Effect of Fenoldopam Continuous Infusion on Glomerular Filtration Rate and Fractional Excretion of Sodium in Healthy Dogs

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Background: Acute kidney injury (AKI) is a common problem in small-animal patients and carries a guarded prognosis with substantial morbidity and mortality. One retrospective study of 99 dogs with AKI reported an overall mortality rate of 56%. Regardless of the underlying etiology, AKI most commonly is associated with a rapid loss of kidney function usually manifested as decreased glomerular filtration rate (GFR), subsequent azotemia, and often decreased urine production. Oligoanuria may indicate more severe kidney injury and is associated with increased mortality, and a study of 29 dogs with hospital-acquired AKI reported an overall mortality rate of 62%, with oligoanuric patients being 20 times more at risk of death. Oligoanuric patients are more difficult to manage medically because they are more prone to morbidities including hypervolemia and hyperkalemia.

Fenoldopam is a selective dopamine-1 (DA-1) receptor agonist that induces renal vasodilatation, increases renal blood flow (RBF), and promotes natriuresis and diuresis in people and dogs. Dopamine-1-like receptors have been identified in the renal brush border and basolateral membranes in dogs, as well as in renal arterioles. As a selective DA-1 agonist, the risk of systemic adverse effects is decreased compared with dopamine. The most important adverse effect of fenoldopam infusion is hypotension, which appears to be dose dependent. Pharmacokinetic studies in dogs are limited, but a recent veterinary study of 6 healthy dogs demonstrated that steady-state plasma concentrations were reached within 10 minutes of fenoldopam infusion (0.8 µg/kg/min), with no observed hypotension.

Although fenoldopam has been shown to increase urine output (UOP), little is known regarding the effect of the drug on GFR. One study in 6 healthy cats showed a significant increase in urine production 6 hours after fenoldopam administration, which was associated with an increase in fractional excretion of sodium (FeNa). In the same study, creatinine clearance, used as an estimate of GFR, initially decreased but subsequently increased by 6 hours, making it difficult to assess whether the increased UOP seen was secondary to increased GFR or to changes in sodium excretion.
excretion. In an experimental model of partial exsanguination in anesthetized dogs, fenoldopam administration maintained RBF, GFR, and natriuresis despite systemic hypotension, whereas these variables failed to be maintained by saline administration alone. Thus far, studies in both human and veterinary medicine have identified variable changes in GFR with fenoldopam infusion, and the mechanism of increased UOP after fenoldopam infusion remains unknown.

The primary objective of our study was to determine the effect of fenoldopam on GFR in healthy dogs. The secondary objective was to determine the change in FeNa after fenoldopam administration.

Materials and Methods

This protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania School of Veterinary Medicine.

Study population

Healthy, privately owned dogs were screened for enrollment. Dogs were eligible for screening if they weighed at least 6 kg, were clinically healthy, and were not receiving any medications other than routine heartworm, flea, and tick preventative medications. Initial patient screening included CBC, tests of renal function, urinalysis on voided urine, and indirect blood pressure (BP) measurement within 30 days of study enrollment. Exclusion criteria included abnormal diagnostic screening test results or dogs receiving medications. All dogs were fasted for 12 hours before GFR evaluation. Water was not restricted before or during the study, and all dogs were conscious throughout the study.

Physiologic measurements

At baseline, 3 measurements of indirect systolic BP, heart rate, and respiratory rate were obtained and averaged. A single axillary temperature also was obtained. At subsequent time points corresponding to blood sample collection, an average of 3 indirect BP measurements, heart rate, and respiratory rate were obtained. Blood pressure was measured indirectly using oscillometric technique on the left hind limb, with dogs in sternal recumbency. Additional BP monitoring was performed while titrating the fenoldopam infusion as described below.

Drug administration

A sterile cephalic IV catheter was placed in each dog. According to the manufacturer’s recommendation, fenoldopam was diluted in 5% dextrose (D5W) to a final concentration of 40 μg/mL. All dogs initially received a continuous rate infusion (CRI) of fenoldopam at 0.2 μg/kg/min. Blood pressure was measured 5 minutes after starting treatment. If no hypotension was observed, the dosage was increased by 0.2 μg/kg/min increments every 5 minutes until reaching the desired dosage of 0.8 μg/kg/min. This target dosage was chosen based on previous pharmacokinetic studies performed using fenoldopam in dogs. This dosage necessitated a fluid administration rate of 1.2 mL/kg/h. Blood pressure was measured before each dose increment to monitor for hypotension. Once the patient had received 0.8 μg/kg/min or the highest tolerated dosage of fenoldopam for 10 minutes, they were considered to have reached steady state. Once at steady state, dogs received the infusion for a total of 300 minutes in order to allow 60 minutes at steady state before performing the 240-minute iohexol clearance test. Blood pressure monitoring was performed every 15 minutes. Given the potential risk of hypotension, the following protocol was outlined for use if hypotension occurred: If systolic BP decreased below 100 mmHg but remained >80 mmHg, the CRI would be discontinued for 10 minutes and BP rechecked; if subsequent BP was <100 mmHg, the CRI would be restarted at a 25% lower rate and BP again monitored. If at any point BP decreased <80 mmHg, the CRI would be discontinued and the dog would receive 10 mL/kg of crystalloid fluid as needed until BP returned to >100 mmHg. The study would be discontinued for the day, and the dog potentially returned at a later date at the owner’s discretion.

Experimental control

The negative control was administration of D5W without fenoldopam, 7 days before or after infusion of 300 mg iohexol. For the control, a sterile cephalic IV catheter was placed and the dogs started on a CRI of D5W at a rate calculated to match the volume administered during the fenoldopam infusion. Per cent dextrose in water was administered for 300 minutes, and GFR and FeNa measurements were performed in the same fashion as during fenoldopam infusion, with iohexol administration occurring 1 hour after the beginning of D5W administration. A 7-day washout period occurred between the control infusion and fenoldopam infusion. To minimize the theoretical risk of iohexol nephrotoxicity decreasing the second GFR measurement, dogs were randomly assigned to treatment order with half of the dogs receiving the D5W alone first and half receiving fenoldopam first.

Glomerular Filtration Rate Measurements

Glomerular filtration rate was measured by iohexol clearance using standard methodology. Sixty minutes after reaching fenoldopam steady state, each patient received a single IV injection of iohexol at a dosage of 300 mg iodine equivalents/kg. Blood samples were collected 120, 180, and 240 minutes after this injection, while the patient continued to receive the fenoldopam or D5W infusion. At each time point, 2 mL of blood was collected and transferred into serum separator tubes. Samples were centrifuged within 30 minutes of collection and sent to Michigan State University for iohexol clearance determination using inductively coupled plasma-mass spectrometry and reported as iohexol clearance in mL/min/kg.

Fractional excretion of sodium

Voided urine samples were obtained before initiation of fenoldopam or D5W infusion and again within 30 minutes of its discontinuation. For dogs that would not void voluntarily, cystocentesis was performed to obtain a urine sample. Urine sodium and creatinine concentrations were measured on both samples. Blood samples were obtained at the same time points for measurement of serum creatinine and sodium concentrations. The FeNa was calculated using the following formula:

\[
FE_{Na} = 100 \times \left( \frac{[Na_{\text{urine}} \times \text{creatinine}_{\text{plasma}}]}{[Na_{\text{plasma}} \times \text{creatinine}_{\text{urine}}]} \right)
\]

Change in FeNa was calculated as postinfusion FeNa – preinfusion FeNa.
Statistics
A power calculation based on previously published GFR data in dogs determined that a sample size of 7 dogs would provide 80% power of detecting a 15% change in GFR. A sample size of 10 dogs was used in the study to ensure adequate power was achieved. Normality of data was assessed using the Shapiro-Wilk test. All variables were considered normally distributed except the fenoldopam GFR measurements. All variables are expressed as mean (±SD) except fenoldopam GFR measurements, which are expressed as median (range). A Wilcoxon signed-rank test was used to compare GFR measurements during fenoldopam and D5W administration. A paired t-test was used to compare change in FeNa after fenoldopam and D5W administration because these data were normally distributed. A statistical software program was used for all analyses. *P < .05 was considered significant for all comparisons.

Results

Signalment

Ten healthy, privately owned dogs were enrolled in the study. There were 5 spayed females, 4 neutered males, and 1 intact male. All dogs were mixed breed, ranging in age from 3 to 12 years (median, 7.5) and weighing 6.8–30.5 kg (median, 20.7 kg). All dogs were systemically healthy on physical examination with no clinically relevant abnormalities on diagnostic screening. Initial serum creatinine concentrations were within normal limits for all dogs on screening laboratory testing (median, 0.9 mg/dL; range, 0.7–1.6 mg/dL), and all urine samples were adequately concentrated (median urine specific gravity, 1.038; range, 1.027–1.048). Randomization resulted in 5 dogs receiving the fenoldopam infusion first, whereas the remaining dogs received the D5W infusion first. The order in which the dogs received D5W versus fenoldopam had no significant effect on measured GFR or FeNa (P = .99).

Glomerular filtration rate was significantly increased during fenoldopam administration (median, 3.33 mL/min/kg; range, 2.14–6.26 mL/min/kg) compared to infusion of D5W alone (median, 2.71 mL/min/kg; range, 1.52–4.97 mL/min/kg; Fig 1). The median increase in GFR was 0.78 mL/min/kg (range, −0.26 to 1.29 mL/min/kg), which was a median increase of 27.0% (range, −7.8% to 71.2%) from placebo. Eight of 10 dogs experienced an increase in GFR during fenoldopam infusion as compared to control infusion, whereas 2 of 10 experienced a decrease in GFR.

Fenoldopam administration was associated with a significant increase in FeNa (P = .0148; Fig 2). The mean change in FeNa during fenoldopam infusion was 0.11, compared with 0.02 while receiving D5W infusion. Administration of D5W alone was not associated with a change in FeNa (P = .73). For all dogs on the day of fenoldopam administration, the mean preinfusion FeNa was 0.16 (SD, 0.13) and the mean postinfusion FeNa was 0.27 (SD, 0.17). For all dogs on the day of D5W administration, the mean preinfusion FeNa was 0.21 (SD, 0.15) and the mean postinfusion FeNa was 0.26 (SD, 0.13). Preinfusion FeNa was not significantly different between placebo and fenoldopam days (*P = .728). The total volume of IV fluid administered was similar during fenoldopam and D5W infusions; each dog received 1.2 mL/kg/h of fluids on both the study day and control.

Adverse effects

No hypotension was observed in any dog, and no alternative dosing protocol was required. The mean systolic BP throughout D5W administration was 148 mmHg (SD, 29 mmHg). The mean systolic BP throughout fenoldopam administration was 147 mmHg (SD, 30 mmHg). Additionally, there were no observed adverse effects from fenoldopam or iohexol administration in any dog.
Discussion

In healthy dogs, administration of fenoldopam as a CRI significantly increased GFR compared with administration of D5W alone. Administration of fenoldopam also significantly increased FeNa, whereas an increase in FeNa was not observed when dogs received D5W alone. At the study dosage of 0.8 µg/kg/min, fenoldopam did not cause hypotension or any other adverse effects. The increase in GFR after fenoldopam likely occurred as a result of increased renal plasma flow (RPF). At effective doses, activation of DA-1 receptors in the renal arteries and arterioles has been shown to cause renal vasodilatation and increased RBF in humans, dogs, and rats.\(^3\)\(^5\)\(^12\)\(^14\) This effect is proposed to cause a subsequent increase in GFR. However, the increased RPF seen in humans has failed to consistently result in increased GFR, and studies in dogs have shown similarly variable results.\(^15\)\(^17\) The results of our study show a significant increase in GFR in healthy dogs associated with fenoldopam administration compared with placebo (D5W). The change from normal baseline GFR, without D5W infusion, in response to fenoldopam was not studied and remains unknown. It is unknown whether this magnitude of GFR increase is clinically relevant or whether a similar increase would be seen in dogs with decreased renal function, as in oligoanuric AKI. The day-to-day variability of GFR when measured by iohexol clearance is not known in dogs. However, because the majority of dogs in our study (8 of 10 dogs) did experience increased GFR, we think this change is unlikely to be a result of day-to-day variation alone and is in fact an effect of the fenoldopam. Additionally, variability in the degree of GFR increase was observed among dogs, suggesting that the response may vary. Two dogs did not experience an increase in GFR during fenoldopam treatment. The reason for this lack of response is unknown, but suggests that not every dog may show a similar response to fenoldopam. Three of the dogs had GFR <2.0 mL/kg/min, but these dogs all were medium to large breed dogs with GFR measurements that were within the reference ranges reported for dogs of their size in a previous study.\(^7\)\(^8\)

The increase in FeNa is consistent with previous studies that show that fenoldopam infusion increases natriuresis. The proposed mechanism for this effect involves DA-1-mediated inhibition of the Na-K-ATPase and Na-H pumps within the renal proximal tubule.\(^19\)\(^21\) Normal urine production is dependent on both GFR and sodium excretion (which is the net result of tubular sodium reabsorption and excretion). The study in cats that identified increased FeNa and UOP showed inconsistent changes in creatinine clearance, making it difficult to assess whether the increased UOP was truly secondary to increased GFR or to changes in sodium excretion.\(^8\) Another study on anesthetized dogs indicated that fenoldopam administration maintained normal FeNa in the face of hypotension because of partial exsanguination, an effect that was not produced by saline administration alone.\(^9\) The results of our study suggest that both natriuresis and increased GFR may be involved in increasing UOP. More studies are indicated to further investigate these mechanisms and to determine whether the same effects are seen in animals with AKI. Because D5W contains no sodium, it was chosen as the control fluid to decrease the potential effect of an increased IV sodium load on FeNa. Although infusion of D5W alone could impact FeNa because of the increased free water administration, dogs were given the same volume of D5W for control and experimental infusions to control for any effect of D5W on FeNa or GFR. The total volume of fluids administered was 1.2 mL/kg/h during both infusions. Fenoldopam reconstituted in D5W does not contain any sodium; therefore, the increased FeNa observed in the patients after fenoldopam administration was not caused by increased sodium administration. Additionally, the dogs were fasted on the morning of both infusions to decrease the effect of PO sodium intake on FeNa because diets were not standardized across all dogs.

Acute kidney injury is a common problem in small animal patients, with mortality rates often exceeding 50%.\(^1\)\(^2\) Restoring renal perfusion with IV fluids, alleviating postrenal obstruction, and treating intrinsic renal disease (eg, antibiotic treatment for pyelonephritis) all may improve GFR. However, patients affected by toxic, inflammatory, ischemic, and idiopathic AKI often have a persistent decrease in GFR that is refractory to medical intervention. This is particularly true in oligoanuric patients, where case fatality remains especially high. Although these oligoanuric dogs are candidates for hemodialysis, it is not always available and is often cost prohibitive for owners. When dialysis is not an option for patients with AKI, therapeutic intervention is aimed at increasing urine production, which could improve control over volume status and electrolyte disturbances. Although pharmacologic conversion to polyuria alone does not necessarily indicate renal recovery, polyuric patients are easier to manage medically, which may result in improved outcome. Drugs such as furosemide and mannitol promote UOP by decreasing renal reabsorption of sodium, rather than by increasing GFR. Thus, a patient may be observed to have higher UOP with no change in serum creatinine concentration. A medication that increases GFR would increase uremic toxin clearance and consequently may improve morbidity and mortality. Thus far, no single medication has been shown to successfully increase GFR, and many treatment options carry the risk of unacceptable adverse effects. In response, a consensus statement for the management of people with AKI recommends against mannitol and dopamine administration.\(^22\)\(^23\) The same document recognizes that furosemide should only be administered for the management of fluid balance, hyperkalemia, and hypercalcemia, but any putative role in amelioration of the course of AKI is unproven.

The results of our study suggest that fenoldopam may have the ability to increase both GFR and renal sodium excretion, which potentially could provide the
dual benefits of increased clearance of uremic solutes and increased UOP in dogs with AKI. Although the results of our study suggest that fenoldopam increases GFR and FeNa in normal dogs, the effect must be further evaluated in dogs with renal dysfunction to truly determine its benefit. The altered renal perfusion, tubular epithelial cell dysfunction, and altered tubular flow rate through the nephron observed in states of renal injury preclude simple extrapolation of the results of our study to a dog with AKI, because it cannot be assumed that a diseased kidney would respond similarly to fenoldopam. A recent retrospective study in dogs and cats with AKI indicated that fenoldopam administration resulted in no improvement in survival to discharge, duration of hospital stay, or renal biochemical variables when compared with AKI patients that did not receive the drug.24 The retrospective nature of this study failed to control for other concurrent treatments as well as the severity of AKI, and no objective measures of GFR or sodium excretion were performed. Prospective controlled clinical studies are warranted to assess the effect of fenoldopam on dogs with AKI.

One limitation of this study was that the study population included only healthy dogs, therefore limiting application of our results to patients with AKI. Additionally, the study had a small sample size; however, it successfully documented significant changes in both GFR and FeNa. Because of financial limitations, RPF was not measured in this study. Several previous studies in people have demonstrated that fenoldopam increases RPF in both normotensive and hypertensive patients.15,16 The changes in RPF were inconsistently associated with a concurrent increase in GFR, and further studies are warranted. Recognizing that iohexol clearance is the gold standard methodology for GFR measurement, iohexol clearance is a validated and widely performed method of assessing GFR that is more practical to perform clinically. Although obtaining more blood samples to calculate GFR using a noncompartamental model may be more accurate, previous research has demonstrated limited sample methods of calculating GFR using iohexol clearance to be acceptable.25 Urine output was not measured in our study because of possible changes in GFR as a result of the sedation required for urethral catheterization.

In conclusion, fenoldopam CRI increases both GFR and FeNa in healthy dogs compared with D5W without observed adverse effects. Additional studies should be performed to investigate these changes during administration of this drug to dogs with renal dysfunction.

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Footnotes

a Corlopam, Hospira, Lake Forrest, IL
b D5W, Abbott Animal Health, Atlanta, GA
c Plasma-lyte, Abbott Animal Health, Atlanta, GA
d Researchrandomizer.org
e Vitro350 Chemistry Analyzer
f Stata 12.0 for Mac, Stata Corporation, College Station, TX
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