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Factors Influencing the Relationship Between the Dose of Amlodipine Required for Blood Pressure Control and Change in Blood Pressure in Hypertensive Cats

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Background: Hypertension is a common problem in elderly cats. In most cats, systolic blood pressure (SBP) of <160 mmHg is achieved in response to amlodipine besylate at either 0.625 or 1.25 mg q24h. The individual cat factors determining dose requirement dose have not been explored.

Aims: To determine whether individual cat factors influence the dose of amlodipine required to achieve adequate blood pressure control and to determine whether factors other than the prescribed dose of drug alter the achieved plasma amlodipine concentrations.

Methods: Fifty-nine hypertensive cats that required 0.625 mg (A) and 41 cats that required 1.25 mg (B) amlodipine to reach a target SBP of <160 mmHg were identified, and plasma amlodipine concentrations were determined. Comparisons were made between groups, and multivariable linear regression models were performed to investigate predictors of antihypertensive response.

Results: Cats that required a greater dose of amlodipine had significantly higher SBP at diagnosis of hypertension (A: (median [25th, 75th percentile]) 182 [175,192] mmHg; B: 207 [194,217] mmHg, $P < .001$), but comparable blood pressure was achieved after treatment. Plasma amlodipine concentrations were directly related to the dose of amlodipine administered. At diagnosis, cats in group B had significantly lower plasma potassium concentration (A: 4.1 [3.8,4.5]; B: 3.8 [3.6,4.2] mEq/L, $P < .01$). Weight did not differ between groups. The decrease in SBP was directly and independently associated with the SBP at diagnosis and the plasma amlodipine concentration.

Conclusions and Clinical Importance: Cats with higher blood pressure at diagnosis might require a greater dose of amlodipine to control their blood pressure adequately. Differences in amlodipine pharmacokinetics between cats do not seem to play a role in the antihypertensive response.

Key words: Chronic kidney disease; Feline; Hypertension.

Systolic hypertension is a common problem in the elderly cat population, particularly in cats with chronic kidney disease (CKD).[1] Left untreated, it can have detrimental effects and lead to damage to organs with a rich arterial and arteriolar supply, such as the eye, kidney, and brain, often referred to as target organ damage (TOD).[1] The goal of antihypertensive treatment is to effectively decrease the risk of TOD.[1] In human medicine, more aggressive treatment is recommended for patients with more severe hypertension.[2]

Abbreviations:

CKD	chronic kidney disease
cTSH	canine thyroid stimulating hormone
IRIS	International Renal Interest Society
LC/MS/MS	high-performance liquid chromatography with tandem mass spectrometric detection
PCK	packed cell volume
PK/PD	pharmacokinetic and pharmacodynamic
TOD	target organ damage
UK	United Kingdom
USG	urine specific gravity

Amlodipine besylate is currently regarded as the first-choice antihypertensive treatment in cats.[1] The first reports on the use of amlodipine besylate for treatment of hypertension in cats were published in 1994,[3,4] and since then, two placebo-controlled clinical trials have been published.[5,6] Amlodipine is a second-generation dihydropyridine and exerts its effects by blocking L-type calcium channels in vascular smooth muscle. It binds and dissociates from its receptor fairly slowly, which accounts for the gradual onset and slow waning of effect.[7] This, in combination with its long plasma half-life, means amlodipine only needs to be administered once every 24 hours.[8] The currently recommended dose for cats is 0.125–0.5 mg/kg, with regular blood pressure checks and potential dose adjustment to achieve adequate blood pressure control.[1] It has been suggested that heavier cats need a higher dose of amlodipine.[5,9,10]

The pathogenesis of hypertension in cats is still poorly understood. Cats with CKD are at greater risk

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of developing hypertension, and plasma creatinine concentration is an independent risk factor for the development of hypertension.[11] Hypertensive cats have lower plasma potassium concentrations than their normotensive counterparts.[12] However, investigations into the activation of the renin–angiotensin–aldosterone system (RAAS) have reported heterogeneous results.[13] As amlodipine is thought to produce its antihypertensive effects by reducing peripheral resistance, investigations into the factors influencing response to amlodipine could help elucidate the pathophysiologic mechanisms driving hypertension in cats with and without CKD.

The aim of this study was to determine the factors influencing the dose of amlodipine required to achieve adequate control of blood pressure in hypertensive cats. We hypothesized that measurement of plasma amlodipine concentration at the point of blood pressure control would help to identify whether individual pharmacokinetics play a role in this. To improve optimization of antihypertensive therapy, comparisons were made between the low-dose and high-dose group, and clinical and laboratory variables were investigated as possible predictors of blood pressure response.

Materials and Methods

Clinics and Case Selection

A population of cats that had undergone diagnosis and therapy for systemic hypertension at two first opinion practices (People's Dispensary for Sick Animals in Bow and Beaumont Sainsbury Animal Hospital in Camden) between January 2001 and December 2013 was identified. These cats had all been invited to the clinic as part of a screening program of elderly cats (≥9 years of age), or because they were suspected to suffer from diseases that were of interest to the veterinary researchers working in the practice (hypertension, CKD, hyperthyroidism, or a combination thereof). Each of these cats had undergone a standardized visit protocol, which included a full history and a physical examination, including blood pressure measurement and blood and urine sampling. A noninvasive Doppler technique[a] was used to measure systolic blood pressure (SBP) after a period of acclimatization. Average SBP was calculated from 5 consecutive readings after discarding the first reading. If average SBP was ≥160 mmHg, indirect fundoscopy was performed after applying one drop of tropicamide 1% to both eyes.

At first visit to the clinic, informed owner consent was obtained to collect blood samples via jugular venipuncture and urine samples by cystocentesis. The standard clinic protocols, information sheets, and consent forms for use of residual samples for research were approved by the Royal Veterinary College's Ethics and Welfare Committee (URN: 2013 1258). Blood samples were collected into lithium heparin and EDTA tubes and held on ice for a maximum of 6 hours before centrifugation[b] and separation. Plasma biochemistry was performed at an external laboratory,[c] and residual sample was stored at −80°C until further analysis. Plasma total T4 concentration was measured in all cats within 6 months of inclusion in the study. All cats diagnosed with hyperthyroidism (total T4 >40 nmol/L with canine thyroid stimulating hormone [TSH] <0.03 ng/mL, or a total T4 >55 nmol/L) were excluded from the study, unless a successful thyroidectomy (confirmed by total T4 measurement) had been performed ≥90 days before inclusion, to allow stabilization of glomerular filtration rate.[14] Urine samples were collected by cystocentesis if possible, and urine dipstick evaluation was performed and urine specific gravity (USG) was measured by refractometry. In addition, microscopic sediment examination was undertaken and, if bacteriuria or pyuria was found, bacterial culture and sensitivity testing was performed. Cats that were being administered Angiotensin Converting Enzyme (ACE) inhibitors or other blood pressure altering medications were excluded.

Systemic hypertension was diagnosed when cats had a SBP ≥170 mmHg on two consecutive visits (reliably placing them in the category that is at moderate risk of developing TOD)[1] or SBP ≥160 mmHg with concurrent evidence of hypertensive retinopathy on indirect fundoscopy. CKD was diagnosed in cats with renal azotemia (plasma creatinine concentration ≥2.0 mg/dL either on two consecutive visits >2 weeks apart or in conjunction with USG <1.035).

Treatment Protocol

All cats were started on 0.625 mg amlodipine besylate (1/8 tablet of a 5-mg human formulation[d]) once daily and invited back for a blood pressure recheck 1–2 weeks later. Target SBP was defined as <160 mmHg and the amlodipine dose was doubled if SBP was ≥160 mmHg on follow-up visits, to a maximum of 2.5 mg amlodipine per day. After adequate antihypertensive control was achieved, a blood sample was obtained to assess any potential changes in kidney function with antihypertensive treatment, and owners were invited back to the clinic every 8 weeks, with blood and urine samples taken every 16 weeks. An overview of this protocol can be found in Figure 1. The samples that were used for amlodipine measurement in this study were all taken at the first visit that blood pressure was considered adequately controlled (SBP <160 mmHg), and only cats that achieved control on 0.625 and 1.25 mg were included. No attempt was made to obtain blood samples at any particular time of day, although all cats were seen and sampled between 9 AM and 1 PM. Owners were instructed to medicate their cat at the same time point every day, but were free to decide at which time this would be.

Measurement Method

Plasma amlodipine concentration was determined using high-performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). Samples of cats not on amlodipine, and cats that were on amoxicillin/clavulanic acid antibiotic therapy, methimazole, and meloxicam were used as controls. Amlodipine was quantified in EDTA feline plasma using amlodipine-d4 as the internal standard over the concentration range of 1–500 ng/mL. Amlodipine was extracted from 50 μL plasma samples by protein precipitation using 200 μL of acetonitrile. The proteins were removed by centrifugation, and the acetonitrile was transferred to another 96-well plate prior to injection on to a Thermo Accucore RP-MS 2.6 μm 80A (2.1 × 50 mm) solid core HPLC column using a CTC autosampler connected to a Jasco XLC UPLC system (Jasco Corporation, HACHIOJI-SHI, TOKYO, Japan). The analytes were chromatographed using a 0.1% (v/v) formic acid acetonitrile gradient flowing at 0.6 mL/min. Amlodipine was quantified by multiple reaction monitoring (MRM) using positive-ion atmospheric pressure ionization on an ABSciex (Concord, Ontario, Canada) API4000 tandem mass spectrometer. The MRM transitions used were m/z 409.2 → 238.0 and 413.2 → 238.0 for amlodipine and amlodipine-d4, respectively. Calibration curves were fitted using a quadratic regression weighted $1/x^2$. Accuracy and precision of the method were evaluated at 3, 30 and 400 ng/mL. Intrabatch accuracy ranged from 92.0 to 111.7%. Interbatch accuracy ranged between 95.5 and 107.5%. Imprecision was <6.5%.

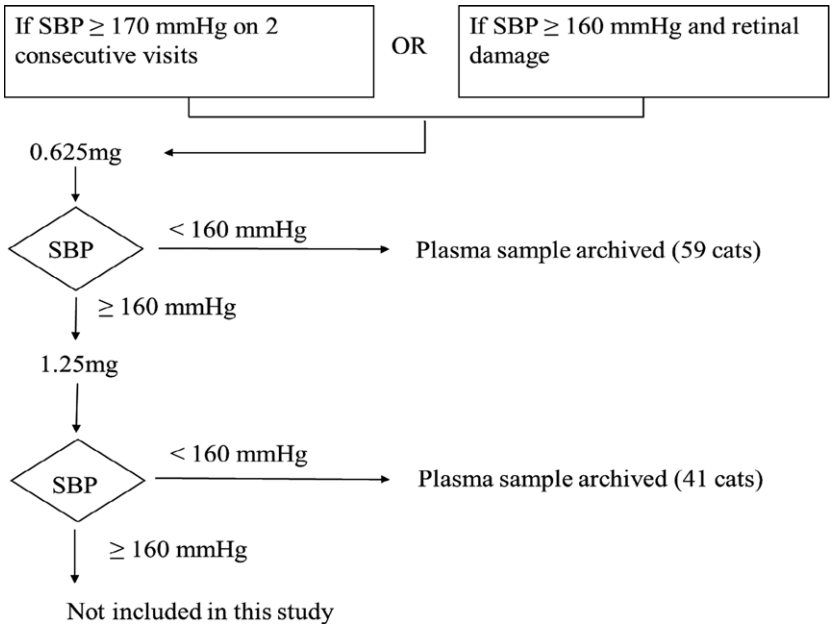

Fig 1. Treatment protocol for the initial BP stabilisation and overview of the groups included in the study.

Statistical Analyses

Statistical analyses of the data were performed using R 3.1.1[e] and GraphPad Prism 6[f] . To investigate differences in clinical presentation, comparisons were made between clinical and biochemical variables of cats that were controlled on 0.625 mg/day (A) and cats that needed a dose increase to 1.25 mg/day (B). Comparisons were made between groups A and B at initial visit using a Student's *t*-test or Mann–Whitney *U*-test where appropriate, and results are described as mean ± SD or median ([25th, 75th percentile]). Cross-sectional comparisons for plasma amlodipine concentrations at first controlled visit were made using a Mann–Whitney *U*-test. Proportion of cats diagnosed with CKD, proportion of cats in International Renal Interest Society (IRIS) stage 2, and proportion of hypokalemic cats were compared between groups using a Fisher's exact test. Significance was set at $P < .05$.

The absolute change in SBP was calculated as the average SBP at diagnosis (averaging the SBP at hypertensive visits) minus the SBP at first controlled visit. Univariable linear regression models were performed with absolute change in SBP in response to amlodipine treatment as the dependent variable and plasma amlodipine concentration, dose in mg/kg, time on treatment in days, weight, age, heart rate, SBP at hypertensive visit, packed cell volume (PCV), plasma creatinine and urea concentration, plasma potassium, sodium, chloride, total calcium, and cholesterol concentration as explanatory variables. Variables were log transformed if necessary to meet normality criteria, and variables significant at the 10% level were included in the multivariable linear regression model without model selection.

Results

Clinical Data

An overview of the clinical and biochemical variables can be found in Table 1, and a schematic representation of the treatment protocol and included subjects can be found in Figure 1. A total of 100 cats (50 female [2 of which were entire] and 50 male neutered) were identified. The majority of cats (73) were domestic short hair, followed by Burmese (8) and domestic long hair (7). At the first time point, SBP was considered effectively controlled, 59 cats were on 0.625 mg/day, and 41 cats were receiving 1.25 mg/day. At first controlled visit, cats that had adequate antihypertensive response to 0.625 mg had been receiving therapy for a median of 14 days, whereas cats that required 1.25 mg had been on treatment with a median of 28 days, which is concordant with the clinic's treatment protocol. The majority of cats (71/100) had been diagnosed with CKD, and the number of cats with CKD was not significantly different between groups ($P = .13$), nor was the number of cats in IRIS stage 2 ($P = .30$).

Cross Sectional Study

Systolic blood pressure at the hypertensive visit differed significantly between groups (A: 182 [175, 192] mmHg; B: 207 [194, 217] mmHg, $P < .001$), but comparable post-treatment SBP was achieved (A: 145.6 [134.0, 152.4] mmHg; B: 146.2 [136.2, 152.4] mmHg, $P = .55$), as shown in Figure 2. Plasma amlodipine concentration was approximately twice as high in cats on 1.25 mg compared to those receiving 0.625 mg (B: 70.5 [48.8, 98.6] ng/mL versus A: 33.1 [24.9, 53.2] ng/mL, $P < .001$), as was the dose in mg/kg that the cats were receiving (B: 0.33 ± 0.09 mg/kg, A: 0.17 ± 0.04 mg/kg; $P < .001$). No significant differences were found between pretreatment values from groups A and B for age, weight, PCV, plasma albumin, creatinine, urea, phosphate, total calcium, sodium, chloride, and cholesterol concentration, and USG. Group B had a significantly lower plasma potassium concentration (mean plasma potassium concentration was 0.3 mEq/L lower

Table 1. Clinicopathologic variables for groups A and B at initial visit.

	Group A	Group B
Dose of amlodipine (mg/cat/24 hour)	**0.625**	**1.25**
N (CKD)	59 (45)	41 (26)
Age (years)	15.3 [13.7, 16.5]	15.0 [13.3, 16.1]
Weight (kg)	3.77 [3.16, 4.49]	3.86 [3.42, 4.40]
SBP (mmHg)	**182 [175, 192]**	**207 [194, 217]**
Heart rate (bpm)	187 [177, 215]	192 [180, 200]
PCV (%)	36 [31, 38]	36 [32, 39]
Albumin (g/dL)	3.1 [2.9, 3.3]	3.2 [3.1, 3.4]
Creatinine (mg/dL)	2.3 [1.8, 2.8]	2.3 [1.7, 2.7]
Urea (mmol/L)	16.0 [12.6, 21.6]	14.5 [10.7, 21.6]
Phosphate (mg/dL)	4.30 [3.39, 4.83]	4.15 [3.31, 5.27]
Total calcium (mg/dL)	10.04 [9.72, 10.52]	10.20 [9.76, 10.62]
Sodium (mEq/L)	153.0 [151.8, 154.6]	153.0 [151.5, 154.5]
Potassium (mEq/L)	**4.1 [3.8, 4.5]**	**3.8 [3.6, 4.2]**
Chloride (mEq/L)	116.8 [115.5, 119.6]	116.9 [115.1, 118.7]
Cholesterol (mg/dL)	200.8 [164.1, 254.8]	200.8 [172.8, 243.2]
USG	1.018 [1.016, 1.024]	1.020 [1.017, 1.022]

SBP, systolic blood pressure; PCV, packed cell volume; USG, urine specific gravity; CKD, chronic kidney disease.

Variables shown in bold are significantly different between the two groups ($P < .05$). All values are presented as median [25th, 75th percentile].

in group B than in group A, $P < .01$; see also Table 1), but the number of hypokalemic cases (reference range potassium 3.50–5.50 mEq/L) did not significantly differ between groups ($P = .22$).

Linear Regression

Plasma amlodipine concentration, dose in mg/kg, SBP at hypertensive visit, and plasma potassium were all associated with the absolute drop in SBP at the 10% level in the univariable analyses (Table 2) and were included in the multivariable model. Plasma amlodipine concentration and the SBP at hypertensive visit remained positively and significantly associated with decrease in SBP in the final model ($P < .001$).

Discussion

Human patients with severe elevations in blood pressure are started on more aggressive antihypertensive treatment (ie, higher doses of medication or multiple medications that are being started at the same time) than patients with moderate blood pressure increases.[15] The aim of antihypertensive treatment is to achieve effective control of SBP as quickly as possible while eliciting few adverse effects, in order to decrease the risk of (further) TOD. Predictors of the dose required to achieve effective blood pressure control in an individual patient could help in achieving this, and human studies have made efforts to identify predictors of response to several different classes of antihypertensive medication.[16–18]

In the current study, cats with a higher SBP at presentation needed a higher dose of amlodipine to decrease the SBP to acceptable levels. In addition, the decrease in SBP associated with amlodipine treatment was independently and positively associated with both the pretreatment SBP and the plasma amlodipine concentration. Administration of a higher dose in mg/kg was associated with proportionately higher plasma amlodipine concentrations. This finding suggests that individual cat variation in amlodipine pharmacokinetics or owner compliance is unlikely to explain the dose required to achieve effective blood pressure control with amlodipine in the majority of cats. However, it is notable that only cats with acceptable control were included in this study, and it cannot be ruled out that compliance plays a role in cats that do not respond to higher doses, such as cats that need a dose of 2.5 mg q24h, or need additional medications such as benazepril. The

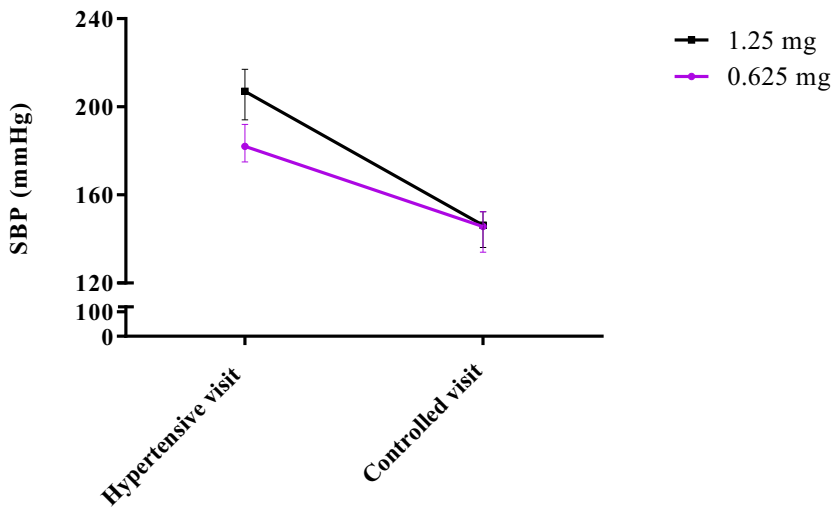

Fig 2. Graphical presentation of the systolic blood pressure (SBP) at hypertensive visit and at first controlled visit for cats on 0.625 and 1.25 mg. Cats that required a dose of 1.25 mg to decrease their SBP to <160 mmHg had significantly higher blood pressure at diagnosis (black line) than did cats that needed 0.625 mg, but comparable SBP after treatment.

Table 2. Univariable linear regression models investigating the association between biochemical and clinical variables and the absolute decrease in SBP.

	Estimate ± SE	*P*-value	n
Plasma amlodipine concentration	**15.7 ± 2.6**	**<.001**	**100**
Dose (mg/kg)	**94.8 ± 18.9**	**<.001**	**99**
Treatment time (days)	0.04 ± 0.06	.499	100
Weight (kg)	−2.31 ± 2.02	.257	99
Heart rate (bpm)	0.02 ± 0.08	.841	98
Hypertensive SBP (mmHg)	**0.89 ± 0.06**	**<.001**	**100**
PCV (L/L)	−0.26 ± 0.35	.459	99
log(Creatinine (mg/dL)	−1.4 ± 6.0	.819	99
Urea (mmol/L)	−0.14 ± 0.35	.683	99
log(Potassium [mEq/L])	**−34.8 ± 16.3**	**<.05**	**99**
Sodium (mEq/L)	0.70 ± 0.77	.366	99
Chloride (mEq/L)	−0.77 ± 0.73	.293	99
log(Total Calcium [mg/dL])	−8.4 ± 30.0	.779	99
Cholesterol (mg/dL)	−0.008 ± 0.04	.830	99

PCV, packed cell volume; SBP, systolic blood pressure.

Variables depicted in bold were significantly associated with the absolute decrease in SBP at the 10% level and were included in the multivariable linear regression model. The plasma amlodipine concentration and hypertensive SBP remained significantly associated with the decrease in SBP on amlodipine treatment.

same direct correlation between plasma amlodipine concentration and decrease in blood pressure occurs in humans and rats.[8,19]

The SBP before treatment was independently associated with the absolute decrease in blood pressure with antihypertensive treatment. This could be explained by the clinical protocols used. Whereas in human hypertensive subjects, specific blood pressure goals have been described for different clinical situations,[2] the target for all cats enrolled in the current study was SBP of <160 mmHg. The greater decrease in blood pressure could therefore be explained by having a higher blood pressure at baseline. However, it is likely that more factors play a role. Studies of human patients have described that blood pressure response to amlodipine is greater with more severe hypertension.[17] This could indicate that in more severely hypertensive subjects, increased peripheral resistance plays a greater role in the pathophysiology of hypertension.[17] Amlodipine lowers blood pressure by acting on the vascular smooth muscle cells, and the direct correlation between drop in blood pressure and plasma amlodipine concentration might indicate that raised systemic vascular resistance is (partly) responsible for the elevation in blood pressure in cats.

Cats that needed a dose increase to 1.25 mg had significantly lower plasma potassium concentration. Plasma potassium concentration is regulated by the RAAS and the kidneys, and there are multiple possible explanations for the finding of lower plasma potassium in less responsive cats. One explanation could be that greater activation of the RAAS occurred in Group B cats compared to Group A cats. Activation of the RAAS is variable in hypertensive cats,[13] and ACE inhibitors show a relative lack of efficacy. This implies that although possibly involved, renin-dependent mechanisms are unlikely to be the main cause of hypertension in feline patients. Other possible underlying causes of hypertension that are associated with low plasma potassium concentration should be explored in cats requiring high doses of amlodipine to treat their hypertension, one of which is nonrenin-dependent increases in plasma aldosterone concentration. The reported incidence of primary hyperaldosteronism is increasing in cats,[20] possibly because of a greater awareness of the disease. Aldosterone was not measured in cats in the current study, and abdominal ultrasound examinations were not routinely performed, and it is therefore unclear whether this disease played a role. It should be noted that the majority of the cats included in this study had concurrent CKD. Hypokalemia is fairly common in cats with CKD and could be due to decreased intake or increased urinary loss of potassium.[21] The hypertensive cats included in this study had comparable renal function and the proportion of cats with CKD and cats with IRIS CKD stage 2 was equal in both groups (Table 1), suggesting that stage of CKD did not have an influence on the observed antihypertensive response. Another explanation could lie within the kidney. Multiple transporters function as regulators of acid–base balance, blood volume, and blood pressure, and defects or disturbances in these transporters, either due to kidney disease or because of genetic mutations, could contribute to hypertension.[22,23] Publications on the genetics of hypertension in cats are currently lacking.

None of the other clinical and biochemical variables predicted the required dose of amlodipine. Plasma creatinine concentration was not significantly different between the groups included in this study and did not function as a predictor of antihypertensive response. Most human hypertensive subjects are diagnosed with essential hypertension, in contrast to cats, most of which have kidney disease. Having CKD significantly increases the risk for a cat to become hypertensive[11] and the majority of cats included in the current study (45/59 cats in group A and 26/41 cats in group B) were diagnosed with CKD. The other cats were considered to have idiopathic hypertension, as no other underlying disease was diagnosed. It is, however, possible that a proportion of these cats suffered from nonazotemic CKD. No correlation was found between creatinine and SBP response, contrary to what has been described in humans.[2] This could possibly be explained by the fact that the cat population is more homogenous in renal function than the human population, as most cats with hypertension suffer from CKD,[1] whereas in humans, CKD accounts for only a minority of the hypertension cases.[2] An alternative explanation could be that habitual drinking and dialysis contributes to fluid loading in humans, whereas CKD in the cat is associated with dehydration or hypovolemia, which tends to lead to reduced blood pressure.[24]

Cats that ultimately needed a greater dose to adequately control their blood pressure had a significantly higher blood pressure at presentation, but both groups had comparable SBP when normotensive control was

achieved. As there was an independent correlation between the absolute decrease in SBP and plasma amlodipine concentration, it could be suggested that cats with a greater SBP at initial presentation need to be started on a higher dose of amlodipine immediately. Based on the association between SBP at hypertensive visit and the required dose, the proposed starting dose for cats with a SBP ≥200 mmHg would be 1.25 mg amlodipine daily. Case reports exist in the literature of severe hypotension following an amlodipine overdose in humans,[25] and therefore, the recommendation is to monitor the patient's blood pressure 1 week after starting the medication. The relationship between plasma amlodipine concentration and absolute reduction in SBP has not been examined in the cat and studies investigating the safety margin of amlodipine and pharmacokinetic and pharmacodynamic (PK/PD) studies need to be performed in order to confirm this.

This study has a number of limitations. Firstly, cats were chosen for this study based on historically acquired data, which means that potentially important clinical information, such as time of last dosing, was missing for most subjects, precluding it from inclusion in the statistical analyses. However, plasma concentrations are expected to have already reached steady state in the cats included in this study, which might mean that time of last dosing was less important information. Secondly, cats only had blood samples taken when there was a clinical indication to do so. This means that we cannot be certain whether the cats that needed a dose increase from 0.625 to 1.25 mg/day were truly receiving the medication at the visit that the dose was increased. However, cats that were on a dose of 1.25 mg/day also had a blood amlodipine concentration that was twice as high as the concentration of cats that were on 0.625 mg, and the cats that needed 1.25 mg to adequately control their blood pressure also had significantly higher blood pressure at presentation. This makes it less likely that compliance was an issue in the less-responsive cats. The fact that there is a direct relationship between oral dose and plasma concentration, with a doubling of the dose of amlodipine resulting in a doubling of the plasma concentration, indicates that differences in oral bioavailability do not seem to play a role in the relative resistance of certain cats.

In conclusion, cats that need a higher dose of amlodipine to reach a target SBP of <160 mmHg have higher SBP at diagnosis of their hypertension, and lower plasma potassium concentration. Clinical response, measured by the decrease in SBP, is correlated with the plasma amlodipine concentration and the SBP at hypertensive visit. Cats with a higher blood pressure at presentation could benefit from a higher starting dose of amlodipine. Based on the data in this study, doses of 1.25 mg of amlodipine might be considered for therapy of systemic hypertension in cats with SBP ≥200 mmHg at diagnosis. Future work is necessary to investigate whether there is a difference in pathophysiological mechanisms causing the hypertension in the cats that respond well and the cats that respond less well.

Footnotes

[a] Parks Electronic Doppler Model 811B; Perimed UK, Bury St Edmunds, UK
[b] Mistral 3000, Sanyo-Gallenkamp, Leicestershire, UK
[c] IDEXX Laboratories, Wetherby, Yorkshire, UK
[d] Istin™ (Pfizer Ltd. Sandwich, Kent, UK)
[e] R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria
[f] GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego, CA

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Conflict of Interest Declaration: None of the mentioned grants or consultancies has a direct relationship with the presented work.

Jonathan Elliott has acted as a consultant for Bayer Ltd, Boehringer Ingelheim Ltd, CEVA Animal Health, Novartis Animal Health, Elanco Ltd, Orion Ltd, Vetoquinol Ltd, Waltham Centre for Pet Nutrition, Idexx Ltd, Royal Canin. He has received grants for research from Orion Ltd and CEVA Animal Health Ltd and consultancies from both these companies that have been involved in the development of the feline formulation of amlodipine.

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Off-label Medication Declaration: The amlodipine that the cats included in the study were receiving was the human variation (Istin 5 mg) as per the footnote in the study. None of these cats were receiving a cat formulation as this was not available in the United Kingdom at the time of the study, and none of the subjects was involved in the clinical trial leading to the registration of the cat-formulation Amodip.

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