Effect of a combination of telmisartan and amlodipine in hypertensive dogs

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SUMMARY
Systemic hypertension (SHT) in dogs is considered a health risk factor. Telmisartan is a well-known antihypertensive agent in humans. There are limited reports about its efficacy in dogs. Five dogs with primary and secondary SHT refractory to the combined treatment of benazepril and amlodipine had a successful control of systolic arterial blood pressure (SBP) when telmisartan was combined with amlodipine. SBP showed a significant reduction after any treatment, but only reached successful control when amlodipine plus telmisartan was administered (median SBP: 215 mmHg before treatment [min-max: 180–240 mmHg]; 180 mmHg for amlodipine plus benazepril treatment [min-max: 170–210 mmHg]; 142 mmHg after amlodipine plus telmisartan treatment [min-max: 120–165 mmHg]). This control remained stable in the long-term follow-up (average 5.2 months). In the cases reported, the telmisartan plus amlodipine treatment showed good efficacy in the control of SHT, regardless of cause, and was well tolerated in all patients.

BACKGROUND
Systemic hypertension (SHT) is described as sustained systolic arterial blood pressure (SBP) over 150 mmHg, although interbreed differences in blood pressure have been described in dogs.1–4

SHT recognition has increased in the last years improving the management of different diseases. SHT causes injury to tissues causing proteinuria, retinopathy and hypertensive encephalopathy. These are called the target organ damage (TOD). The prevalence of hypertension is not perfectly established and varies from 1 to 10 per cent in dogs.3

Primary or idiopathic SHT is considered a rare condition in dogs due to the fact that only few cases have been diagnosed without an identifiable cause,5 but secondary SHT is relatively common and associated with different disorders as primary aldosteronism, hyperadrenocorticism, pheochromocytoma, chronic kidney disease (CKD) and hyperthyroidism as well as with some medications like glucocorticoids, mineralocorticoids, erythropoietin, non-steroidal anti-inflammatory drugs and inhibitors of tyrosine kinase.3–5,9

Idiopathic SHT is considered a health risk factor in itself. Severe consequences of SHT, described when SBP is over 180 mmHg, are retinopathy, intraocular haemorrhage and hypertensive encephalopathy, while the threshold for tissue injury is assumed to be 160 mmHg in cats and most breeds of dogs.4,10 Other conditions, including left ventricular hypertrophy,11 proteinuria and further loss of functional kidney tissue,12 can be a cause or consequence of SHT. In addition, secondary SHT is considered an additional progression factor of the underlying disease.

Although the importance of SHT in dogs and cats has been reported,13 even with the consensus in management, there are few reports with respect to the ideal treatment, benefits and adverse effects of them.2 The key point is treating the primary disease and controlling SHT avoiding deleterious effects as described in human medicine like exacerbation of azotaemia with angiotensin converting enzyme inhibitors (ACEI).14

The ACVIM Consensus Statement guidelines for the management of hypertension in dogs and cats propose different strategies including ACEI, calcium channel blockers (CCB), β-blockers and diuretics. Monotherapy and daily dose administration is the first choice to control SHT, but some patients are refractory and need a combination of different drugs to achieve good control of SHT.12

ACEIs are widely used as first-line treatment for SHT in dogs due to the role of the renin-angiotensin-aldosterone system (RAAS) in its development, but they provide an incomplete block of angiotensin II production that can result in poor control of SHT. This phenomenon, called ‘aldosterone breakthrough’, is due to the release of angiotensin II by other sites compared with those regulated by the ACE and independent of the dose of ACEI administered.15

Amlodipine, a CCB, either by switching or as add-on therapy, is the alternative treatment when dogs are refractory to ACEI6,16; however, aldosterone breakthrough may also occur in combined treatments with amlodipine and ACEI.17

Although diuretics are frequently administered to hypertensive people, these agents are not first-choice drugs for veterinary patients, mainly in CKD where dehydration and volume depletion may prove problematic, but can be useful in hypertensive animals in which volume overload is apparent (eg, those with oedema).1

Sodium restriction activates the RAAS axis, so a restricted sodium diet for the treatment of hypertension is not recommended. It is necessary to use antihypertensive agents that interfere with the RAAs, especially for hypertension associated with CKD in dogs.3
Finally, the efficacy of antihypertensive agents can be reduced with other drugs such as NSAIDs, glucocorticoids, etc. These types of drugs have direct renal effects or have effects on aldosterone secretion which produce increase in blood pressure.18

If an antihypertensive agent of choice is not completely effective, the usual approach is to increase the dosage or add an additional drug.14 18 However, certain combinations like ACEI and angiotensin II receptor blocker (ARB) must be used with caution or avoided, as recent publications in humans showed a higher risk of kidney failure in these cases.14 19 20

Telmisartan, an ARB, is a novel drug used in veterinary medicine to reduce proteinuria associated with CKD in cats.21 Telmisartan, with a different mode of action than ACEI, blocking the effects of angiotensin II by selective binding to the AT1 receptor, inhibits angiotensin II-induced smooth muscle contraction, resulting in vasodilation, reduction in peripheral resistance and subsequent decrease in blood pressure.22 23

Telmisartan provides effective blood pressure control over 24 hours and has renoprotective properties in humans. This fact has been demonstrated in hypertensive patients including the elderly and those with comorbid conditions such as diabetes and renal impairment.24–27 This drug decreased serum glucose and serum triglyceride levels, and acted as partial agonist of the peroxisome proliferator-activated receptor-γ. It has been associated with significant reduction in left ventricular mass index, wall thickness and left atrial volumes.22 28

In dogs, it has been described that a daily oral dose of telmisartan produces vasodilation, diuresis and natriuresis without influencing potassium or creatinine excretion, and prevents potassium depletion by inhibiting the release of aldosterone in a dose-dependent manner.29 30 The standard recommended dose in the management of proteinuria in dogs is 1 mg/kg.24 It has also been reported to have an effect on blood pressure in dogs at a 1 mg/kg daily dose.31

To our knowledge, this is the first report about the use of telmisartan in dogs refractory to standard hypertensive treatment.

### CASE PRESENTATION

The five dogs reported in this paper presented at the Complutense Veterinary Teaching Hospital for different medical reasons (described below). The common disorder was SHT; four had different identifiable concomitant diseases and one had none.

In all cases, SBP was measured as part of the physical exam protocol using a Doppler device (Uni Huntleigh; Vettex). The dogs were in lateral recumbency. The cuff was chosen according to the diameter of the extremity (40 per cent of the circumference of the limb) and placed on the non-recumbent thoracic limb). The Doppler probe was placed over the common digital artery just proximal to the metacarpal pad or the mid-plantar artery just proximal to the metatarsal pad. A handheld manometer was used and an experienced person maintained a consistent deflation rate while taking the reading. Measurements were obtained in a quiet room by an experienced person and by that same person in all cases, as described elsewhere.2 At least six measurements were taken over 10–12 minutes after a period of acclimation, extreme readings were discarded and the average of the measurements obtained was used for evaluation of progression.

Hypertension was diagnosed and staged following the Guidelines for the Identification, Evaluation and Management of Systemic Hypertension in Dogs and Cats.3 It was considered SHT when SBP was higher than 150 mmHg (Table 1).

| Case presentation | Diagnosis were severe primary hypertension with TOD |
|-------------------|--------------------------------------------------|
| Case 1 | Miniature Schnauzer, female, eight years old, 7.8 kg in weight. The dog was presented for blindness. Eye fundus exam revealed tortuous vessels, no other relevant finding. The SBP was 190 mmHg. Cell blood count (CBC), biochemistry, tyrosine (T₄) and urinalysis (urine protein to creatinine ratio [UPC] and urine specific gravity [USG]) were within normal range (Tables 2 and 3). Abdominal ultrasound, echocardiogram and chest radiograph showed no abnormalities. |

### TABLE 1: Classification of blood pressure in dogs based on risk for target organ damage

| Risk category | SBP (mmHg) | Risk of TOD |
|---------------|------------|-------------|
| I             | <150       | Minimal     |
| II            | 150–159    | Mild        |
| III           | 160–179    | Moderate    |
| IV            | >180       | Severe      |

SBP, systolic blood pressure; TOD, target organ damage.

Blood and urine tests, and abdominal ultrasound were performed in each dog, and chest radiographs were taken when considered necessary.

Differential diagnosis for SHT included hyperthyroidism, hyperadrenocorticism, CKD and diabetes mellitus, as well as other potential previous hypertensive treatment. None of the dogs were obese.3 Appropriate management was established for any concomitant condition, a complete description of the patient’s associated disease medical management is outside the scope of the cases presented. Glucocorticoids, NSAID and tyrosine kinase inhibitors were avoided in all of the cases presented.

### Case description

#### Case 1

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### TABLE 2: Reference values of cell blood count and biochemical parameters performed in the five cases described

| Parameter                            | Reference range                  |
|--------------------------------------|----------------------------------|
| Haematocrit (%)                      | 37–55                            |
| Haemoglobin                          | 12–18 g/dl                       |
| Red blood cell (x10¹²/l)             | 5.3–8.5                          |
| White blood cell (x10³/l)            | 6.0–17.0                         |
| Albumin                              | 2.4–3.9 g/dl                     |
| Alkaline phosphatase                 | 15–120 µkat/l                    |
| Creatinine                           | 0.5–1.3 mg/dl                    |
| Alkaline phosphatase                 | 0.24–1.92 µkat/l                 |
| Glucose                              | 74–126 mg/dl                     |
| Serum total protein                  | 5.8–7.5 g/dl                     |
| Urea                                 | 15–57 mg/dl                      |
| Thyroxine                            | 1.48–4.5 µg/dl                   |
| TSH (UI/ml)                          | 0.0–59 UI/ml                     |
| Urinary specific gravity             | 1.015–1.050                      |
| Urine protein/creatinine ratio       | <0.5                             |

TSH, thyroid stimulating hormone.
follow-up, echocardiogram revealed mild left ventricular hypertrophy and SBP was 180 mmHg. It was decided to add amlodipine (Astudal; Almirall SA) (0.2 mg/kg/24 hours, oral). Two weeks later, SBP still remained the same. It was decided to switch from benazepril to telmisartan (Semintra; Boehringer Ingelheim España) (1 mg/kg/24 hours, oral). Two weeks later, SBP was 160 mmHg. At the follow-up at eight months, mean SBP was within normal range. The dog is still alive (Table 4).

Case 2
Cocker spaniel, female, 12 years old, 10.9 kg in weight. The dog was presented for mammary carcinoma follow-up. Physical exam revealed a systolic cardiac murmur, intensity 3/6 with maximal intensity at mitral area. The SBP was 180 mmHg without evident TOD. CBC, biochemistry and T4 were within normal range (Table 2). Echocardiogram confirmed chronic mitral valve disease (CMVD) B1 according to ACVIM classification. Diagnosis was mammary carcinoma + CMVD stage B1, CKD IRIS 1, severe SHT, no TOD. Treatment was instituted with benazepril (0.25 mg/kg/12 hours, oral). One month later, SBP rose to 220 mmHg. It was decided to add amlodipine (0.2 mg/kg/24 hours, oral). One week later, SBP was slightly lower. Four months later, SBP was elevated again, so it was decided to switch from benazepril to telmisartan (1 mg/kg/24 hours, oral). At the two-month follow-up, mean SBP in sequential measurements was 130 mmHg (±10 mmHg) (Table 4). At that point, the owners decided on euthanasia due to poor evolution of the degenerative disc disease diagnosed and treated for the previous month (Tramadol [Tramadol; Normon SA] 2 mg/kg/12 hours + gabapentin [Gabapentina; Grupo Alter] 10 mg/kg/12 hours).

Case 3
Crossbreed, female, 14 years old, 7 kg in weight. The dog was presented for a second opinion for heart murmur. Physical exam revealed a 4/6 systolic cardiac murmur with point of maximal intensity at mitral area. The dog's urine analysis was consistent with CKD IRIS 1 according to International Renal Interest Society (Table 3). Diagnosis was mammary carcinoma + CMVD stage B2, CKD IRIS 2, severe SHT. Treatment was started with benazepril (0.25 mg/kg/24 hours, oral). Three weeks later, SBP was 220 mmHg. It was decided to add amlodipine (0.2 mg/kg/24 hours, oral). One week later, SBP was slightly lower. Four months later, SBP was elevated again, so it was decided to switch from benazepril to telmisartan (1 mg/kg/24 hours, oral). At the two-month follow-up, mean SBP was 165 mmHg (±10 mmHg) (Table 4). At that point, the owners decided on euthanasia due to poor evolution of the degenerative disc disease diagnosed and treated for the previous month (Tramadol [Tramadol; Normon SA] 2 mg/kg/12 hours + gabapentin [Gabapentina; Grupo Alter] 10 mg/kg/12 hours).

### TABLE 3: Urea, creatinine and urinary value results in the five cases presented before treatment for the control of systolic blood pressure and after the control of the systolic blood pressure with telmisartan and amlodipine treatment

| Pretreatment | Post-treatment |
|--------------|---------------|
| Urea (mg/dl) | Creatinine (mg/dl) | USG | UPC | Urea (mg/dl) | Creatinine (mg/dl) | USG | UPC | Follow-up (months) |
| Case 1       | 44            | 1.1          | 1.037 | 0.05 | 51            | 1.4          | 1.029 | 0.1  | 8               |
| Case 2       | 183           | 1.2          | 1.016 | 1.3  | 176           | 1.2          | 1.015 | 2.3  | 2               |
| Case 3       | 140           | 4.8          | 1.020 | 0.24 | 343           | 7.7          | 1.011 | 1.1  | 5               |
| Case 4       | 40            | 1            | 1.037 | –    | 31            | 0.9          | 1.030 | –    | 5               |
| Case 5       | 56            | 0.8          | 1.020 | 1.2  | 60            | 0.9          | 1.025 | 1    | 6               |

UPC, urine protein to creatinine ratio; USG, urine specific gravity.

### TABLE 4: Final diagnosis, treatment schedule and changes in systolic blood pressure over time in the five cases presented

| Patient | Diagnosis | Pretreatment (SBP mmHg) | Benazepril (0.25 mg/kg twice a day) | Benazepril + amlodipine (0.25 mg/kg twice a day + 0.2 mg/kg once a day) | Telmisartan + amlodipine (1 mg/kg twice a day + 0.2 mg/kg once a day) | Follow-up |
|---------|-----------|-------------------------|------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|-----------|
| Case 1  | Miniature Schnauzer, female, 8 years, 7.8 kg | 190 | 180 (month 4) | 170 (week 2) | 160 (week 2) | 120 (±10) (8 months) |
| Case 2  | Cocker spaniel, female, 12 years, 10.9 kg | 180 | 220 (month 1) | 170 (week 4) | 150 (week 2) | 130 (±5) (month 2) |
| Case 3  | Mongrel, female, 14 years, 7 kg | 240 | – | 210 (week 1) | 140* (0.3 mg/kg ADP week 1) | 150 (±5) (month 5) |
| Case 4  | Miniature Schnauzer, male, 10 years, 8 kg | 220 | – | 190 (week 3) | 200 (month 2.5) | 160* (0.4 mg/kg ADP week 2) | 160 (±15) (months 1–5) |
| Case 5  | American cocker spaniel, male, 14 years, 7.8 kg | 240 | – | 190 (week 3) | 180 (week 2) | 165* (0.4 mg/kg ADP week 2) | 165 (±15) (months 1–6) |

ADP, amlodipine; CKD, chronic kidney disease; CMVD, chronic mitral valve disease; IRIS, International Renal Interest Society; SBP, systolic blood pressure; SHT, systemic hypertension; TOD, target organ damage.

* Systolic blood pressure achieved with the dose of amlodipine showed in brackets
intensity at mitral area. SBP 240 mmHg. CBC and Tc were within normal range (Table 2). Biochemistry showed abnormal urea, creatinine and urinalysis measurements. Echocardiogram confirmed CMVD stage B2. The left ventricle to left atrium pressure gradient was 235 mmHg. Abdominal ultrasound showed no other findings but CKD. Chest radiographs without abnormalities (Table 3).

**Diagnosis was CMVD stage B2 + CKD stage IRIS 2, severe SHT, no TOD**

Treatment was initiated with benazepril (0.25 mg/kg/12 hours, oral) plus amlopidine (0.17 mg/kg/24 hours, oral). One week later, SBP persisted high. Amlodipine dose was increased to 0.3 mg/kg/24 hours, orally. One week later, SBP still remained high. It was decided to change benazepril for telmisartan (1 mg/kg/24 hours, oral). Two weeks later, SBP was within normal range. At the follow-up at five months, mean SBP in sequential measurements was stable. At that point, the owners decided on euthanasia due to poor evolution of CKD (Table 4).

**Case 4**

Miniature Schnauzer, male, 10 years old, 8 kg in weight. The dog was presented due to the presence of a cardiac murmur. Physical exam revealed no other abnormalities but 3/6 systolic cardiac murmur with point of maximal intensity at mitral area. SBP was 220 mmHg. CBC, biochemistry and Tc were within normal range (Table 2). Urinalysis showed urolithiasis (oxalate) as single finding. Echocardiogram confirmed CMVD and revealed systemic and pulmonary hypertension (PH) with right ventricle to right atrium gradient of 53.7 mmHg, and left ventricle to left atrium pressure gradient of 207 mmHg, and left ventricle to left atrium gradient of 207 mmHg (Table 3).

**Diagnosis was CMVD stage B2, severe SHT, no TOD, PH, urolithiasis**

Therapy was instituted with benazepril (0.25 mg/kg/12 hours, oral), pimobendan (0.25 mg/kg/12 hours, oral) and amlodipine (0.2 mg/kg/24 hours, oral). Two weeks later, SBP was maintained high. Addition of furosemide (Seguril; Sanofi España) (1 mg/kg/24 hours, oral) was decided. Three weeks later, the SBP was maintained high. Then benazepril was switched to telmisartan (1 mg/kg/24 hours, oral). Two weeks later, SBP was again high and it was decided to increase the dose of amlopidine (0.4 mg/kg/24 hours, oral). One week later, SBP was closed to normal. At the six-month follow-up after the initial presentation (three months from blood pressure stabilisation), the blood pressure was 165 mmHg (±10 mmHg) (Table 4). In this period, the dog was treated with NSAIDs due to lameness (meloxicam 0.1 mg/kg/24 hours) when needed. Afterwards, the animal was lost to follow-up.

Although the number of cases is low, a small statistical analysis was performed. The median of SBP before treatment was 215 mmHg (range 180–240 mmHg). While SBP after treatment with benazepril plus amlopidine remained high (median 180 mmHg, range 170–210 mmHg), SBP after treatment with telmisartan plus amlopidine clearly reduced (median 142 mmHg, range 120–165 mmHg). Non-parametric Wilcoxon test was statistically significant for all treatments, but special interest is the significant improvement in the control of SBP when telmisartan was administered instead of benazepril (P=0.043).

**DISCUSSION**

This report describes the management of SHT in five dogs with different conditions, with and without underlying disease. All the dogs included were over 10 years old; these data are in agreement with the recommendations to screen dogs at this age. A relevant association has been demonstrated elsewhere between high blood pressure and declining renal function in dogs. Moreover, hypertension in dogs with chronic renal failure is correlated to shorter survival times. So it is important to control SHT in an effective way.

The cases presented different final diagnosis, but SHT with or without TOD was the consistent feature. This observation is in agreement with the results described by Brown et al in which idiopathic and secondary SHT has been diagnosed in dogs. The control of SHT was not achieve with standard dosage of benazepril plus amlopidine, so other treatment strategies were needed. The results of this case series showed good control of SBP when telmisartan was added to amlopidine. The reason of the failure in the control of SBP with benazepril plus amlopidine could be the aldosterone escape which means synthesis of aldosterone by other route independent of ACE.

Retinopathy and/or choroidopathy secondary to SHT has been described in dogs. In these situations, the most important goal is to control the SBP to prevent other TOD from developing in the patient. The recovery of the vision use to be unusual as it happened with the evolution of the first case described.

Chronic renal failure could explain the high blood pressure, SHT is also associated with the development of CKD as well. So it is difficult to know which is the responsible of the clinical state of the patient with those concomitant pathological situations. Again, it is essential to control the SBP and to reduce the proteinuria in the affected dogs. Telmisartan has been proven to reduce the proteinuria in a dog in a more effective way than ACEI. In cases 2 and 3, a moderate increase in UPC has been observed, although the primary goal: lowering SHT was achieved. The other comorbidities of the patients could have affected this finding.

Intermittent myoclonic episodes could be caused by SHT. Systolic hypertension causes identifiable brain lesions on MRI. In the case presented, there were no anomalies in MRI, but there are no descriptions of duration for MRI changes due to SHT.
CMVD phase B2 was considered less likely to be the cause of either SHT or neurological signs.\(^{33}\) However, the presence of left ventricular hypertrophy resembles chronic high blood pressure.

The most common adverse effects of telmisartan described in humans were headache, dizziness and nausea.\(^{28}\) No adverse events associated with the concomitant administration of telmisartan and amiodipine were observed in the present study; however, dizziness, mild nausea and headaches are difficult to determine in veterinary medicine patients, although in this study there were no behaviour changes suggesting the presence of these adverse effects.

These results show that telmisartan, at the dose of 1 mg/kg, added to amiodipine seemed to have worked in these five dogs with SHT refractory to conventional treatment and that it did not cause any major adverse effect.

There are several limitations of this report. First, the collecting data were done at different time intervals; secondly, the retrospective nature of the data and the low number and the different conditions of the cases. Further studies are needed to confirm these observations.

**Contributors** Conception or design of the work: ACV, MADG, JGG. Data collection: ACV, MADG, EGAA, AR. Data analysis and interpretation: ACV, MADG, JGG. Drafting the article: ACV, MADG, EGAA, AR, JGG. Critical revision of the article: ACV, JGG. Final approval of the version to be published: ACV, MADG, EGAA, AR, JGG.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** JGG is an employee of Boehringer Ingelheim Spain.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Further data is available upon reasonable request to the corresponding author.

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