Case Report

Short-term infusion of ultralow-dose dopamine in an adult horse with acute kidney injury: A case report

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A B S T R A C T

Much is known regarding a good prognosis of acute kidney injury (AKI) is achieved with adequate, intensive, and early treatment, which leads to acceleration of the renal blood flow rate and associated urination. Low-dose dopamine (1 to 5 μg/kg bwt per min) is a treatment option for AKI in humans but remains controversial for use in horses because of the lack of extensive clinical trial data. A 19-year-old Westfalen horse gelding was referred to the Animal Medical Center with a 1-hour history of mild abdominal pain and anorexia after dressage exercise for 1 hour. Since elevated serum levels of blood urea nitrogen (BUN) and creatinine were found on days 4 and 5, the horse was diagnosed with AKI. In addition to basic hydration therapy with lactated Ringer’s solution, we decided to use ultralow-dose dopamine because of the possibilities of the upregulation of dopamine receptors in the affected kidney and general large animal specificity of drug doses. Infusions with 0.04 and 0.02 μg/kg bwt per min for 1 hour on days 6 and 7, respectively, were effective in decreasing serum levels of BUN and creatinine accompanied with a diuretic effect. Thus, short-term infusion of ultralow-dose dopamine may be useful in controlling the renal blood flow rate and clinical conditions in horses with AKI.

Introduction

Equine acute kidney injury (AKI) arises from two major conditions: decreased renal perfusion (pre-renal AKI) and primary renal dysfunction (intrinsic AKI). Most horses with AKI commonly manifest with antipathological clinical aspects, such as colic and colitis, which leads to hypovolemia and reductions in renal blood flow (decreased renal perfusion) (Geor, 2007; Groover, Woolums, Cole & LeRoy, 2006; Seanor, Byars & Bputcher, 1984). Pain sensation occasionally induces sympathicotonic vasocontraction (Macfeld, 2010; Touj et al., 2017). In addition to pain-associated vasoconstriction, anoxemia and diaphoresis give rise to both hypovolemia and reductions in renal blood flow (Geor, 2003). Therefore, persistent pain may become a serious risk factor for renal failure. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used as first-line drugs to control various pain intensities (Duz, Marshall & Parkin, 2019). However, continuous administration of NSAIDs poses a risk of renal damage to horses (Geor, 2003). Thus, IV fluid therapy is important in improving the circulating blood volume, if the affected horse shows signs of dehydration.

Blood urea nitrogen (BUN) and creatinine levels in the peripheral blood are useful parameters for the initial diagnosis and assessment of the development of AKI (Agrawal & Swartz, 2000). Elevated plasma or serum levels of BUN and creatinine are strongly associated with pre-renal failure or intrinsic failure (Geor, 2003). If adequate fluid therapy is performed at the early stage of pre-renal failure, renal blood flow improves, and both parameters return to normal levels within a few days (Geor, 2003). Blood levels of electrolytes, such as sodium, chloride, potassium, and calcium, are helpful in examining renal functions; these levels vary depending on the urine flow in AKI (Agrawal & Swartz, 2000). When horses with AKI are oliguric, they commonly develop hyperpotassemia. Urinalysis is also performed to evaluate renal functions; particularly, specific gravity is an adequate parameter reflecting urine concentration ability (Kohn & Chew, 1987).

The basic treatment principle for AKI includes rehydration, increased renal perfusion, and optimization of renal functions. Fluid administration is effective for normalizing or elevating circulating blood volume,

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which accelerates renal blood flow. In addition, for horses with oliguria, diuretics, or vasodilators, such as mannitol, furosemide, or dopamine, have been advocated. However, therapy with those reagents has not been confirmed to improve kidney circulation in horses and are not recommended in horses with AKI because of its adverse effects. When low-dose dopamine was infused IV into healthy horses, renal blood flow, and urine volume were increased (Trim, Moore & Clark, 1989). Dancker, Hopster, Rohn and Kastner (2018) analyzed the effects of different doses of dopamine perfusion in healthy Warmblood horses (1, 2, or 5 µg/kg bwt per min). They stated that dopamine increased cardiac output but decreased microvascular blood flow and tissue oxygen concentration, indicating that the doses of dopamine that they used in the study may induce ischemia in peripheral organs and tissues. However, in humans with AKI, low-dose dopamine infusion lacks evidence to verify its therapeutic ability, including prevention of kidney dysfunction and improvement of patients’ mortality (Friedrich, Adhikari, Herridge & Beyene, 2005; Lauschke, Teichgraber, Frei & Echardt, 2006). Dopamine is also clinically used for acute cardiovascular failures to gain peripheral pressure with decreased audible intestinal sounds, and anorexia, but no sweating (Table 1). Head descent, slight respiratory distress and increased breathing (15 breaths per min > 8–10 breaths in a normal condition of the case horse), tachycardia (48 beats per min), and slight congestion in the oral mucosa (CRT 2–3 s) were observed. After the exercise, defecation and urination were not noticed. A decreased appetite was detected. Based on the owner’s notification, the clinical aspects, and auscultation findings, the horse was diagnosed with mild abdominal pain. To ameliorate mild colic-like abdominal pain and dehydration, we performed IV (drip) infusion with 12 mL of 5% flunixin meglumine (DS Pharma Animal Health, Osaka, Japan) and 2 L of sodium 1-lactate Ringer’s solution (Otsuka Pharmaceutical, Tokyo, Japan) with 50 mL of levaginin® (10 mg/mL taurine, 2 mg/mL vitamin B1, 200 µg/mL vitamin B2, 5 mg/mL vitamin B3, 500 µg/mL vitamin B6, and 2.5 µg/mL vitamin B12) (Kyoritsu Seiyaku, Tokyo, Japan) twice a day. We were not able to collect any ascites. Since clinical manifestation of the case horse was almost recovered, the case horse started to feed (Dravers Brok®, HAVENS, Netherland, and Timothy hey, USA) and drink water in 1 hour after the treatment and 10 L of osmotic-balanced oral rehydration solution (Otsuka Pharmaceutical, Tokyo, Japan) was administered PO.

Clinical findings and progression

Initial abnormalities that the groom of the horse observed were depression, inappetence for drink and fruits, pawing, looking at the flank, and lifting the upper lip of the horse. We performed a physical examination at the stable. On presentation (Day 1), the case horse (590 kg bwt) manifested with slight hyperthermia (rectal temperature: 37.8 °C using DIGIFLASH Digital Thermometer (GENIA SA, France); normal reference interval of the case horse using the thermometer is 37.3–37.6 °C) and mild dehydration (> 4%) by a skin tent test on the skins of neck and shoulder (Murray, 1997). Also, the pain of abdominal pressure with decreased audible intestinal sounds, and anorexia, but no sweating (Table 1). Head descent, slight respiratory distress and increased breathing (15 breaths per min > 8–10 breaths in a normal condition of the case horse), tachycardia (48 beats per min), and slight congestion in the oral mucosa (CRT 2–3 s) were observed. After the exercise, defecation and urination were not noticed. A decreased appetite was detected. Based on the owner’s notification, the clinical aspects, and auscultation findings, the horse was diagnosed with mild abdominal pain. To ameliorate mild colic-like abdominal pain and dehydration, we performed IV (drip) infusion with 12 mL of 5% flunixin meglumine (DS Pharma Animal Health, Osaka, Japan) and 2 L of sodium 1-lactate Ringer’s solution (Otsuka Pharmaceutical, Tokyo, Japan) with 50 mL of levaginin® (10 mg/mL taurine, 2 mg/mL vitamin B1, 200 µg/mL vitamin B2, 5 mg/mL vitamin B3, 500 µg/mL vitamin B6, and 2.5 µg/mL vitamin B12) (Kyoritsu Seiyaku, Tokyo, Japan) twice a day. We were not able to collect any ascites. Since clinical manifestation of the case horse was almost recovered, the case horse started to feed (Dravers Brok®, HAVENS, Netherland, and Timothy hey, USA) and drink water in 1 hour after the treatment and 10 L of osmotic-balanced oral rehydration solution (Otsuka Pharmaceutical, Tokyo, Japan) was administered PO.

### Table 1

| Items               | Reference intervals | Days after treatment |
|---------------------|---------------------|----------------------|
| Clinical signs      |                     |                      |
| Vigor               | –                   | –                    |
| Appetite            | NO†                 | Dec‡                 |
| Defecation          | NO                  | Nor                  |
| Urination           | NO Dec              | Nor                  |
| Abdominal pain      | ++                  | –                    |
| Dehydration         | 4–6 (Mild)§         | >4%                  |
| Body temperature (°C) | 37.0–37.5.§          | 37.8                  |
| Blood examination   | CBC                 |                      |
| WBC (10³/µL)       | 5.2–10.1†           | 8.0                   |
| RBC (10³/µL)       | 660–970§            | 742                   |
| Hb (g/dL)          | 11.8–15.9§          | 11.6                  |
| Hct (%)            | 34–46§              | 41.0                  |
| MCV (fl)           | 43–55§              | 55.2                  |
| MCH (pg)           | 15–20†              | 15.6                  |
| MCHC (g/dL)        | 34–37§              | 28.2                  |
| ALB (g/dL)         | 2.9–3.6§            | 3.5                   |
| ALP (U/L)          | 88–261§             | 109                   |
| ALT (U/L)          | 19–22               | 19                    |
| BUN (mg/dL)        | 10–22‡              | 20                    |
| Creatinine (mg/dL) | 0.8–1.5§            | 2.7                   |
| Ca (mg/dL)         | 10.8–12.9§          | 13.0                  |
| Na (mmol/L)        | 134–142§            | 128                  |
| K (mmol/L)         | 2.4–4.8§            | 5.1                   |
| TP (g/dL)          | 5.4–7.0§            | 6.4                   |
| GLU (mg/dL)        | 71–122§             | 118                   |

*Not observed †Decreased Normal ‡Increased §[Murray, 1997] †[Green, Gates & Lawrence, 2005] §[Reference Intervals, 2020]
The case horse drank the solution by himself.

The next morning (Day 2), although audible intestinal sounds and defecation had normalized and pain had disappeared, slight hyperthermia, declined vigor, decreased appetite (50–60% comparing to normal), and slight dehydration persisted (Table 1). Heart rate (30 beats per min) and respiratory rate (10 breaths per min) were improved. However, slight congestion in the oral mucosa (CRT 2–3 s) was observed. The owner complained of persistent decreased urination. Therefore, 2 L of sodium 1-lactate Ringer’s solution with 25 mL of levaginin® was administered IV (drip). To address to the slight dehydration, 10 L of oral rehydration solution (Otsuka Pharmaceutical) was administered PO.

On day 3 (May 14), appetite of the horse was not recovered (40–50% comparing to normal). Since the rectal temperature of the case horse had increased (rectal temperature: 38.3 °C), 12 mL of 5% flunixin meglumine was infused IV. Subsequently, the rectal temperature returned to the normal level (37.5 °C). Serum samples were obtained from the cervical vein before IV infusion, and blood examination was carried out using the VetScan VS2 Chemistry Analyzer (Abaxis, California) and Particle Counter PCE-310 (ERMA, Tokyo, Japan). As shown in Fig. 1, slight elevation in serum levels of BUN and creatinine were detected. Baselines of these parameters of the case horse were BUN 10–15 mg/dL and creatinine 0.9–1.4 mg/dL, respectively. Comparing the creatinine level to the ordinary levels of the horse, the veterinary AKI classification of the horse on day 3 was stage 1–2 (Thoen & Kerl, 2011). To address to the slight dehydration and decreased urination, 10 L of osmotic-balanced oral rehydration solution (Otsuka Pharmaceutical) was administrated PO again. The case horse drunk the solution by himself.

On days 4 and 5, blood creatinine approached the critical level (4.2 mg/dL). Appetite of the horse was decreased (30% comparing to normal). At this stage, we diagnosed the horse with AKI associated with acute colic and dehydration (Table 1 and Fig. 1). To accelerate renal blood flow, 6 L of sodium 1-lactate Ringer’s solution with 100 mL of levaginin® and 10 mL of Mycillin Sol (250 mg/mL dihydrostreptomycin sulfate, 200,000 U/mL benzylpenicillin procaine, and 2 mg/mL procaine hydrochloride) (Meiji Seika Pharma, Tokyo, Japan) were injected IV (drip) and IM, respectively. We used antibiotics because WBC was slightly elevated for the past data of the case horse (4800–6000/μL).

On day 6 (May 17), appetite of the horse was still low (30–40% comparing to normal). We collected urine samples and found low urine specific gravity (1.020), hematuria (+), proteinuria (3+), glucose (3+), and pH 9.0 (Combur Test®, Roche Diagnostics, Tokyo, Japan), confirming renal failure. Since plasma levels of BUN and creatinine had not improved in the blood examination, we planned low-dose dopamine therapy to increase the renal blood flow. However, this therapeutic method is controversial, and there has been no reliable evidence for its clinical application in equines. Since, in general, an optimal dose/kg bwt of drugs is low in large animals compared to that in small animals (Plumb, 2018), short-term infusion of ultralow-dose dopamine was designed. Dopamine hydrochloride (Nippon Shinyaku, Kyoto, Japan) diluted in 6 L of sodium 1-lactate Ringer’s solution with 50 mL of levaginin® was administered at the IV (drip) injection rate of 0.04 μg/kg bwt per min for 1 hour and 10 mL of Mycillin Sol was injected IM.

On day 7 (May 18), the owner noticed increased urination, polydipsia, and improved vigor. Slight dehydration and decreased appetite (50% comparing to normal) were detected. With the blood test, improvement of renal condition was indirectly confirmed by serum creatinine and BUN levels (Fig. 1); thus, dopamine hydrochloride diluted in 6 L of sodium 1-lactate Ringer’s solution with 50 mL of levaginin® was administered at the rate of 0.02 μg/kg bwt per min for 1 hour and 10 mL of Mycillin Sol was injected IM.

On day 8 (May 19), no abnormalities were found in the clinical condition. Serum BUN had returned to the normal level whereas plasma creatinine had not (Fig. 1). Polyuria, mild polydipsia and slight dehydration were observed. Therefore, we discontinued dopamine infusion. A total of 5 L of sodium 1-lactate Ringer’s solution with 50 mL of levaginin® was injected IV (drip) and 10 mL of Mycillin Sol was injected IM.

On day 9 (May 20), no abnormalities were found in the clinical condition. Serum BUN had returned to the normal level whereas plasma creatinine had not (Fig. 1). Urinalysis performed on day 10 was unremarkable. To evaluate the serum levels of creatinine, we continued to monitor blood examination. On day 41 (June 21), we concluded that the horse was completely cured based on clinical aspects and blood parameters.

Discussion

Initial problems that owners stated on the horse were signs of mild colic gradually after his dressage exercise and the horse could not take the osmotic-balanced drink that his groom always prepared for him. By the day, no abnormality was observed on the blood biochemistry at a periodic medical examination on February 2. Since slight elevation of serum creatinine was found on day 3, we think that AKI in this case was triggered by a combination of abdominal pain and dehydration.

Pain-related excitement of the sympathetic nerve is one of the causes of AKI in horses (Groover et al., 2006; Seanor et al., 1984). It induces vasoconstriction, which leads to a decline in the renal blood flow. In this case, we found colic-like symptoms in the case horse a couple of days before the horse showed renal dysfunction, suggesting that pain might be one of causes of the renal failure. Flunixin meglumine is an effective medicine for horse colic to control pain without any significant side effects of intestinal motility if therapeutic doses are administered; thus, most clinicians choose this NSAID as the first-line drug for abdominal pain relief and pyretolysis (Duz et al., 2019; Stick et al., 1988). However, NSAIDs administration is a potential risk factor for renal dysfunction and for enhancing nephrotoxic effects impairing tubular epithelial cells.
of aminoglycoside antibodies, such as gentamicin and streptomycin (Mingeot-Leclercq & Tulkens, 1999). In this case, therefore, flunixin meglumine and Mycillin, including dihydrostreptomycin, were not administered on the same day.

Hydration is the basic treatment strategy for AKI. We tried to hydrate the horse with fluid therapy including IV infusion and PO administration to the case horse; however, volume and timing might be insufficient to recovered renal blood flow of the horse, and it might be another cause of the renal failure. Although sodium lactate Ringer’s solution was injected IV (drip) once a day from day 1 to day 11 except on day 3, this treatment was inadequate to accelerate renal blood flow in the horse at the early stage. To upregulate renal blood flow rate and glomerular filtration rates, diuretics and vasodilators can be used. Furosemide, a commonly used diuretic antihypertensive drug, blocks the Na-K-2Cl cotransporter in cells of the ascending limb of the loop of Henle, leading to decreased urine concentration (Ponto & Schoenwald, 1990), but horses with intrinsic renal failure may occasionally show a poor response to furosemide (Hinchcliff & Muir, 1991). When mannitol, an osmotic diuretic drug, is administered to patients with dehydration or pre-renal failure, there is a possibility of serious complications, such as AKI, in humans with dehydration (Geor, 2007).

Dopamine increases the renal blood flow detected by an ultrasonic flow probe after intravenous infusion for 60 min at 2.5 μg and 5.0 μg/kg bwt per min in conscious healthy horses (Trim et al., 1989). Low-dose dopamine (1 to 3 μg/kg bwt per min) was used previously because of its pharmacologic effects, such as renal vasodilation, increased glomerular filtration rate, and urination in healthy humans, but a meta-analysis (Friedrich et al., 2005) clearly demonstrated that low-dose dopamine has neither prohibitory nor therapeutic effects on AKI. Although dopamine doses (kg bwt per min) to horses were determined based on human doses, an optimal dose is generally lower in large animals than in small animals (Plumb, 2018). In addition, dopamine D1-like receptors expressed in the kidney are upregulated in humans with hypertension as compared to normal healthy controls (Andrejak & Hary, 1986; Schoors & Dupont, 1991). Therefore, we decided to administer ultralow doses of dopamine for this horse. After 0.04 and 0.02 μg/kg bwt per min of dopamine was administered IV (drip) for 1 hour on days 6 and 7, decreased serum levels of BUN and creatinine were detected in addition to increased urination. Clinical aspects, including appetite, vigor, and defecation improvement, suggested that treatment with ultralow-dose dopamine for 2 days may be successful in accelerating the glomerular filtration rate and urination. The dopamine concentration we used in the study was 0.02–0.04 μg/kg bwt per min, which was one-hundredth of the concentration of the low dose. Therefore, we expressed the dose as “ultralow” for ascertaining the effective dose in horses with AKI. On day 2 after the second treatment with dopamine, serum BUN levels were within the normal range; however, serum creatinine reached the normal level 32 days after the second treatment. Therefore, to evaluate renal functions and achieve a favorable prognosis, serum creatinine levels must be examined even after the other blood parameters and clinical aspects return to normal levels. Geor (2007) described the prognosis of AKI based on serum creatinine levels; in the case with less than 5 mg/dl of serum creatinine, a good prognosis is expected with adequate, intensive, and rapid therapy. This is a case report; therefore, additional trials must take place to confirm our result to establish another option for treatment of an AKI in horses.

Conclusion

When ultralow-dose dopamine (0.02 or 0.04 μg/kg bwt per min) was administrated for 1 hour to the horse diagnosed with AKI with a peak serum creatinine of 4.3 mg/dl, the kidney functions might be recovered, and urination were effectively induced. To the best of our knowledge, this is the first report on the effectiveness of ultralow-dose dopamine to improve AKI in a horse. After the first treatment with 0.04 μg/kg bwt per min, the expected diuretic effect was achieved. Therefore, 0.02 μg/kg bwt per min was injected the next day to avoid excessive polyuria and dehydration. The attempt with a short-term infusion of ultralow-dose dopamine may be useful in controlling the renal blood flow rate and clinical conditions in horses with AKI.

Ethical statement

The study was performed in accordance with the guidelines and regulation by the University Animal Care and Use Committee of the Tokyo University of Agriculture and Technology.

Conflict of interest

The authors have declared that no conflict of interest exists.

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