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Pharmacodynamic assessment of diuretic efficacy and braking in a furosemide continuous infusion model

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Abstract *Introduction:* Diuretic failure is a potential life-ending event but is unpredictable and poorly understood. The objectives of this study were to evaluate pharmacodynamic markers of furosemide-induced diuresis and to investigate mechanisms of diuretic braking in dogs receiving constant rate infusion (CRI) of furosemide.
Animals: Six healthy male dogs.
Methods: Raw data and stored samples from one arm of a previously published study were further analyzed to mechanistically investigate causes of diuretic braking in these dogs. Urine volume was recorded hourly during a 5-h furosemide CRI. Urine and blood samples were collected hourly to measure serum and urine electrolytes, urine aldosterone, and plasma and urine furosemide. Serum electrolyte fractional excretion was calculated. Urine sodium concentration was indexed to urine potassium (uNa:uK) and urine furosemide (uNa:uFur) concentrations, plasma furosemide concentration was indexed to urine furosemide concentration (pFur:uFur), and urine aldosterone was indexed to urine creatinine (UAldo:C). Temporal change and the relationship to urine volume were evaluated for these measured and calculated variables.
Results: Urine volume was significantly correlated with urine electrolyte amounts and with uNa:uK. The ratio of pFur:uFur decreased during the infusion, whereas furosemide excretion was unchanged.
Conclusions: There was a strong relationship between urine volume and absolute urine electrolyte excretion. Urine volume was strongly correlated to uNa:uK, giving it potential as a spot indicator of urine production during diuresis. The decrease in

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uNa:uK over time during the infusion is consistent with mineralocorticoid modification of urinary electrolyte excretion, supporting renin–angiotensin–aldosterone activation as a cause of diuretic braking in this model.

Introduction

Abbreviations

CHF	congestive heart failure
CRI	constant rate infusion
FE	fractional excretion
pFur:uFur	plasma furosemide to urine furosemide ratio
RAAS	renin angiotensin aldosterone system
sCr	serum creatinine
UAldo:C	urine aldosterone to creatinine ratio
uCl	urine chloride
uCr	urine creatinine
uFur	urine furosemide
uK	urine potassium
uNa	urine sodium

Furosemide is the most commonly administered diuretic for the treatment of congestive heart failure (CHF) in dogs [1]. Several studies have demonstrated increased urine production after oral and parenteral administration of furosemide, but there are no other specific measures of efficacy reported, and diuretic dosage is not always correlated to diuretic response in the clinical setting [2–8]. Defining diuretic efficacy is important for the identification and management of patients with poor diuretic responsiveness and continued CHF despite appropriate treatment [9]. Multiple factors can affect the clinical response to a diuretic medication, including gastrointestinal absorption of the drug, renal tubular secretion of the drug, neurohormonal activation, and the development of true diuretic resistance [9].

Diuretic resistance is a clinically important problem identified in up to 17% of people with CHF [10]. Early identification is important because this phenomenon is associated with a poor prognosis [9,11]. Although diuretic resistance is suspected to occur in dogs with CHF, it has not been defined using indicators of pharmacodynamic response to furosemide [1,12]. Urine output is an ideal indicator of diuretic response, but it is difficult to quantify in patients, and the finding of decreased urine production does not provide mechanistic information that might be useful in restoring diuretic responsiveness in refractory CHF. Several metrics, other than urine volume, have been proposed to quantify diuretic responsiveness, including weight loss, resolution of CHF, urinary sodium (uNa) concentrations, and fractional excretion (FE) of sodium [10,13]. The relationship of blood-to-urine furosemide concentrations is also necessary to understand the action of furosemide [14,15]. The knowledge provided by such metrics may aid in the development of therapeutic strategies to restore urine production in patients with refractory CHF. Hypochloremia, reduced spot uNa, low FE of sodium, low urine sodium to urine furosemide (uNa:uFur) and low urine sodium to urine potassium (uNa:uK) have been associated with a clinical diagnosis of diuretic resistance in people but are unexplored in dogs [10,11,13,16,17].

Diuretic braking is the abrupt reduction in urine production shortly after diuretic initiation, contributing to the initial loss of diuretic responsiveness [18]. Our laboratory demonstrated that urine production stimulated by a constant rate infusion (CRI) of furosemide, while initially high in dogs and horses, declines towards baseline after several hours, despite constant urine furosemide concentrations [6,7,19]. These findings are consistent with diuretic braking and the timing is compatible with renin–angiotensin–aldosterone system (RAAS) activation as a cause [6].

The study described herein evaluated measures of serum and urine electrolytes, urine aldosterone to creatinine ratio (UAldo:C), uNa:uFur and plasma furosemide to urine furosemide ratio (pFur:uFur) for the determination of diuretic efficacy and elucidation of the causes of diuretic braking in dogs. We hypothesized that urinary electrolyte excretion and furosemide excretion would be directly related to urine volume, and that indicators of RAAS activation would increase concurrently or before urine volume began to decline during furosemide CRI.

Animals, materials and methods

The raw data utilized for this study were obtained from a previously published study which compared the effects of two diluents used for a furosemide

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