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Case Report

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Treatment of acute kidney injury associated with cyclosporine overdose in a dog using hemodialysis and charcoal hemoperfusion

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Abstract

Objective – To describe the management of cyclosporine overdose using hemodialysis and hemoperfusion in a dog.

Case Summary – A 6-year-old, spayed female Australian Shepherd was presented for treatment of cyclosporine overdose and acute kidney injury. Five days prior to presentation, the dog had been diagnosed by its referring veterinarian with immune-mediated thrombocytopenia. Treatment was initiated with prednisone, but since no response was noted, azathioprine (50 mg PO q 24 h) and cyclosporine (6 mg/kg IV q 24 h) were added. On day 4, an overdose of cyclosporine (33 mg/kg IV) was administered accidentally. Upon presentation, serum biochemistry panel revealed azotemia [creatinine, 521.6 μmol/L (5.9 mg/dL); BUN, 59.3 mmol/L (166 mg/dL)], increased activities of liver enzymes, and hyperbilirubinemia. Due to the presumed diagnosis cyclosporine overdose and acute kidney injury, a combined hemodialysis and charcoal hemoperfusion treatment was planned. Hemosorba CH-350 charcoal hemoperfusion cartridge was placed in series upstream in the extracorporeal circuit from the hemodialyzer. A 3-hour treatment was performed and a total of 0.74 L/kg of blood was processed. Pretreatment blood cyclosporine concentration was 960 nmol/L (1154 ng/mL) and decreased to 440 nmol/L (529 ng/mL) posttreatment (54% fractional reduction, 18% per hour). Thirty-one hours following treatment, blood cyclosporine concentration was 220 nmol/L (265 ng/mL; 1.5% decrease per hour). Twelve days following presentation to our hospital, the dog was euthanized due to lack of response to medical management.

New or Unique Information Provided – Combined hemodialysis and charcoal hemoperfusion treatment can significantly reduce blood cyclosporine concentrations following acute intoxication or overdosage, and should be considered as an option for decontamination in such cases.

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Keywords: AKI, canine, dialysis, intoxication

Abbreviations

AKI	acute kidney injury
HD/cHP	hemodialysis and charcoal hemoperfusion
RI	reference interval
VMTH	Veterinary Medical Teaching Hospital

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The authors declare no conflicts of interest.

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Introduction

Extracorporeal blood purification therapies are used to eliminate endogenous and exogenous toxins and to treat drug overdose.[1,2] The veterinary applications of extracorporeal therapy have become more sophisticated and current modalities to remove toxins or drugs include conventional hemodialysis, hemoperfusion, and therapeutic plasma exchange.[1–4] If the target toxin is a low molecular weight molecule, not protein bound, and its volume of distribution is low, conventional hemodialysis techniques can be used to remove it effectively. However, if molecular size (>1,500 Daltons) or protein binding restricts effective elimination by diffusive hemodialysis, hemoperfusion may be utilized as an alternative technique.[1,5] In contrast to hemodialysis, during hemoperfusion blood flows directly over a sorbent column commonly composed of activated charcoal.[1,5] Large or protein-bound substances can bind to the adsorptive material in the column and are removed from

circulation. Despite the growing availability of these different modalities, to date, there is little evidence to prescribe the optimal use of these extracorporeal therapies.

Case Summary

A 6-year-old, spayed female Australian Shepherd weighing 22.6 kg was presented to the Emergency Service of the Veterinary Medical Teaching Hospital (VMTH), for further evaluation and treatment of cyclosporine overdose and acute kidney injury (AKI). Five days prior to presentation, the dog was presented to the referring veterinarian with a complaint of vulvar bleeding (Day 1). A CBC revealed normocyctic, normochromic, nonregenerative anemia [hematocrit 0.2 L/L (20%); reference interval (RI), 0.4–0.55 L/L (40–55%)] and marked thrombocytopenia [5×10^{12}/L ($5 \times 10^3/\mu$L); RI, $150-400 \times 10^{12}/\mu$L ($150-400 \times 10^{12}$/L)]. No spherocytes were observed on the peripheral blood smear. Serum biochemistry panel was unremarkable. A tentative diagnosis of immune-mediated thrombocytopenia was made and treatment with prednisone (1.25 mg/kg PO q 12 h) and doxycycline (5 mg/kg PO q 24 h) was initiated. Blood transfusions were required to prevent further decreases in hematocrit, azathioprine (50 mg PO q 24 h) was added on Day 2, and cyclosporine (6 mg/kg IV q 24 h) was added on Day 3. On Day 4, an overdose of cyclosporine (33 mg/kg IV) was administered accidentally, but the error was not recognized until Day 5. Serum biochemistry panel on Day 5 revealed azotemia with BUN concentration 62 mmol/L (175 mg/dL; RI, 1.8–7.5 mmol/L [5–21 mg/dL]), creatinine concentration 292 μmol/L (3.3 mg/dL; RI, 26.5–106.1 μmol/L [0.3–1.2 mg/dL]), hyperphosphatemia of 4.5 mmol/L (13.8 mg/dL; RI, 0.97–2.02 mmol/L [3.0–6.2 mg/dL]), hypoalbuminemia of 12 g/L (1.2 g/dL; RI, 33–44 g/L [3.0–4.4 g/dL]), and hyperbilirubinemia of 108 mmol/L (6.3 mg/dL; RI, 0.0–3.4 mmol/L (0.0–0.2 mg/dL]). The dog was diagnosed with AKI presumed secondary to cyclosporine overdose, and was referred to the VMTH for further management.

Upon presentation at the VMTH, the dog was obtunded but responsive. Physical examination revealed tachypnea (58 /minute) with normal lung sounds, yellow mucous membranes, skin petechiation, and melena. A CBC revealed normocytic, normochromic, nonregenerative anemia (hematocrit 0.2 [20%]; RI, 0.4–0.55 [40–55%]), leukocytosis (33.2×10^9/L [$33.2 \times 10^3/\mu$L]; RI, $6.0–13.0 \times 10^9$/L [$6.0–13.0 \times 10^3/\mu$L]), mature neutrophilia (26.4×10^9/L [$26.4 \times 10^3/\mu$L]; RI, $3–10.5 \times 10^9$/L [$3–10.5 \times 10^3/\mu$L]), and thrombocytopenia (5×10^9/L [$5 \times 10^3/\mu$L]; RI, $150–400 \times 10^9$/L [150–400/ x $10^3/\mu$L]). Serum biochemistry panel revealed azotemia (creatinine 521 μmol/L [5.9 mg/dL]; RI, 26.5–106.1 μmol/L [0.3–1.2 mg/dL]; BUN 59.3 mmol/L [166 mg/dL]; RI, 1.8–7.5 mmol/L [5–21 mg/dL]), hyperphosphatemia [4.6 mmol/L (14.3 mg/dL); RI 0.97–2.02 mmol/L [3.0–6.2 mg/dL]), hypoproteinemia (34 g/L [3.4 g/dL]; RI, 54–76 g/L [5.4–7.6 mg/dL]), hyperbilirubinemia (132 μmol/L [7.7 mg/dL]; RI, 0.0–3.4 mmol/L [0.0–0.2 mg/dL]), and increased activities of alkaline phosphatase (284 U/L [284 IU/L]; RI, 21–170 U/L [21–170 IU/L]), alanine aminotransferase (115 U/L [115 IU/L]; RI, 19–67 U/L [19–67 IU/L]), and gamma glutamyl transferase (13 U/L [13 IU/L]; RI, 0–6 U/L [0–6 IU/L]). Abdominal ultrasound revealed kidneys of normal size and architecture, a mildly enlarged and hyperechogenic pancreas and liver, and a scant volume of free abdominal fluid. Thoracic radiographs revealed mild alveolar infiltrates in the right cranial and middle lung lobes. Based on the clinicopathologic data the dog, was calcified as Grade IV AKI, nonoliguric.

Due to the presumed diagnosis cyclosporine overdose and AKI, a combined hemodialysis and charcoal hemoperfusion (HD/cHP) treatment was planned with the aim to decrease the blood cyclosporine concentration and simultaneously to treat the acute uremia. A temporary hemodialysis catheter[a] was placed in the dog's right external jugular vein, and the extracorporeal HD/cHP treatment was initiated 36 hours following administration of the cyclosporine overdose. A standard hemodialysis procedure was used with a Hemosorba CH-350 charcoal hemoperfusion cartridge[b] placed in series upstream in the extracorporeal circuit from an Optiflux 160R hemodialyzer. Optiflux 160R hemodialyzer.[c] A 3-hour treatment was performed, and a total of 16.8 L (0.74 L/kg) of blood was processed during the treatment. A standard dialysate with a potassium concentration of 3 mEq/L, sodium concentration of 145 mEq/L, and bicarbonate concentration of 30 mEq/L was delivered at 500 mL/min.

Serial blood samples were obtained before and after the HD/cHP treatment. Blood aliquots for cyclosporine analysis were refrigerated at 4°C until analyzed within 24 hours using high performance liquid chromatography.

Pre-treatment blood cyclosporine concentration was 960 mmol/L (1154 ng/mL) and decreased to 440 mmol/L (529 ng/mL) post treatment (54% fractional reduction). The hourly removal during HD/cHP was 18% per hour. Thirty-one hours post treatment, blood cyclosporine concentration was 265 ng/mL (49% fractional reduction, 1.5% per hour; Figure 1). Serum creatinine concentration decreased during the dialysis from 521 μmol/L (5.9 mg/dL) to 150 μmol/L (1.7 mg/dL) with a creatinine reduction ratio of 71%. The following day, serum creatinine concentration was 2.5 mg/dL, and 2 days later, it had improved to 97 μmol/L (1.1 mg/dL); therefore, dialysis was discontinued.

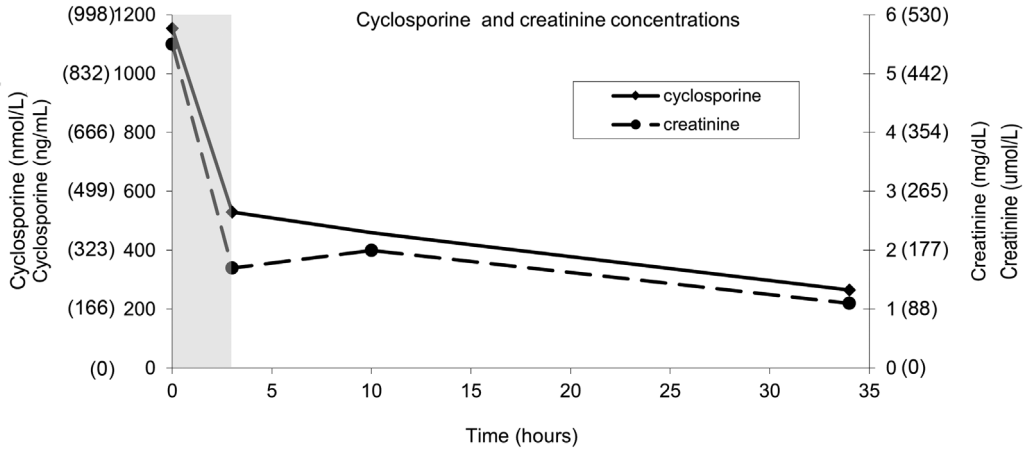

Figure 1: Cyclosporine and creatinine concentrations during the first 36 hours hospitalization and treatment with hemodialysis and charcoal hemoperfusion. The shaded area indicates the HD/cHP interval. HD/cHP, hemodialysis combined with charcoal hemoperfusion.

Despite the immunosuppressive therapy described above, thrombocytopenia persisted and the dog required multiple packed RBC transfusions due to persistent bleeding and decreases in hematocrit. Twelve days following presentation to the VMTH the dog was euthanized due to lack of response to medical management. Gross postmortem examination revealed hemorrhage in multiple organs, and hepatic and splenic enlargement. The liver was diffusely brown with an enhanced reticular pattern, and 10–20 multifocal firm, tan exophytic nodules that extended into the parenchyma. Liver histopathology demonstrated multifocal hemorrhages and marked extramedullary hematopoiesis. The surface of the kidneys contained multifocal pinpoint to 0.5 cm diameter, red, round foci that extended into the cortex on cut section. Histopathologically, moderate multifocal tubular changes were observed in the kidneys, which consisted of vacuolar degeneration, interstitial edema, and evidence of tubular loss. These changes were assessed to be the result of the cyclosporine nephrotoxicity. The intestines were filled with dark moist fecal material. All lung lobes contained red foci, pinpoint to 0.5 cm in diameter on the surface and throughout the parenchyma, and multiple hemorrhages were observed on histopathologic examination.

Discussion

This report describes the utility of extracorporeal therapies in the management of acute cyclosporine overdose in companion animals. A combination of HD and cHP was effective to decrease cyclosporine concentration, and thus should be regarded as a therapeutic option in severe cyclosporine intoxication. To the best of the authors' knowledge, this report is the first to demonstrate that cyclosporine concentrations can be reduced substantially using HD/cHP.

Cyclosporine is a calcineurin inhibitor widely used in human and veterinary medicine as an immunosuppressive agent. Its use has become routine in veterinary medicine as part of multidrug therapy for the management of refractory immune-mediated diseases and in renal transplantation. Due to individual variability of cyclosporine bioavailability and metabolism in dogs, it is recommended to follow blood concentration after the initiation of therapy to assure efficacy and to prevent toxicosis.[6]

Cyclosporine is a 1,200 Dalton molecule that is metabolized mainly in the liver and the intestine by CYp3A enzymes.[6] Once in the circulation, cyclosporine distributes widely, accumulating in the skin, liver, kidneys, and fat of dogs, resulting in a large volume of distribution of 4 L/kg.[7] There are numerous pharmacologically inactive metabolites that are eliminated via the biliary system. The plasma half-life of cyclosporine is approximately 9 hours.[7,8]

Cyclosporine overdose has been associated with a variety of clinical consequences both in people and in dogs,[7] and these include nephrotoxicity.[9,10] The pathogenesis of cyclosporine-induced nephrotoxicity is not fully understood but includes impairment of glomerular filtration rate elicited by intense vasoconstriction and, more chronically, irreversible interstitial fibrosis.[11] Acute nephrotoxicity often is reversible when therapy is discontinued.[12] In veterinary medicine, AKI has been reported infrequently following cyclosporine therapy, and current evidence suggests dogs are less prone to its nephrotoxicity compared to people.[13]

Hemodialysis typically is used for removal of uremic toxins, but also can be used for removal of drugs and exogenous poisons.[1,2,4] In order to be effectively removed by hemodialysis, toxins should have a low molecular weight (<1,500 Daltons), a low volume of distribution, and minimal plasma protein binding.[1] The spectrum of toxins that can be removed effectively by extracorporeal techniques is extended when hemodialysis is combined with sorbent hemoperfusion.[1,5,14,15] Activated charcoal is the sorbent used most commonly for combined hemodialysis and hemoperfusion for toxin elimination in veterinary therapeutics, but there is little information on the spectrum of toxins and the relative efficacy of this therapy for drug overdosage and poisoning. The use of hemodialysis alone has been shown to remove cyclosporine relatively ineffectively,[16] and the effectiveness of combined HD/cHP, although not well established, was suggested to be minimally effective.[14]

The decision to use an adjunctive extracorporeal blood purification technique to accelerate drug elimination in this case was based on the severity (Grade IV) of the AKI and the likelihood it resulted from the cyclosporine overdose. The half-life of cyclosporine in dogs is relatively short,[17] but in the absence of its assessment at presentation, it was impossible to predict how much time would be required until the blood cyclosporine concentration would decline to nonnephrotoxic concentrations.

The molecular weight of cyclosporine is 1,200 Daltons. Since hemodialysis is a diffusive therapy, clearance is highly affected by molecular size, not only because large molecules are less likely to fit into the holes of the dialysis membrane, but also since larger molecules move more slowly (ie, lower molecular kinetics) compared to smaller molecules, which thereby decreases the likelihood of interaction with the dialysis membrane when blood is moving across the dialyzer. Cyclosporine would have limited clearance with the use of a conventional hemodialyzer available in the 1970s and 1980s, but use of a modern high efficiency dialyzer, with greater middle molecule clearance, might provide some minimal adjunctive removal for any unbound drug component. The decision to combine HD with cHP was also related to the fact that cyclosporine is highly protein bound,[18] and therefore cannot be removed effectively using hemodialysis alone. In addition, efficient clearance of cyclosporine by maximizing the extracorporeal blood flow during the treatment would have predisposed to the rapid reduction of BUN concentration and subjected the dog to dialysis disequilibrium. With combined HD/cHP the hemodialysis component permitted the simultaneous gradual and safe correction of the azotemia, electrolyte, acid–base, and fluid consequences of the AKI concurrent with adsorptive removal of cyclosporine.

Therapeutic plasma exchange is another potential therapeutic modality that could have been considered; however, it is less available, more expensive, and does not address the azotemia or the large distribution volume for cyclosporine. Additional methods that have been suggested to treat cyclosporine overdose include phenobarbital, which was used to induce cytochrome P-450 enzymes to promote increased endogenous clearance, calcium channel blockers, pentoxifylline, thromboxane A_2-receptor antagonists, and dopaminergic agonists.[19–22] Nevertheless, evidence regarding the clinical efficacy of these modalities in acute overdosage is lacking.

It is likely that the blood cyclosporine concentration that induced AKI in this case was significantly higher than the concentration measured prior to the HD/cHP treatment, since the overdose was given 36 hours before the first sample was obtained. Blood cyclosporine concentrations >832 mmol/L (>1,000 ng/mL) are associated with decreased kidney function and damage.[23] The fact that the overdose was given parenterally likely contributed to the acute intoxication. The oral bioavailability of cyclosporine in dogs is only 20–27%,[24] and thus a bioequivalent oral dose would have been considerably higher than one provided parenterally. Parenterally overdosed human patients are more prone to develop clinical signs of overdosage compared to orally overdosed patients.[25]

The HD/cHP therapy in this case facilitated removal of uremic toxins and accelerated the removal of cyclosporine from the blood. Cyclosporine clearance following an intoxication follows first order kinetics, and can be described with a single-pool model using the following equation: $Ct = C0 \cdot e^{-Kt}$, where Ct and C0 represent plasma concentrations at time t and at time 0, respectively; K = elimination rate constant; and t = time after the first measurement or after starting extracorporeal therapy. During HD/cHP, the total elimination rate constant (K_{tot}) is the sum of the intrinsic elimination rate constant (K_{int}) and the extracorporeal elimination rate constant for the combined hemodialysis and hemoperfusion (K_d). For this dog: $K_{tot} = 0.28/h$, $K_{int} = 0.02/h$ (as calculated from the decrease post dialysis), and $K_d = 0.26/h$ (13 times higher than K_{int}). Therefore, ~34 hours would have been required in this dog to achieve the same degree of clearance achieved with 3 hours of HD/cHP treatment. Without the HD/cHP treatment, the kidney would have been exposed to toxic concentrations of cyclosporine for a longer period that likely would have induced more profound and potentially unrecoverable kidney injury. One should take into consideration that a rebound might occur after a HD/cHP treatment, which could necessitate additional treatments. In this case, since kidney function continued to improve after the HD/cHP treatment, it was assumed that blood

cyclosporine concentration was likely sufficiently low and the risk for nephrotoxicity had decreased. Since kidney function continued to improve, further treatments were not required.

From the available data, it is not possible to determine the respective contributions of hemodialysis and hemoperfusion to the combined K_d. Since cyclosporine is a middle-sized molecule and protein bound, it is likely the relative contribution of the hemoperfusion was higher compared to dialysis. This information can be obtained readily by collecting samples for analysis from the inlet and outlet of each device during the treatment, but this information was not available for the current patient. The decrease in cyclosporine concentration in this dog from a toxic concentration to a therapeutic concentration likely facilitated the rapid recovery of kidney function following HD/cHP treatment. With many intoxications, the offending toxin is not known precisely and the initial and end-treatment concentrations are not available in real time. Treatment is initiated empirically to accommodate the broadest spectrum of potential toxicants and of indefinite duration to provide expectation for toxin elimination. The spectrum of toxic substances cleared by HD/cHP and their elimination kinetics in animals requires additional study and cataloging to facilitate the future indications and protocols for the extracorporeal management of drug overdoses and poisoning. In severe cases managed with charcoal hemoperfusion, where maximal reduction of the toxicant is required over the shortest period of time, replacing a potentially saturated activated charcoal cartridge during the treatment and extending the duration of treatment should be considered.[4,5] Presuming the activated charcoal was providing most of the cyclosporine clearance, a greater reduction of the blood concentration could have been expected with a more prolonged treatment combined with replacement of a potentially saturated hemoperfusion cartridge.

This case report demonstrates combined HD/cHP treatment can significantly reduce blood cyclosporine concentrations following acute intoxication or overdosage and should be considered an option for decontamination in such cases. It especially is likely to be beneficial in animals suffering extremely high blood cyclosporine concentrations when days may be required for significant reduction to therapeutic concentrations to occur by endogenous clearance alone.

Footnotes

[a] 11.5Fr 24 cm HemoCath Double Lumen Catheter, Medcomp Inc., Harleysville, PA.
[b] Asahi Medical Co., Ltd., Tokyo, Japan, surface area 300,000 m^2.
[c] Optiflux 160R hemodialyzer, Polysulfone membrane, surface area 1.5 m^2 Fresenius Medical Care, Waltham, MA.

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