The Effects of the Loop Diuretics Furosemide and Torasemide on Diuresis in Dogs and Cats

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ABSTRACT. Torasemide is a new loop diuretic that combines the effects of furosemide and spironolactone. There are no reports on the effects of torasemide in cats and dogs. This study compared the diuretic effects of furosemide and torasemide in cats and dogs. With pressure overload cardiac hypertrophy were given oral placebo, torasemide 0.3 mg/kg, or furosemide 1 mg/kg or 3 mg/kg. Con trol and mitral regurgitation dogs were given oral placebo, torasemide 0.2 mg/kg, and furosemide 2 mg/kg for 7 days. Urine samples were obtained at baseline and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hr after each drug dose. Urine volume and urine Na+ and K+ were measured. Both furosemide and torasemide increased urine volume 1 hr after administration. Furosemide caused a dose-dependent increase in urine volume that peaked at 2–3 hr in cats and dogs. The diuretic effect of furosemide disappeared 6 hr after administration, while that of torasemide peaked 2–4 hr after administration and persisted for 12 hr in cats and dogs. In MR dogs, torasemide for 7 days signifi cantly decreased urine potassium excretion. Plasma aldosterone increased with torasemide, whereas there was no change with furosemide. In conclusion, about 1/10 concentration of torasemide was as potent as furosemide and had a longer diuretic effect in cats and dogs. These data suggest that torasemide is useful for treating congestive heart failure or edema in cats and dogs.

KEY WORDS: diuretic agent, feline, heart failure, renal function, urine.

Torasemide is a pyridyl sulfonylurea with a chemical structure between those of loop diuretics and Cl– channel blockers [5, 13, 20]. The main tubular site of action of torasemide is the ascending limb of the loop of Henle, where it interacts with the Na+, 2Cl–, K+ cotransporter localized in the luminal surface [19, 20]. Torasemide and furosemide cause a significant, dose-dependent increase in urine flow and the urinary excretion of sodium and potassium [14]. Torasemide has more potent, longer-acting diuretic activity than furosemide [3]. Congestive heart failure, which is characteristically associated with fluid retention and shortness of breath, is a leading cause of morbidity and mortality. Therefore, animals with congestive heart failure require management with diuretics, such as thiazide, bumetanide, and furosemide. Furosemide is the diuretic most frequently used for edema. Although torasemide has beneficial effects in chronic congestive heart failure in humans [8], there are fewer clinical reports than on furosemide. In veterinary medicine, there are no reports on the dose or diuretic effects of torasemide for dogs and cats. Therefore, this study compared the diuretic effects of torasemide and furosemide in dogs and cats.

MATERIALS AND METHODS

This study followed the Guidelines for Institutional Laboratory Animal Care and Use of the School of Veterinary Medicine and Animal Science at Kitasato University.

Cat study: This study used 8 clinically healthy domestic short hair cats (4 males, 4 females, 3–5 years old), weighing 3.0–4.0 kg, in which routine laboratory tests, including blood tests and urinalysis, were normal. The cats were housed in cages and fed commercial feed twice daily (Hill’s, Colgate, Japan). Water was given ad libitum.

Iatrogenic pressure overload left ventricular cardiac hypertrophy (LVH): Before surgery to induce experimental LVH, all cats were tranquilized with butorphanol (0.1–0.2 mg/kg) and diazepam (5 mg/kg), anesthetized with ketamine (5–10 mg/kg) and isoflurane, and intubated. During surgery, the cats were anesthetized with isoflurane (1.5–2.0%) with 100% O2. Body temperature was measured with an anal probe and maintained at 37–38°C with a heating pad. The heart rate was also monitored.

The chest was opened at the fourth intercostal space under sterile conditions. The pericardium was opened, and the ascending aorta dissected. An aortic band was made with 1 nylon suture, so that it produced a thrill at the descending aorta. The chest was closed in layers and evacuated using standard procedures. The cats were placed on an antibiotic regimen (ampicillin sodium) for 5 days postoperatively. Follow-up care included daily monitoring of the heart rate, respiratory rate, and temperature. The heart and lungs were auscultated daily. Serial chest X-rays were taken in each cat to identify the onset of pulmonary venous congestion. One month after surgery, echocardiography was performed to confirm LVH. The experiments were performed 6–9 months after inducing LVH.

LVH cats were given oral placebo, torasemide 0.3 mg/kg, or furosemide 1 mg/kg or 3 mg/kg. The dosage of torasemide was decided by preliminary study. Each drug was given at randomly, and each administration interval was for 2 weeks. Urine samples were obtained with a bladder
catheter (3 or 4 Fr), and water intake was measured at baseline and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hr after each drug dose. The urine was centrifuged (1,500 g × 10 min), and the supernatant was used to measure Na⁺ and K⁺.

**Dog study:** This study used 10 clinically healthy mongrel dogs of either sex, 1–2 years old, weighing 7–11 kg, in which routine laboratory tests, including blood tests and urinalysis, were normal. The dogs were housed in cages and fed commercial feed twice daily (Hill’s, Colgate, Japan). Water was given *ad libitum*.

**Iatrogenic mitral regurgitation:** Five dogs served as controls and five dogs underwent surgery to induce mitral regurgitation (MR). The surgical procedure was as described previously [15]. The dogs were placed on an antibiotic regimen (ampicillin sodium) for 5 days postoperatively. Follow-up care was as described in the cat study.

Control and MR dogs were given oral placebo, furosemide 2 mg/kg, or torasemide 0.2 mg/kg for 7 days. The dosage of torasemide was decided by preliminary study. Each drug was given at random, and each administration interval was for two weeks. Urine samples were obtained with a bladder catheter (4–8 Fr), and water intake was measured at baseline and 1, 2, 4, 6, 8, 12, and 24 hr after each drug dose on 1 and 7 day administration. The urine was centrifuged (1,500 g × 10 min), and the supernatant was used to measure Na⁺ and K⁺. Blood samples in EDTA were taken from the saphenous vein before drug administration. Plasma was analyzed for renin activity, angiotensin II, and aldosterone by radioimmunoassay (RIA).

All the data are expressed as the mean ± SD. Analysis of variance (ANOVA) was used to compare results, followed by Tukey’s test. A value of *p* < 0.05 was considered statistically significant.

**RESULTS**

**Cat study:** The echocardiography, X-ray, and clinical sign were not changed during study. Both furosemide and torasemide increased urine volume 1 hr after administration. Furosemide caused a dose-dependent increase in urine volume, which peaked at 2 (1 mg/kg) or 3 (3 mg/kg) hr. The diuretic effect of furosemide disappeared 6 hr after administration. The diuretic effect of torasemide peaked 4 hr after administration and persisted for 12 hr (Fig. 1A). The 24-hr urine volume with furosemide 3 mg/kg or torasemide 0.3 mg/kg was significantly greater than with placebo or furosemide 1 mg/kg (Fig. 2A). The 24-hr urinary sodium excretion with furosemide 3 mg/kg or torasemide 0.3 mg/kg was significantly greater than with placebo or furosemide 1 mg/kg (Fig. 3A). The 24-hr urinary potassium excretion with torasemide 0.3 mg/kg was significantly greater than with placebo, or furosemide 1 mg/kg or 3 mg/kg (Fig. 4A).

**Dog study:** The echocardiography, X-ray, and clinical sign were not changed during study. Both furosemide and torasemide increased urine volume 1 hr after administration. The significant diuretic effect of furosemide disappeared 6 hr after administration. The diuretic effect of torasemide peaked 2 hr after administration and lasted for 12 hr (Fig. 1B). The 24-hr urine volume with furosemide or torasemide was significantly increased compared with placebo in control and MR dogs (Fig. 2B). The 24-hr urinary sodium excretion did not differ for placebo and furosemide, in control, while it was increased with torasemide (Fig. 3B). The 24-hr urine sodium excretion with furosemide or torasemide was significantly increased compared with placebo in MR dogs. The 24-hr urinary potassium excretion with torasemide in 7 day administration was significantly decreased compared with 1 day administration in control and MR dogs (Fig. 4B). The plasma renin activity in control and MR dogs did not differ with placebo (1.9 ± 0.2 and 1.9 ± 0.2 ng/ml/hr, respectively), furosemide (1.9 ± 0.3 and 1.8 ± 0.2 ng/ml/hr), and torasemide (1.4 ± 0.3 and 1.7 ± 0.3 ng/ml/hr). The plasma angiotensin II concentration in the control and MR dogs with torasemide (220 ± 172, *p* < 0.05 and 268 ± 113 pg/ml, *p* < 0.05, respectively) and furosemide (266 ± 135 pg/ml, *p* < 0.05) in MR dogs were significantly decreased compared with 1 day administration in control and MR dogs (Fig. 4B). The plasma renin activity in control and MR dogs did not differ with placebo (1.9 ± 0.2 and 1.9 ± 0.2 ng/ml/hr, respectively), furosemide (1.9 ± 0.3 and 1.8 ± 0.2 ng/ml/hr), and torasemide (1.4 ± 0.3 and 1.7 ± 0.3 ng/ml/hr). The plasma angiotensin II concentration in the control and MR dogs with torasemide (220 ± 172, *p* < 0.05 and 268 ± 113 pg/ml, *p* < 0.05, respectively) and furosemide (266 ± 135 pg/ml, *p* < 0.05) in MR dogs were significantly decreased compared with 1 day administration in control and MR dogs (Fig. 4B). The plasma renin activity in control and MR dogs did not differ with placebo (1.9 ± 0.2 and 1.9 ± 0.2 ng/ml/hr, respectively), furosemide (1.9 ± 0.3 and 1.8 ± 0.2 ng/ml/hr), and torasemide (1.4 ± 0.3 and 1.7 ± 0.3 ng/ml/hr). The plasma angiotensin II concentration in the control and MR dogs with torasemide (220 ± 172, *p* < 0.05 and 268 ± 113 pg/ml, *p* < 0.05, respectively) and furosemide (266 ± 135 pg/ml, *p* < 0.05) in MR dogs were significantly
increased compared with placebo (35 ± 32 and 41 ± 27 pg/ml, both p<0.05) and furosemide in the controls (51 ± 53 pg/ml). The plasma aldosterone concentration in control and MR dogs with torasemide (95.9 ± 5.1 and 87.0 ± 6.1 pg/ml, respectively) was significantly increased compared with placebo (75.7 ± 4.8 and 74.9 ± 7.8 pg/ml) and furosemide (78.5 ± 5.0 and 76.3 ± 6.6 pg/ml) (Fig. 5).

DISCUSSION

In this study, although cardiac hypertrophy and left atrial and ventricular enlargement were confirmed by echocardiography in all the cats and dogs, none of the animals showed clinical signs. Since the animals were category II in the New York Heart Association (NYHA) classification [2], it may not have been appropriate to give diuretic agents at this stage. Nevertheless, this is the first report comparing the diuretic effects of furosemide and torasemide in cats and dogs, and our data indicate that torasemide has a diuretic effect equivalent to 1/10 of the dose of furosemide. This is important for the clinical use of torasemide in cats and dogs.

Torasemide is effective in patients with edema caused by congestive heart failure [8]. Torasemide has high bioavail-

ability (>80%) and a rapid rate of absorption in patients with chronic renal failure or cirrhosis [7, 9, 11], whereas that of furosemide is diminished in both cirrhosis [4] and congestive heart failure [1, 16, 17]. Since torasemide revealed long diuretic action comparing furosemide in cats and dogs, torasemide is able to decrease administration time and increasing quality of life in treating severe congestive heart failure in cats and dogs.

The urinary excretion rate of furosemide is very high after intravenous administration and decreases rapidly in dogs [12]. In contrast, the urinary excretion rate of torasemide is much lower, and decreases gradually [12]. The plasma concentration of torasemide also decreases more slowly. The slower transfer rate from plasma to the nephron leads to the longer-lasting diuretic action of torasemide compared with furosemide [12]. In both cats and dogs, a diuretic effect was observed 12 hr after the administration of torasemide, whereas the effect of furosemide diminished at 5–6 hr. These pharmacological properties of torasemide may be beneficial, not only in congestive heart failure, but also in other forms of edema in cats and dogs.

Torasemide has a diuretic profile similar to the combina-
tion of a diuretic and a potassium-sparing drug [13]. In combination therapy, spironolactone depresses the enhanced potassium excretion caused by furosemide or trichlormethiazide in a dose-dependent manner [13]. The potassium loss with torasemide is lower than with furosemide, despite similar aquaresis and natriuresis [5, 14]. Torasemide causes significant, dose-dependent inhibition of the amount of receptor-bound aldosterone, whereas furosemide has no effect on aldosterone receptors [14]. This may explain the decreased urinary potassium with torasemide. In addition, torasemide inhibits aldosterone secretion from adrenal cells in vitro [6]. In the cat study, aquaresis, natriuresis, and kaliuresis were similar with torasemide and furosemide, while in the control dogs, less kaliuresis was observed compared with placebo. A decrease in urinary potassium with torasemide may require administration for several days, because kaliuresis with a single torasemide dose did not differ from placebo in cats or dogs, whereas kaliuresis was not observed after administration for 7 days in control and MR dogs.

Furosemide increased plasma angiotensin II in MR dogs, but there was no change in control dogs. Since no edema was seen in the MR dogs, the diuresis caused by furosemide may reduce the circulatory blood volume and renal blood flow, stimulating the renin-angiotensin system [15]. This suggests that the use of diuretics should depend on the degree of edema and they should be used in combination with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Torasemide increased both plasma angiotensin II and aldosterone. The increase in angiotensin II is due to decreased circulatory blood volume, as with furosemide, while the increased in aldosterone might occur because torasemide prevents circulatory aldosterone from binding to its receptor, just as receptor blockers and enzyme inhibitors increase the receptor agonist or substrate [10, 18].

In conclusion, the diuretic effects of torasemide were about 10 times greater at same dose and longer lasting than those of furosemide in cats and dogs. Torasemide administration for several days makes the decrease of urine potassium. These results suggest that torasemide is useful for treating congestive heart failure and edema in cats and dogs.

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