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DIURETIC DOSE EQUIPOTENCY BETWEEN TORASEMIDE AND FUROSEMIDE IN HEALTHY DOGS
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OBJETIVOS DEL TRABAJO / OBJECTIVES OF THE STUDY
Furosemide is the only loop diuretic recommended for the treatment of congestive heart failure in dogs by the 2009 ACVIM consensus guidelines¹ for the diagnosis and treatment of canine chronic valvular heart disease. Loop diuretics increase water and salt renal excretion. In dogs with congestive heart failure, they relieve the patient from clinical signs of pulmonary edema and/or ascites and effusions. Torasemide was developed as a new loop diuretic drug for the treatment of congestive heart failure in dogs. Torasemide has a higher bioavailability, longer half-life and suggested myocardial anti-fibrotic effects which makes it a potential good diuretic for congestive heart disease in dogs²⁻³. Given the historical importance of furosemide in this indication, it is important to know the potency conversion factor between both drugs regarding the diuretic activity. The objective of the study was to determine an equipotent dose of torasemide versus furosemide. As there is no validated animal model for this chronic disease, healthy dogs were used as surrogates.

MATERIAL Y MÉTODO / MATERIAL AND METHODS
Eight healthy beagle dogs aged 11 to 17 months and weighing 10.9 to 16.7 kg at start of dosing received single oral doses of furosemide (0.5, 1.5, 3, 6, 10 mg/kg) and single oral doses of torasemide (0.1 and 0.6 mg/kg) in a Latin square cross-over design with 1 dog receiving no drug on each session (control group). A wash out period of 7 days was observed between each administration. As the maximal diuretic effect of furosemide was not reached, 2 additional doses (20 and 40 mg/kg) of furosemide were given to all dogs as a parallel design with the highest dose (40 mg/kg) being administered after a wash out period of 32 days. Animals were placed in metabolic cages 24 hours prior to drug administration (baseline) and remained there for 24 hours post dosing. Each session was divided into baseline and post-dose urine collections. At the end of baseline period, the urinary bladder of each animal was emptied by abdominal palpation and the collected volume (if any) was added to the last sample collected. Oral water loading corresponding to 3 % of bodyweight was performed for each animal, followed by urinary bladder emptying after one hour, immediately prior treatment. Twenty-four hours after drug administration, the urinary bladder of each animal was emptied again by abdominal palpation and the collected volume (if any) was added to the last sample collected. Total excreted urine volume (TEUV) over 24 hours after administration was used as a primary endpoint. The urine volume normalized by the bodyweight (TEUV/kg) and the increase percentage of urine relative to baseline (TEUV%) were other primary endpoints. The obtained mean TEUV values after furosemide dosing were fitted using the following E_max model: \( E = E_0 + \left(\frac{E_{\text{max}} \cdot D}{D + E_{50}}\right) \) with \( E \) being the mean TEUV value obtained after administration of dose \( D \). Basic model parameters (\( E_0 \), \( E_{\text{max}} \) and \( E_{50} \)) were calculated using the Phoenix WinNonlin software. With the calculated model, mean TEUV values obtained after torasemide dosing were used to back calculate the equipotent furosemide dose. The same \( E_{\text{max}} \) model was used with TEUV/kg values. With mean TEUV% values, the \( E_{\text{max}} \) model without \( E_0 \) was used.

RESULTADOS / RESULTS
No abnormal clinical signs were observed throughout the study. Decreased appetite was observed for the highest dose group of furosemide (40 mg/kg) compared to the control group. Water consumption increased in all treated groups except for the lowest furosemide group (0.5 mg/kg) and was proportional to urine output. The mean TEUV of all baseline values was 190.8 mL with a standard deviation (sd) of 21.98 mL. After the lowest dose of furosemide (0.5 mg/kg) TEUV was 460.5 mL (sd = 110.3 mL) and it was 1627 ml (sd = 191.9 mL) after the dose of 20 mg/kg. The highest furosemide dose (40 mg/kg) resulted in a TEUV of 1591 mL (sd = 232.8 mL) showing that the maximal diuretic effect was reached at...
the dose of 20 mg/kg. The mean TEUV values increased in a dose dependent manner between 0.5 and 20 mg/kg. The mean TEUV after a dose of 0.1 mg/kg of torasemide was 684.6 mL (sd = 228.4 mL) and was 1362 mL (sd = 233.7 mL) after the dose of 0.6 mg/kg. Results are summarized in Figure 1. The obtained $E_{\text{max}}$ model parameters were the following: $E_0 = 386.4$ mL, $E_{\text{max}} = 1578$ mL and $ED_{50} = 9.12$ mg/kg. Using the mean TEUV after a dose of 0.1 mg/kg of torasemide resulted in an equipotent furosemide dose of 2.13 mg/kg. With the mean TEUV obtained after a torasemide dose of 0.6 mg/kg, the resulting equipotent furosemide dose was 14.7 mg/kg. Using the mean TEUV/kg values obtained after a dose of 0.1 and 0.6 mg/kg of torasemide, the equipotent furosemide doses were 2.28 and 14.7 mg/kg respectively. The mean TEUV% values did not fit very well to the $E_{\text{max}}$ model. However, using the TEUV% obtained after a torasemide dose of 0.1 mg/kg resulted in an equipotent furosemide dose of 1.61 mg/kg. Using the TEUV% values obtained after a torasemide dose of 0.6 mg/kg resulted in an aberrant equipotent furosemide dose.

CONCLUSIONES / CONCLUSIONS
Thus in healthy dogs a single oral torasemide dose is about 20 times more potent than a single oral furosemide dose for inducing diuresis. This potency difference has to be taken into account when switching from furosemide to torasemide for the treatment of clinical signs of congestive heart failure. As this result was obtained in healthy dogs after a single oral dose, for dogs suffering from congestive heart failure, other considerations (tolerance, disease status…) should also be taken into account.

BIBLIOGRAFÍA / BIBLIOGRAPHY