 6.6 mg/kg flunixin meglumine for 5 days showed significant gastrointestinal ulceration on necropsy,[2] although treating our cria with TPE seems to have prevented any such ulceration clinically. No additional diagnostics were performed to rule out subclinical ulcerations. To date, flunixin has been poorly studied in camelids. Published data indicate that flunixin is protein-bound to a higher degree and is cleared at a lower rate in llamas than in other studied species,[3] which justified our decision to proceed with TPE despite the initial intravenous lipid emulsion (ILE) therapy. Although the reduction in flunixin from about 62 to 4.8 μg/mL over 7 hours could be explained by native metabolism in a healthy adult llama where the drug has an elimination half-life of 1.5 hours,[3] this is not expected in the current case. Neonatal foals have slower flunixin clearance compared with adult horses,[4] and the decreased renal function in this cria further decreased the expected drug clearance.

The treatment of flunixin meglumine toxicity in the current case was complicated by preexisting urinary tract abnormalities. The bilateral hydronephrosis and ureteral abnormalities were severe in this cria but consistent with previously reported congenital abnormalities in camelids. Both ectopic ureters resulting in hydroureter and hydronephrosis,[5,6] and various forms of renal or ureteral agenesis and aplasia,[7–9] have been reported.

ILE therapy was used in the current case while TPE was being arranged, and therefore its success alone could not be evaluated. ILE has been described for treatment of a variety of drug toxicities in veterinary patients,[10] including goats[11] and equines,[12–14] and is thought to be most effective for lipid solute toxicants such as local anesthetics and ivermectin. ILE has been previously used for treating nonsteroidal anti-inflammatory drug toxicities in dogs[15,16] and so was a reasonable treatment option in this case.

Although TPE and dialysis modalities are often unavailable to large animal patients due to their inherent large size and the costs associated with such treatments, our current report suggests that TPE can be used in select cases of highly protein-bound drug toxicosis, including flunixin overdose, especially when no antidote is available. Renal replacement therapy has been performed in large animal neonates for acute kidney injury due to oxytetracycline toxicity[17] or after resuscitation,[18] but TPE as a treatment for drug overdose has not been previously reported in large animal species. Even in the face of congenital defects of the urinary tract, the cria reported here sustained no apparent additional kidney injury or clinically manifesting gastrointestinal ulceration after flunixin meglumine overdose after TPE treatment. Although there are numerous published reports of TPE use in small animals, to our knowledge, this is the first report of such a treatment protocol in a large animal patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

[a] FlunixiJect, Bimeda-MTC Animal Health Inc, Cambridge, ON, Canada.
[b] Intralipid 20%, Baxter International Inc, Deerfield, IL.
[c] Mila International Inc, Florence, KY.
[d] Medcomp, Harleysville, PA.
[e] PRISMAFLEX System, Baxter International Inc, Deerfield, IL.
[f] PRISMAFLEX TPE 2000 set, Baxter International Inc, Deerfield, IL
[g] 6% Vetstarch, Zoetis, Kalmazoo, MI.
[h] CriaGamm, Lake Immunogenics, Ontario, NY.
[i] Cornell University Animal Health Diagnostic Center, Ithaca, NY.
[j] Abbott Laboratories, North Chicago, IL.
[k] Naxcel, Zoetis Inc, Kalamazoo, MI.

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