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Short- and long-term effects of hydrochlorothiazide in dogs with relapsing congestive heart failure due to myxomatous mitral valve disease: a retrospective analysis of 38 cases

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KEYWORDS
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Diuretic resistance;
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Abstract *Introduction/Objectives:* Information on the use of hydrochlorothiazide (HCTZ) in dogs with relapsing congestive heart failure (CHF) due to myxomatous mitral valve disease (MMVD) is limited. Therefore, the aim of this study was to provide data on HCTZ's short- and long-term effects in canine MMVD.
Animals, Materials and Methods: Signalment, clinical, diagnostic, therapeutic, and outcome data of dogs with relapsing CHF due to MMVD treated with HCTZ were retrospectively reviewed. The initial time point was the day HCTZ was introduced for a CHF relapse. Optimized criteria were used to determine the appropriate timings for evaluating HCTZ's short-term effects on laboratory and echocardiographic variables and its long-term impact on CHF management.
Results: Thirty-eight dogs were included. The initial median dose of HCTZ was 0.8 mg/kg/die. At a median of seven days after HCTZ prescription, creatinine, urea, and total calcium levels significantly increased, while sodium and potassium levels significantly decreased (P: from 0.045 to <0.0001). While no dog developed severe electrolyte abnormalities, some dogs showed severe increases in creatinine

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and urea. After a median of 95 days, no significant echocardiographic changes developed (P: from 0.74 to 0.13). Episodes of CHF were more frequent before (median: one every 68 days) than after (median: one every 124 days) HCTZ prescription (P=0.006).
Study Limitations: The study limitations included the retrospective design of the study; not all dogs were included both in the short- and long-term analysis.
Conclusions: In canine MMVD, HCTZ is useful in long-term management of relapsing CHF. However, in the short term, HCTZ can cause laboratory abnormalities, primarily increased creatinine and urea.

Abbreviations

CHF	congestive heart failure
CKD	chronic kidney disease
HCTZ	hydrochlorothiazide
MMVD	myxomatous mitral valve disease
RI	reference interval
T0	timing of hydrochlorothiazide prescription
$T1_{echo}$	timing of the first echocardiographic recheck used for the short-term analysis
$T1_{lab}$	timing of the first serum biochemistry recheck used for the short-term analysis
T2	timing of the last recheck used for the long-term analysis

Introduction

Congestive heart failure (CHF) is the most common complication of canine heart diseases, including myxomatous mitral valve disease (MMVD) [1—5]. In dogs with this condition, diuretic therapy is essential to improve quality of life and prolong survival. Loop diuretics are the first-choice treatment as they are generally effective in controlling CHF symptoms in most dogs due to their ability to improve diuresis by blocking the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the Henle loop (which accounts for ~25—30% of the re-absorption of filtered sodium from glomerular membranes) [1—6]. However, some dogs continue to experience CHF relapses despite progressively increasing doses of loop diuretics [1—5]. For managing these cases, one therapeutic option is to combine loop diuretics with other diuretic classes to target different sites within the nephron, thus enhancing diuresis. Among the various diuretics that can be used for this purpose is hydrochlorothiazide (HCTZ), which belongs to the thiazide diuretic class [1—7]. Hydrochlorothiazide works primarily by inhibiting the electroneutral sodium-chloride cotransporter on the luminal side of the distal convoluted tubule, which accounts for ~5—8% of the filtered sodium present in the tubular fluid [1,4,6,7]. Consequently, as the sodium concentration increases in the tubule, an osmotic gradient develops, causing more water to be excreted in the urine [1,7].

Although HCTZ is generally assumed to be beneficial as an adjunct to loop diuretics to treat relapsing CHF in dogs [1—4] and is frequently cited among drugs used in various veterinary reports [8—16], it is noteworthy that, to date, only one study has been published on its effects in dogs with naturally acquired CHF [17]. Furthermore, the sample size of that study was small (14 animals) and the follow-up data, including information related to possible side-effects and outcome related to treatment, were limited [17]. As a result, our knowledge of the actual efficacy and safety of HCTZ in dogs with CHF remains scarce.

Therefore, the aims of this study were to retrospectively evaluate a population of dogs with relapsing CHF due to MMVD that had been treated with HCTZ and to provide a detailed description of selected short- and long-term data.

Materials and methods

Study population

Cases of client-owned dogs seen between 2014 and 2024 that received oral HCTZ for the management of relapsing CHF due to MMVD, diagnosed according standard criteria (i.e. the presence of a left systolic apical heart murmur and thickened and/or prolapsing mitral valve leaflets on two-dimensional echocardiography associated with mitral valve regurgitation on color flow Doppler interrogation

[3]), were retrospectively searched in our databases. For the purposes of this study, only dogs with sufficient data from case records to provide information on the short- and/or long-term effects of HCTZ were included. For both types of analysis, a minimum of two evaluations was required for inclusion in the study, ensuring that data from at least two time points were available for each dog. For both short- and the long-term analyses, the initial time point (T0) was the day HCTZ was prescribed for the first time due to a relapse of CHF. Subsequently, different timings were considered for the investigation of the short- and long-term effects of HCTZ.

Short-term analysis

For the short-term analysis, two different time points after T0 were considered: the time of the first recheck after prescribing HCTZ that included a serum chemistry profile ($T1_{lab}$) and the time of the first recheck after prescribing HCTZ that included echocardiography ($T1_{echo}$). These timings were chosen to improve precision in attributing potential laboratory and echocardiographic effects to the drug. This decision was based on the assumption that the longer the time that passes, the greater the likelihood of additional confounding factors arising, which could complicate attributing laboratory and echocardiographic changes to HCTZ. Furthermore, it is important to specify that only dogs with no other therapy changes between T0 and $T1_{lab}$, as well as T0 and $T1_{echo}$, except those related to HCTZ, were included in the short-term analysis. This approach was taken to further optimize the interpretation of the short-term effects of HCTZ on laboratory and echocardiographic variables by avoiding potential interference from other drugs.

Long-term analysis

For the long-term analysis (T2), two different time points were considered based on the progression of the cardiovascular therapeutic plan. If no changes other than those related to HCTZ occurred after its prescription, the timing of the last available recheck (for dogs alive at the end of the study) or the time of death (for dogs that had died before the study's conclusion) was considered. However, if adjustments in other cardiovascular drugs occurred after the HCTZ prescription (e.g. an increase in the dose of furosemide or torasemide or a switch from furosemide to torasemide), the time of the last available recheck before such a therapeutic change was purposely considered. This approach was chosen to optimize the interpretation of the long-term effects of HCTZ on CHF management by avoiding potential interference from other drugs. For the purposes of the long-term analysis, adjustments in HCTZ administration (i.e. dose increases or decreases and temporary interruptions lasting $\leq$14 days) were allowed. However, dogs in which HCTZ was permanently discontinued were excluded from this analysis.

Analyzed data

For dogs that met the inclusion criteria, four operators (G. R., C. M., C. V., and H. P.) reviewed medical records to retrieve selected data, including signalment; the number of dogs with left, right, or bilateral CHF; the number of CHF episodes documented before HCTZ prescription; type and dose of cardiovascular drugs prescribed before HCTZ; the number and type of concomitant systemic diseases; daily dose and frequency of administration of HCTZ (i.e. twice daily, once daily, and every other day); the time from the first CHF episode to HCTZ prescription; serum concentrations of selected laboratory variables (details below) obtained from the most recent serum chemistry profile performed before HCTZ prescription and at $T1_{lab}$; the time between HCTZ prescription and $T1_{lab}$; selected echocardiographic variables (details below) obtained from the most recent echocardiography performed prior to HCTZ prescription and at $T1_{echo}$; the time between HCTZ prescription and $T1_{echo}$; the number of CHF episodes documented after HCTZ prescription; the number of dogs for which the HCTZ dose was increased, decreased, or discontinued over time; reasons for dose reduction and interruption; type of possible clinical signs that developed at the time of dose reduction/interruption; duration of each interruption; and outcome data. For the outcome analysis, the dogs were classified as alive, deceased from cardiac-unrelated causes, or deceased from cardiac-related causes. The latter was also classified as sudden death, CHF, or euthanasia because of worsening cardiac condition [15,18]. The time in days from T0 to the last available follow-up and death was recorded for any dog alive at the end of the study and for deceased dogs, respectively.

Serum chemistry variables

In light of the potential hematologic effects of HCTZ reported in the human and veterinary literature (e.g. azotemia and electrolyte imbalances) [1–4,6,7], particular attention was paid to reviewing serum concentrations of total protein,

Table 1 Specific laboratory variables and relevant cut-offs used in this study to classify normal values and mild, moderate, and severe abnormalities.

Variable	RI	Abnormality	Mild	Moderate	Severe
Total protein (mg/dL)	5.6–7.3	Decrease	4.8–5.5	3.9–4.7	<3.9
		Increase	7.4–8.3	8.4–9.5	>9.5
Albumin (g/dL)	2.75–3.85	Decrease	2–2.74	1.5–1.99	≤1.49
		Increase	3.86–4.4	4.5–5	>5
Creatinine (mg/dL)	0.75–1.4	Increase	1.41–1.59	1.6–2.5	>2.5
Urea (mg/dL)	17–48	Increase	49–69	70–203	>203
Sodium (mEq/L)	143–151	Decrease	133–142	132–128	≤127
		Increase	152–161	162–166	≥167
Potassium (mEq/dL)	3.8–5	Decrease	3.3–3.7	2–3.2	<2
		Increase	5.1–5.9	6–6.9	≥7
Calcium (mg/dL)	9.3–11	Decrease	8–9.2	7.5–7.9	<7.5
		Increase	11.1–12	12.1–14	>14

RI: reference interval.

albumin, creatinine, urea, sodium, potassium, and total calcium. These values were obtained from the most recent serum chemistry profile performed prior to the prescription of HCTZ and at $T1_{lab}$. The variables were compared with the relevant hospital reference intervals (RIs) to identify potential abnormalities. Whenever a variable fell below or exceeded the relevant RI, the abnormality was classified as mild, moderate, or severe according to the available veterinary literature; when veterinary data were unavailable, the human medical literature was consulted [19–26]. If multiple veterinary references were available for classifying abnormalities for a specific variable, an effort was made to select the most appropriate one in light of the type of animals included in this study (e.g. to characterize acute kidney compromise that could occur in the short term after HCTZ administration, a previously proposed modified classification system for kidney injury, based solely on creatinine concentration, was used [22]). Lastly, if neither veterinary nor human medical literature provided guidance for classification, cut-off points were purposefully established adapting general recommendations applied to some variables in human medicine.[d] According to this approach, abnormalities for which no specific references were available in literature were defined as mild, moderate, or severe when the measured values were below or above the relevant lower or upper RI by up to 15%, 15–30%, or more than 30%, respectively. The specific RIs for the variables investigated in this study, along with pertinent cutoffs for classifying laboratory abnormalities, are reported in Table 1.

Echocardiographic variables

In light of the potential echocardiographic effects of HCTZ cited in the human and veterinary literature (e.g. reduction in the dimensions of the left cardiac chambers) [17,27], the most recent echocardiography performed prior to the prescription of HCTZ and the one obtained at $T1_{echo}$ were reviewed. For the purpose of this study, particular attention was paid to the review of the following echocardiographic variables: left ventricular end-diastolic and end-systolic diameters normalized for body weight, left ventricular end-diastolic and end-systolic volumes indexed to body surface area, and the left atrium-to-aorta ratio [28–30]. In each dog, echocardiographic examinations and measurements were reviewed by the previously mentioned operators.

Statistical analysis

Statistical analysis was performed using commercially available statistical software.[e] All continuous variables were checked graphically, and their distribution was checked using the Shapiro-Wilk test. Descriptive statistics included the report of mean ± standard deviation and median and interquartile range (25th–75th quartile) for normally and non-normally distributed data, respectively. The Wilcoxon signed-rank test and the paired *t*-test were used to compare data

[d] Common Terminology Criteria for Adverse Events. Version 5. Published: November 27, 2017. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

[e] Prism 10.3.1, GraphPad Software, San Diego, U.S.A.

between different time points. P values<0.050 were considered statistically significant.

Results

Study sample

Forty-six dogs received HCTZ during the study period. However, eight dogs were not included due to incomplete data records or because they received HCTZ for the management of a heart disease different from MMVD. Therefore, the study sample ultimately included 38 dogs. The demographic and clinical characteristics of the study population are reported in Table 2. Table 2 also provides details on cardiovascular therapies used before prescribing HCTZ. All dogs received a loop diuretic before study inclusion; this was either furosemide (administered twice daily and three times daily in 14/22 [63.6%] and 8/22 [34.4%] dogs, respectively) or torasemide (administered once daily and twice daily in 1/16 [6.2%] and 15/16 [93.8%] dogs, respectively). Furthermore, in all cases, the loop diuretic was combined with at least two other cardiovascular drugs, one of which was

Table 2 Selected demographic, clinical, and therapeutic data of the dogs at the time of study inclusion.

Variable	
Number of dogs	38
Age (years)	11.3 (9.8—13)
Body weight (kg)	9.2 (7.1—13.8)
Sex (M/F)	30/8
Breed	Mixed breed (13 dogs) Dachshund (five dogs) Cavalier King Charles spaniel (four dogs each) Pinscher (three dogs each) Chihuahua, Jack Russell, and Poodle (two dogs each) American Staffordshire terrier, Basset hound, Cocker spaniel, English pointer, German shepherd dog, Golden retriever, and Italian hound pointer (one dog each)
Concomitant arrhythmias (Y/N)	20/18
Type of arrhythmias	Atrial fibrillation (11 dogs) Ventricular tachyarrhythmias (five dogs) Focal atrial tachycardia (four dogs)
Congestive heart failure (L/R/B)	29/3/6
Type of cardiovascular drug prescribed before the introduction of HCTZ and relative dose (range)	Pimobendan (38 dogs): 0.68 mg/kg/day (0.5—0.9 mg/kg/day) Furosemide (22 dogs): 6.1 mg/kg/day (5.5—8.1 mg/kg/day) Benazepril (22 dogs): 0.44 mg/kg/day (0.31—0.58 mg/kg/day) Spironolactone (20 dogs): 2 mg/kg/day (1.5—2.73 mg/kg/day) Torasemide (16 dogs): 0.8 mg/kg/day (0.7—1.46 mg/kg/day) Digoxin (10 dogs): 10 μg/kg/day (7—13.5 μg/kg/day) Amiodarone (seven dogs): 7.5 mg/kg/day (6.55—11.53 mg/kg/day) Diltiazem (seven dogs): 2.5 mg/kg/day (2.25—4.1 mg/kg/day) Sotalol (two dogs): 4 mg/kg/day and 5 mg/kg/day Amlodipine (one dog): 0.2 mg/kg/day Enalapril (one dog): 0.54 mg/kg/day Sildenafil (one dog): 4.6 mg/kg/day
Systemic diseases (Y/N)	25/13
Number of concomitant systemic diseases	One systemic disease (13 dogs) Two systemic diseases (eight dogs) Three systemic diseases (four dogs)
Type of systemic diseases	Chronic enteritis/gastroenteritis (16 dogs) CKD (IRIS stages 1 and 2) (12 dogs) Chronic cholangitis/cholangiohepatitis (nine dogs) Medically controlled hyperadrenocorticism (two dogs) Medically controlled leishmaniasis and pheochromocytoma (one dog each)

B: biventricular; CKD: chronic kidney disease; F: female; HCTZ: hydrochlorothiazide; IRIS: International Renal Interest Society; L: left; M: male; MMVD: myxomatous mitral valve disease; R: right.

always pimobendan. Additionally, eight of 38 (21.1%) dogs received four or more cardiovascular drugs in conjunction with the loop diuretic. Despite this, the management of CHF was considered unsatisfactory, with a median of three (two to four) CHF episodes occurring prior to the prescription of HCTZ. Taking into account the frequency of CHF episodes over time, a median of one episode every 68 days (23—147 days) was documented before prescribing HCTZ. This value was calculated by dividing the number of CHF episodes by the days between the first CHF episode and T0. The median time from the first CHF episode to the HCTZ prescription was 176 days (85—370 days). Taking into account the doses of HCTZ prescribed across the entire study sample, the median initial daily dose was 0.8 mg/kg (0.6—1.5 mg/kg). Hydrochlorothiazide was administered twice daily in 14 of 38 (36.9%) dogs, once daily in 17 of 38 (44.7%) dogs, and once every other day in seven of 38 (18.4%) dogs.

Short-term analysis—serum chemistry variables

Six of the 38 dogs (15.8%) were excluded from the short-term analysis of serum chemistry variables due to the absence of a recheck with bloodwork or changes in other cardiovascular therapies after the HCTZ prescription. Therefore, this analysis ultimately included 32 of 38 (84.2%) dogs. Among these dogs, the median number of serum chemistry rechecks performed up to the last available follow-up or death was 3 (1—7). When considering only the first serum chemistry recheck after prescribing HCTZ, the median time between T0 and $T1_{lab}$ was seven days (5—22 days). No dog included in the short-term analysis of serum chemistry variables developed clinical signs related to the occurrence of new diseases between T0 and $T1_{lab}$, except for one dog that developed a tooth root abscess. Table 3 provides details on laboratory abnormalities documented before prescribing HCTZ and at $T1_{lab}$. A comparison of serum chemistry findings obtained at the two time points revealed a significant increase in creatinine, urea, and calcium, as well as a significant decrease in sodium and potassium (Table 4).

Short-term analysis—echocardiographic variables

Fourteen of the 38 dogs (36.8%) were excluded from the short-term analysis of echocardiographic variables due to the absence of a recheck with echocardiography or changes in other cardiovascular therapies after the prescription of HCTZ. Therefore, this analysis ultimately included 24 of 38 (63.2%) dogs. The median time between the HCTZ prescription and $T1_{echo}$ was 95 days (63—152 days). No dog included in the short-term analysis of echocardiographic variables developed clinical signs related to the occurrence of new diseases or the worsening of already known diseases between T0 and $T1_{echo}$, except for the previously mentioned dog that developed a tooth root abscess. No significant differences were found when comparing echocardiographic findings obtained before prescribing HCTZ and at $T1_{echo}$ (Table 5).

Long-term analysis

Over time, the HCTZ dose was modified in 10 of 38 (26.3%) dogs. Specifically, the dose was increased in eight of 10 (80%) dogs, reaching a median final daily dose of 1.4 mg/kg (0.8—2.4 mg/kg). In six of these dogs, the final dose was divided into two daily administrations, while two dogs received it once daily. In the remaining two of 10 (20%) dogs, the HCTZ dose was decreased. Both dose reductions were made upon detecting an increase in creatinine and urea along with an extracardiac sign deemed clinically relevant in the context of the dogs' entire medical history, justifying the therapeutic change based on the cardiologist's judgment. Specifically, the first case involved a dog with underlying chronic gastroenteritis and stage 1 chronic kidney disease (CKD), who was initially receiving HCTZ at a dose of 0.5 mg/kg twice daily. This was in combination with torasemide (0.7 mg/kg/day) and three other cardiovascular drugs aimed at managing CHF. After the prescription of HCTZ, the dog experienced a mild increase in creatinine and urea, accompanied by a decrease in appetite. This led to a reduction in the HCTZ dose to 0.5 mg/kg once daily. The second case involved a dog with underlying stage 1 CKD, who was initially receiving HCTZ at a dose of 0.8 mg/kg twice daily. This was in combination with torasemide (0.6 mg/kg/day) and two other cardiovascular drugs aimed at managing CHF. After the prescription of HCTZ, the dog developed a tooth root abscess and experienced a moderate increase in creatinine and urea, associated with a decrease in appetite. This led to a reduction in the HCTZ dose to 0.8 mg/kg once daily.

Additionally, HCTZ administration was discontinued in five of 38 (13.2%) dogs. This therapeutic choice was made at the time of detection

Table 3 Laboratory abnormalities from the most recent serum chemistry performed before prescribing hydrochlorothiazide (pre-HCTZ) and the first one conducted after the introduction of the drug ($T1_{lab}$).

Variable	No. of dogs with abnormalities pre-HCTZ		No. of dogs with abnormalities at $T1_{lab}$		No. of dogs with new onset of abnormalities	
Total protein	Decrease (total = 5) Mild = 5	Increase (total = 4) Mild = 4	Decrease (total = 3) Mild = 3	Increase (total = 7) Mild = 6 Moderate = 1	Decrease = 0	Increase = 4
Albumin	Decrease (total = 7) Mild = 7	Increase (total = 1) Mild = 1	Decrease (total = 3) Mild = 3	Increase (total = 1) Mild = 1	Decrease = 0	Increase = 1
Creatinine	Increase (total = 11) Mild = 3 Moderate = 7 Severe = 1		Increase (total = 20) Mild = 2 Moderate = 13 Severe = 5		Increase = 9	
Urea	Increase (total = 19) Mild = 6 Moderate = 12 Severe = 1		Increase (total = 25) Mild = 2 Moderate = 16 Severe = 7		Increase = 6	
Sodium	Decrease (total = 5) Mild = 4 Moderate = 1	Increase (total = 2) Mild = 2	Decrease (total = 15) Mild = 14 Moderate = 1	Increase (total = 1) Mild = 1	Decrease = 12	Increase = 1
Potassium	Decrease (total = 11) Mild = 11	Increase (total = 1) Mild = 1	Decrease (total = 18) Mild = 14 Moderate = 4	Increase (total = 0) —	Decrease = 11	Increase = 0
Calcium	Decrease (total = 0) —	Increase (total = 0) —	Decrease (total = 0) —	Increase (total = 2) Mild = 2	Decrease = 0	Increase = 2

The second and third columns of the table present the absolute number of cases in which laboratory abnormalities were documented pre-HCTZ and at $T1_{lab}$, respectively. The fourth column provides information on the fluctuation of abnormalities over time by comparing the laboratory parameters documented for each dog pre-HCTZ and at $T1_{lab}$. This approach considers cases in which a laboratory value fell within the relevant reference interval (RI) both pre-HCTZ and at $T1_{lab}$, fell below or exceeded the relevant RI both pre-HCTZ and at $T1_{lab}$, fell below or exceeded the relevant RI pre-HCTZ but then fell within the RI at $T1_{lab}$, and fell within the relevant RI pre-HCTZ but then fell below or exceeded the RI at $T1_{lab}$. In this way, a picture of the laboratory abnormalities that actually developed after HCTZ prescription is provided.
RI: reference interval.

Table 4 Comparison of the values from the most recent serum chemistry performed before prescribing hydrochlorothiazide (pre-HCTZ) and the first one conducted after the introduction of the drug ($T1_{lab}$).

Variable	Pre-HCTZ	$T1_{lab}$	P
Total proteins (mg/dL)	6.5 ± 0.8	6.6 ± 0.9	0.48
Albumin (g/dL)	3.1 (2.8—3.4)	3.3 (3—3.5)	0.43
Creatinine (mg/dL)	1.3 (1—1.6)	1.7 (1.2—2.1)	**0.044**
Urea (mg/dL)	72 (56—93)	129 (100—178)	**<0.0001**
Sodium (mEq/L)	146 ± 4.4	143 ± 5	**0.02**
Potassium (mEq/dL)	4.1 ± 0.5	3.8 ± 0.5	**0.03**
Calcium (mg/dL)	10.5 ± 0.5	11.2 ± 0.3	**0.045**

Normally and non-normally distributed data are reported as mean ± standard deviation and median (25th—75th quartile), respectively. In bold: values with statistical differences.

Table 5 Selected findings from the most recent echocardiography performed before prescribing hydrochlorothiazide (pre-HCTZ) and the first one conducted after the introduction of the drug ($T1_{echo}$).

Variable	Pre-HCTZ	$T1_{echo}$	P
LVIDDn	2.2 (2.06—2.42)	2.18 (1.86—2.39)	0.62
LVISDn	1.26 (1.16—1.39)	1.15 (1.01—1.24)	0.19
EDVI (mL/m^2)	170 (137—204)	188 (150—214)	0.74
ESVI (mL/m^2)	42 (37—57)	40 (28—46)	0.53
LA/Ao	2.5 ± 0.5	2.6 ± 0.4	0.13

Normally and non-normally distributed data are reported as mean ± standard deviation and median (25th—75th quartile), respectively.
EDVI: left ventricular end-diastolic volume indexed to body surface area; ESVI: left ventricular end-systolic volume indexed to body surface area; LA/Ao: left atrium-to-aorta ratio; LVIDDn; left ventricular end-diastolic systolic diameter normalized for body weight; LVISDn: left ventricular end-systolic systolic diameter normalized for body weight.

of an increased creatinine and urea. Also in this case, these increases were associated with extracardiac signs deemed clinically relevant in the context of the dogs' entire medical history, justifying the therapeutic change based on the cardiologist's judgment. Specifically, all these dogs had underlying extracardiac diseases, including chronic gastroenteritis in two cases; chronic cholangiohepatitis in one case; stage 1 CKD in one case; and an association of chronic gastroenteritis, chronic cholangiohepatitis, and stage 2 CKD in the remaining case. Before the prescription of HCTZ, three of these dogs were receiving a combination of furosemide (mean dose of 8 mg/kg/day) and three cardiovascular drugs aimed at managing CHF. The remaining two dogs were receiving torasemide (doses of 0.6 mg/kg/day and 0.7 mg/kg/day), which was associated with two other cardiovascular drugs aimed at managing CHF in one case and three in the other one. The increase in creatinine was mild in four cases and moderate in the remaining one. The increase in urea was moderate in four cases and severe in the remaining one. Concomitant clinical signs included anorexia in two dogs; decreased appetite and diarrhea in one dog; depressed mentation and decreased appetite in one dog; and depressed mentation, decreased appetite, and diarrhea in the remaining dog. The HCTZ interruption was temporary in two dogs as it was re-introduced once extracardiac signs resolved (after 10 and 14 days, respectively). In contrast, HCTZ was not re-introduced in the remaining three dogs, and these dogs were excluded from the long-term analysis of HCTZ effects on CHF management. An additional 14 dogs were excluded from the long-term analysis due to changes in other cardiovascular therapies after HCTZ prescription. As a result, the long-term analysis ultimately included 21 of 38 (55.3%) dogs.

The median number of CHF episodes documented between T0 and T2 was 1 (0—2). Considering the frequency of CHF episodes after the prescription of HCTZ, a median of one episode every 124 days (56—198 days) was documented between T0 and T2. Comparing findings obtained at T0 with those at T2, both the number of CHF episodes and the frequency of CHF episodes decreased significantly after HCTZ prescription ($P \leq 0.0001$ and 0.006, respectively).

Outcome

At the end of the study, three of 38 (7.9%) dogs were alive, while 35 of 38 (92.1%) had died. Among the living dogs, the median time from HCTZ prescription to the last available follow-up was 283 days (149—385 days). Among the deceased dogs, cardiac-unrelated and cardiac-related deaths were documented in five of 35 (14.3%) and 24 of 35 (68.6%) dogs, respectively. In the remaining six of 35 (17.1%) cases, the exact cause of death could not be conclusively established due to the retrospective nature of the study. Cardiac-unrelated deaths were all represented by euthanasia; this was due to neurological compromise/complications in two dogs, progressive worsening of renal function in two dogs with CKD, and complications associated with pancreatitis in the remaining dog. Cardiac-related deaths were predominantly represented by euthanasia (15/24 [62.5%] dogs); the remaining cases included sudden death (7/24 [29.2%] dogs) and CHF (2/24 [8.3%] dogs). The median time from HCTZ prescription to death was 131 days (43—242 days).

Discussion

This study provides a comprehensive evaluation of HCTZ use in dogs with relapsing CHF due to naturally acquired heart disease.

Our analysis of the effects of HCTZ on serum chemistry variables yielded interesting results that enhance our understanding of the short-term hematologic effects of this drug in dogs. In particular, the significant increase in creatinine and urea after HCTZ prescription deserves attention. This finding is generally consistent with the only previous veterinary study focused on the use of HCTZ in dogs with CHF [17], as well as with several publications in human medicine [6,7,31—34]. The increase in creatinine and urea is primarily attributed to the intrinsic mechanism of HCTZ, which increases water elimination through urine, thereby promoting volume depletion and, in some cases, leading to prerenal azotemia [6,7,31—33]. Second, after the prescription of HCTZ, we observed a significant decrease in sodium levels. This finding aligns with reports in human medicine, where HCTZ is one of the most common causes of drug-induced hyponatremia, with up to 14—30% of patients treated with thiazides becoming hyponatremic [31,35—39]. Although several mechanisms have been hypothesized to contribute to the pathogenesis of thiazide-induced hyponatremia, two are considered the most relevant. One is related to the primary mechanism of action of this class of drugs as thiazides inhibit sodium reabsorption in the distal renal tubule [36,37,40]. The other mechanism is associated with volume depletion due to natriuresis, which leads to secondary non-osmotic vasopressin secretion, ultimately contributing to dilutional hyponatremia [36,37,40]. Third, the prescription of HCTZ was followed by a significant decrease in potassium levels and a significant increase in calcium levels. These results are not surprising when considering findings from human medical literature; indeed, hypokalemia and hypercalcemia have been documented in 7—56% [41—43] and up to ~2% of patients treated with HCTZ [44,45], respectively. Hypokalemia primarily occurs due to increased sodium delivery to the distal tubule, caused by inhibition of the sodium-chloride cotransporter in the distal convoluted tubule by HCTZ. Then, in the collecting duct, sodium is exchanged for potassium, leading to increased potassium excretion [46]. Additionally, the volume depletion caused by HCTZ can activate the renin-angiotensin-aldosterone system, leading to increased potassium excretion in the collecting ducts due to aldosterone [46]. The inhibition of the sodium-chloride cotransporter also explains the risk of developing hypercalcemia as it leads to increased sodium delivery to the distal tubule and volume depletion. In response to this, increased calcium re-absorption occurs in the distal convoluted tubule through the activation of the sodium-calcium exchanger on the basolateral membrane of the tubular cells. As a result, hypocalciuria and hypercalcemia may develop [47].

Although the significant fluctuations of the aforesaid laboratory parameters might suggest a comparable clinical relevance at first glance, we believe that our results indicate a different interpretation. Let us take, for example, the electrolytes we analyzed. Despite the comparison of relative findings obtained before prescribing HCTZ and at $T1_{lab}$ documented a significance difference, no dog developed severe electrolyte imbalances in the short term and most had only mild abnormalities. In contrast, a different pattern was observed for renal values. In fact, at $T1_{lab}$, only a small proportion of dogs had a mild increase in creatinine and urea, while the majority showed moderate to severe increases. Additionally, seven dogs became symptomatic after the prescription of HCTZ, predominantly exhibiting gastrointestinal signs. When the dog that developed a tooth root abscess was excluded from this analysis (as this condition was considered the most likely explanation for its decreased appetite), the remaining six

dogs had a clinical condition that could be potentially attributed to uremic syndrome. In light of our results, we consider it reasonable to perform regular monitoring of serum chemistry in dogs receiving HCTZ (as even evidenced by the number of serum chemistry rechecks performed in our study sample up to the last available follow-up or death), ideally starting within the first week after the prescription of this drug. Indeed, this approach may allow for the prompt identification of laboratory changes that may be interpreted as clinically relevant in the context of the dogs' entire medical history, regardless of the absolute numerical value (i.e. even if it cannot be classified as severe). An example of this scenario is dogs experiencing an increase in creatinine after HCTZ prescription that also develop signs such as anorexia or diarrhea. Indeed, this represents a potentially risky association, where the clinical signs are likely the most worrisome factor as they may further increase the risk of exacerbating volume depletion and prerenal azotemia.

Our short-term analysis of the effects of HCTZ on echocardiographic variables demonstrated no significant changes in the dimensions of left-sided cardiac chambers. This result contrasts with findings from the only previous study on the use of HCTZ in dogs with CHF [17] but aligns with part of the existing human medical literature. Indeed, in humans, HCTZ administration is unlikely to significantly decrease the dimensions of left-sided cardiac chambers in the short term, and a period longer than one year may be required to observe meaningful echocardiographic changes [27,48]. Our results may have been influenced not only by the HCTZ doses we administered and the timing of $T1_{echo}$ but also by the specific echocardiographic variables we evaluated. Indeed, although the echocardiographic variables we analyzed are among the most commonly used ones in canine cardiology to assess the dimensions of left-sided cardiac chambers [30,49], they were limited. Therefore, the fact that additional measurements might have revealed drug-induced echocardiographic changes cannot be excluded. Nevertheless, our findings may still be clinically useful. For example, they suggest that the short-term effects of HCTZ should not be assessed through echocardiographic evaluation of potential changes in the dimensions of left-sided cardiac chambers, especially when relying only on the echocardiographic variables reported here.

Our long-term analysis provided valuable data on the clinical effects of HCTZ, demonstrating improved control of CHF after the prescription of this drug, as indicated by a reduced number of CHF episodes and a longer interval between CHF relapses. Comparison of our findings with those of other studies involving dogs with naturally acquired heart diseases is limited by the lack of prior veterinary investigations specifically focused on the long-term effects of HCTZ on the management of canine CHF. However, some similarities emerge when comparing our results with data from human medicine. Indeed, different studies have demonstrated that adding HCTZ to standard treatments helps increase urine output and reduce body weight in patients with heart diseases, thereby improving the signs of congestion [6,34,50,51]. Knowledge of diuretic pharmacology and renal physiology is important to understand why the prescription of HCTZ in cases of relapsing CHF, despite ongoing loop diuretic administration, was effective in our study sample as well as in human medicine. The efficacy of combining loop diuretics with thiazides mainly relies on their synergistic effects as diuresis is enhanced by the simultaneous inhibition of sodium re-absorption at two distinct sites, contributing to the so-called 'sequential nephron blockade' [1,4,6]. The benefits provided by the addition of HCTZ become further evident if resistance to loop diuretics (i.e. failure to achieve relief from signs of CHF despite adequate doses of a loop diuretic) develops [6]. Diuretic resistance is a complex phenomenon to which both extrarenal and renal causes contribute and which is characterized by both functional and anatomical modifications primarily involving the renal tubules [1,5,6,52]. Although a detailed description of all mechanisms of diuretic resistance is beyond the scope of our report, it is important to consider that many causes of this phenomenon involve mechanisms of sodium re-absorption, which ultimately counteract the water loss promoted by loop diuretics [5,6,52]. Among these mechanisms, the predominant one is suspected to be the progressive hypertrophy and hyperplasia of epithelial cells in the distal tubule, which allows this site of the nephron to re-absorb more sodium than expected in healthy individuals [52]. This helps explain why adding thiazide diuretics, which inhibit sodium re-absorption in the distal tubule, is often the first-line choice to overcome diuretic resistance in humans [52] and is one of the proposed strategies in dogs with relapsing CHF [5].

A final consideration should be made regarding the HCTZ doses we administered. In this study, the median initial daily dose was 0.8 mg/kg, with only eight dogs having an increased dose over time, reaching a median final daily dose of 1.4 mg/kg. Although the HCTZ doses we administered were

generally lower than those reported in many veterinary books for the management of canine CHF (e.g. starting dose of 1—2 mg/kg once or twice daily, which can be increased up to 2—4 mg/kg twice daily) [1,2], the tendency to avoid relatively high doses is consistent with the only previous original study on the use of HCTZ in dogs with CHF (i.e. mean daily dose of 0.55 ± 0.19 mg/kg) [17], as well as with part of human medical literature [53]. In general, the rationale behind the choice of using relatively low doses is that, unlike loop diuretics, which are 'high-ceiling' diuretics, HCTZ is known to be a 'low-ceiling diuretic' [7,54]. In other words, while diuresis is expected to increase in a dose-dependent manner over a wide range of dosages with loop diuretics, the maximal diuretic response is typically achieved at relatively low dosages with thiazides [7,54]. This helps explain why, in many cases, a good clinical response was achieved without the need to prescribe relatively high doses of HCTZ, which do not necessarily lead to a linear increase in diuresis and may expose patients to drug-related side-effects. However, it should be considered that our study was not designed to define the ideal dose of HCTZ in the management of canine relapsing CHF, and this still needs to be conclusively defined in dogs with MMVD. Therefore, further studies are necessary to provide additional insights into this topic.

Limitations

This study has some limitations. First, the retrospective design precluded the standardization of the timing for diagnostic procedures and therapeutic interventions. Second, only a subset of dogs included in the study was analyzed for the short- and long-term assessments. However, it is worth noting that each subpopulation (i.e. the 32, 24, and 21 dogs considered at $T1_{lab}$, $T1_{echo}$, and T2, respectively) comprised more dogs than those included in the only previous study on the use of HCTZ in dogs with CHF [17]. Third, we did not evaluate the effects of HCTZ on electrolytes other than sodium, potassium, and calcium. Moreover, we did not assess acid-base status or perform urinalysis. Since changes in electrolytes other than those we investigated (e.g. hypomagnesemia), metabolic alkalosis, and urinary abnormalities (e.g. hypocalciuria) may develop in humans treated with HCTZ [55], further studies are needed to expand the analysis of laboratory changes associated with this drug in dogs. Fourth, given the design of this study, it was not possible to identify the potential risk factors associated with reduced tolerability of this drug. Therefore, further investigations are needed to provide clear evidence on this matter. Fifth, both short- and long-term results may have been influenced by the type of variables, relative cut-offs, and timings considered for the analyses, as well as the way we used HCTZ. Reasonably, the administration of this drug at different doses and/or for different durations could lead to different laboratory, echocardiographic, and clinical findings. Therefore, our results should be carefully contextualized in light of the specific characteristics of the study design and the sample of dogs.

Conclusions

Our results suggest that HCTZ is useful in the long-term management of dogs with relapsing CHF due to MMVD. At the same time, it is important to consider that, in the short term, HCTZ can cause electrolyte abnormalities, as well as increased creatinine and urea, with the latter two abnormalities being the most clinically relevant. Therefore, regular rechecks are advised when prescribing HCTZ in dogs with CHF due to MMVD.

Conflicts of Interest Statement

The authors do not have any conflicts of interest to disclose.

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