Companion Animal

Secondary hypertension and its treatment in cats

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Secondary hypertension and its treatment in cats

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Abstract

Secondary hypertension, due to an underlying disease, is common in older cats especially in cats with CKD and/or hyperthyroidism. Systolic blood pressure (SBP) should be measured whenever an associated disease is diagnosed and persistent SBP >160mmHg should prompt treatment to prevent or reverse target organ damage (TOD). Amlodipine and telmisartan are licensed in the UK for treating feline hypertension and both drugs have been evaluated in prospective, randomised, placebo-controlled clinical trials in hypertensive cats with SBP 160-200mmHg that did not have evidence of TOD. Initial reductions of 20-30mmHg can be expected with either medication and cats should be re-evaluated after 14 days and dose adjustments made as required. No studies have compared the performance of one drug against the other and either medication should be selected as the first-line treatment for feline hypertension. At present, there is more data in the literature to support the use of amlodipine in cats with severe hypertension (SBP >200mmHg) or with evidence of ocular or neurological TOD.

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Abstract

Secondary hypertension, due to an underlying disease, is common in older cats especially in cats with CKD and/or hyperthyroidism. Systolic blood pressure (SBP) should be measured whenever an associated disease is diagnosed and persistent SBP >160mmHg should prompt treatment to prevent or reverse target organ damage (TOD). Amlodipine and telmisartan are licensed in the UK for treating feline hypertension and both drugs have been evaluated in prospective, randomised, placebo-controlled clinical trials in hypertensive cats with SBP 160-200mmHg that did not have evidence of TOD. Initial reductions of 20-30mmHg can be expected with either medication and cats should be re-evaluated after 14 days and dose adjustments made as required. No studies have compared the performance of one drug against the other and either medication should be selected as the first-line treatment for feline hypertension. At present, there is more data in the literature to support the use of amlodipine in cats with severe hypertension (SBP >200mmHg) or with evidence of ocular or neurological TOD.

Keywords: feline, telmisartan, amlodipine, target organ damage, CKD

Key points:

Secondary hypertension is common in older cats, particularly in cats with CKD and/or hyperthyroidism.

The aim of treatment is to manage or ideally prevent hypertensive target organ damage.

There are two licensed options for treatment of feline hypertension: amlodipine and telmisartan.

Either amlodipine or telmisartan should be selected as the first-line treatment.

The need for polypharmacy to management feline hypertension is rare.

Cats should be re-evaluated after 2 weeks and dose adjustments made as needed.

Main article

What is secondary hypertension?

There are three types of hypertension, or high blood pressure in cats; primary (idiopathic), secondary and situational (previously referred to as "white coat" hypertension). Secondary hypertension, where the hypertension develops in association with an underlying disease process or due to a medication or toxin, is the most common type of hypertension in cats (Acierno et al. 2018; Taylor et al. 2017). The conditions typically associated with hypertension occur with increasing prevalence in older cats, therefore the prevalence of secondary hypertension also increases with advancing age (Bijsmans et al. 2015; Conroy et al. 2018). The most common cause of hypertension in cats is chronic kidney disease (CKD) (Conroy et al. 2018; Elliott et al. 2001; Maggio et al. 2000; Sansom et al. 2004). Other conditions associated with high rates of hypertension include hyperthyroidism (Conroy et al. 2018; Elliott et al. 2001), acute kidney injury (AKI) (Cole et al. 2017) and hyperaldosteronism (although this condition is uncommon). Additionally, pheochromocytoma and Cushing's syndrome (Henry et al. 1993; Valentin et al. 2014) can cause hypertension, but both are rare in this species. Cats with diabetes mellitus can be documented to have concurrent hypertension, but it is not clear that it occurs with a higher frequency than in the background cat population (Al-Ghazlat et al. 2011). Documentation of any of these conditions should prompt blood pressure measurement; details on performing these measurements and when to do so are covered elsewhere [ref Companion Animal article on blood pressure measurement and when it is needed].

Systemic hypertension is usually diagnosed based on the measurement of systolic blood pressure (SBP). If a high definition oscillometric (HDO) machine is used for blood pressure measurement, then diastolic and mean arterial blood pressure values will also be obtained. However, Doppler machines are more commonly used in primary-care and referral practice, which only provide measurement of

SBP, and SBP measurement is considered most reliable in cats. As SBP rises, the risk of target organ damage (TOD) increases. Target organs are typically those with a rich arteriolar supply and include the eyes, brain, heart and kidneys. Although the exact point at which SBP is high enough to cause damage to these organs will vary between individuals, chronic sustained elevations in SBP typically above 170-180mmHg put cats at high risk for such damage occurring (Maggio et al. 2000; Mathur 2002; Sansom et al. 2004). The classification system for interpretation of feline blood pressure provided by the American College of Veterinary Internal Medicine (ACVIM) therefore has four categories of SBP measurement, detailing the risk of target organ damage (see Table 1) (Acierno et al. 2018).

When to instigate treatment

The aim of treatment is to reverse or ideally prevent TOD from occurring, therefore treatment of cats with moderate to high risk of TOD is recommended. Clinicians may worry that documentation of SBP >160mmHg might be due to situational hypertension, especially in a stressed cat. The following steps can be considered to aid in differentiating between situational and true hypertension:

- Allow the cat a short period of time to acclimatise in the clinic prior to blood pressure measurement.
- Make blood pressure measurement as calm as possible by performing it in a quiet room, ideally with the owner present.
- Obtain 5 similar consecutive readings and take an average of these. If average SBP >160mmHg, perform a fundic examination to check for evidence of TOD.
- Treatment should be initiated in all cats with evidence of ocular TOD. For further information on ocular TOD, see [Ref to Companion Animal article on ocular TOD].
- If there is no evidence of ocular TOD, recheck SBP on another day, ideally within the next 2 weeks. Start treatment if average SBP is still >160mmHg.

The prevalence of secondary hypertension in association with its common underlying conditions means that the likelihood of a cat having true hypertension rather than situational hypertension is high. Therefore, it is reasonable to err on the side of caution and initiate treatment in all cats suspected of secondary hypertension with repeatable SBP measurements >160mmHg. If an occasional cat is actually suffering from situational hypertension, the risk of hypotension with treatment is low (see below) and this is likely to be outweighed by the benefit of preventing TOD in all truly hypertensive cases.

Treatment options

In the UK, there are two licensed medications for the treatment of feline hypertension: amlodipine and telmisartan. One of these medications should be selected as the first-line treatment for each individual case. A summary of both medications is shown in Table 2.

Amlodipine

Amlodipine, is a calcium channel antagonist, acting on the L-type (long acting type) calcium channels that are mostly found in vascular smooth muscle. Administration of amlodipine blocks activation of these channels with action potentials and therefore prevents an influx of calcium needed to cause muscle contraction. Its action is therefore greater in more severely hypertensive patients where the vascular smooth muscle is more constricted. Amlodipine has been used for many years to treat feline hypertension prior to a cat specific licensed formulation being produced, and numerous studies have found that a reduction in SBP of 30-60mmHg can be expected (Elliott et al. 2001; Maggio et al. 2000; Mathur 2002; Snyder et al. 2001). Additionally, studies have demonstrated the utility of amlodipine to successfully treat TOD, including reversal of blindness in cats with hypertension induced retinal detachment (Maggio et al. 2000), cessation of seizures in cats with hypertensive encephalopathy (Kwiatkowska et al. 2019), and reduction of urine protein-to-creatinine ratio (UPC) (Jepson et al. 2007).

A chewable licensed form of amlodipine (see Table 2) was evaluated in a multicenter, prospective, double-blinded, placebo-controlled, parallel group study in Europe (Huhtinen et al. 2015). Enrolled cats (n=77) had persistent SBP ≥165mmHg but less than 200mmHg, although occasional cats with SBP >200mmHg could be included if the attending veterinarian was happy to do so. Cats with ocular or neurological TOD signs were excluded due to the placebo-controlled study design. Cats were randomized to amlodipine 0.125mg/kg PO q24h or placebo for 28 days, with a dose increase after 14days if required, and subsequently all cats were treated with amlodipine for up to 3 months. Less than a third of cats had idiopathic hypertension, with the majority having CKD or hyperthyroidism. Amlodipine was shown to be successful in treating hypertension, with 63% of cats achieving SBP <150mmHg or a reduction in SBP of ≥15% by 28 days, compared to 18% of cats receiving placebo. Adverse effects were uncommon and there was no difference between groups. No cats were documented to develop hypotension despite the fact that 15.6% of the cases were also receiving an angiotensin converting enzyme inhibitor (ACEi) during the study. Palatability for taking the tablet was high, at 80% in the amlodipine group.

Plasma amlodipine concentrations are directly related to the oral dose of amlodipine administered. The dose required by an individual cat to successfully control their hypertension can vary, but cats with a higher SBP at diagnosis require a higher amlodipine dose to achieve adequate control of their SBP. A study of 100 hypertensive cats treated with amlodipine found that cats with SBP >200mmHg were more likely to require a dose of 1.25mg q24h to reduce their SBP to <160mmHg compared to cats with SBP <200mmHg, where a dose of 0.625mg q24h was usually sufficient (Bijsmans et al. 2016).

Telmisartan

Telmisartan is an angiotensin II receptor blocker (ARB). As part of the renin-angiotensin-aldosterone system (RAAS), angiotensin II binds to two receptors, AT_1 and AT_2. Activation of the AT_1 receptor is

associated with a number of undesirable effects in CKD including vasoconstriction, proteinuria, glomerular hypertrophy, fibrosis and aldosterone release, whereas activation of the AT_2 receptor is associated with potentially beneficial effects in CKD including vasodilation, vascular protection and anti-fibrosis (Ni et al. 2020). As an ARB, telmisartan preferentially blocks the AT_1 receptor. This prevents constriction of the efferent arteriole in the glomerulus, thereby reducing glomerular pressure and proteinuria, and results in a lowering of systemic blood pressure. The RAAS is still not completely understood and recent work has shown that there are a number of additional angiotensin peptides whose actions may complement those of angiotensin II at the AT2 receptor, and whose concentrations can be affected by telmisartan in cats (Huh et al. 2021). However, further work is required to elucidate the actions of these additional peptides and the full benefits of telmisartan treatment.

Telmisartan has been shown to effectively lower blood pressure in awake healthy cats with surgically implanted pressure sensing telemetry devices and to prevent changes in SBP induced by administration of angiotensin I boluses (Jenkins et al. 2015). The effects of telmisartan administered in this setting were also shown to still be present after 24 hours. In contrast, benazepril was less effective and its effects much more short-lived. For this reason, and based on anecdotal use in the clinic, the use of benazepril for treatment of feline hypertension is no longer recommended.

Telmisartan has also been evaluated in two large prospective, randomised, double-blinded, placebo-controlled clinical trials, one performed in the USA (Coleman et al. 2019) and one in Europe (Glaus et al. 2019). The initial dosing regime was slightly different between the two studies, but otherwise the study design was analogous with a 28day placebo-controlled phased followed by an extended telmisartan use phase. Both studies included over 200 cats with persistent SBP 160-200mmHg and no evidence of ocular TOD. In the European study hypertension was idiopathic in just under 60% of cats and secondary to CKD, hyperthyroidism or both these comorbidities in the remaining cats (Glaus et al.

2019). In the USA study, hypertension was idioapathic in approximately 30% of cases and secondary to CKD, hyperthyroidism or both these comorbidities in the remaining cats (Coleman et al. 2019). Coleman et al administered telmisartan orally at 1.5mg/kg q12h for 14 days, followed by 2mg/kg q24h for 14 days. Glaus et al administered telmisartan orally at 2mg/kg q24h for 28 days. Across the two studies, 52-53% cats in the telmisartan groups achieved an SBP <150mmHg or a reduction of ≥15% in SBP by 28 days, which was significantly more cats than in the placebo groups, where 28% of cats achieved the same result. The incidence of serious adverse effects was similar between telmisartan and placebo treated groups, therefore likely due to comorbid conditions in these older cat populations. In one of the studies, multiple day vomiting occurred more frequently in the cats receiving telmisartan, but did not necessitate cessation of medication (Coleman et al. 2019). Hypotension occurred in 1-2% of cats. A possible concern when initiating treatment with an ARB is the potential for serum creatinine to increase due to a reduction in glomerular filtration rate with the change in glomerular pressures. This should be monitored for and treatment should never be initiated in dehydrated cats. However, notably, no significant changes in creatinine were seen in the cats in both studies mentioned above.

The use of telmisartan for more severe hypertension and in cats with evidence of TOD is less well reported. One case report of a cat with severe systemic idiopathic hypertension, demonstrated successful resolution of SBP 220-230mmHg with 2mg/kg telmisartan following a need to stop amlodipine due to development of gingival hyperplasia, and failure of benazepril 0.7mg/kg q24h to control SBP as monotherapy (Desmet and van der Meer 2017). No studies have reported on the use of telmisartan in cats with ocular TOD, however, telmisartan at 1mg/kg q24h has been shown to significantly reduce proteinuria in IRIS stage 2-4 cats with UPC >0.2 for 18 months (study end point) (Sent et al. 2015).

The placebo effect

One thing to note from these placebo-controlled trials, is that in all three studies there was a placebo effect seen, with 18-28% of cats achieving SBP <150mmHg or a reduction in SBP of ≥15% by 28 days despite all cats having to demonstrate persistently elevated SBP on two separate clinic visits prior to starting medication. This emphasises two things; firstly, that cats are likely to acclimatise to repeated blood pressure measurements and that repeated visits to establish the need for antihypertensive medication is advised if no evidence of TOD is present, and secondly, that rates of hypotension are very low with both of these medications, even if administered to cats that may have had reduction in their SBP without pharmaceutical intervention.

Does treating hypertension increase survival time?

There is no study demonstrating that treating cats with hypertension extends their survival time, but likely this is due to the lack of a control population, i.e. a group of cats that were not treated for their hypertension. Unexpectedly, studies have failed to demonstrate an association between how well controlled SBP is and survival time in hypertensive cats (Elliott et al. 2001; Jepson et al. 2007; Littman 1994; Syme et al. 2006), but the use of antihypertensive treatments in these studies may have masked the effect of hypertension on survival time. Survival is strongly associated with UPC at diagnosis and treatment of hypertension significantly reduces UPC (Jepson et al. 2007), emphasising the importance of treating hypertension to prevent TOD.

Can I combine medications?

Data of a small number of cats (n=10) receiving amlodipine for hypertension and telmisartan for management of proteinuria suggested that combination therapy is well tolerated (Sent et al. 2015). Anecdotally, compliance in administering medications is likely to decrease with polypharmacy, therefore, efforts should be made to use one medication to its full effect prior to introducing a second

medication. In the rare event that a cat's hypertension cannot be controlled with either amlodipine or telmisartan alone, combination of these medications should be trialled and the cat carefully re-examined to monitor for adverse effects including increases in serum creatinine and development of hypotension.

Conclusion

Secondary hypertension in common in older cats, especially in cats with CKD and/or hyperthyroidism. Both amlodipine and telmisartan are licensed in the UK for treating feline hypertension and both drugs have been evaluated in prospective, randomised, placebo-controlled clinical trials in hypertensive cats with SBP 160-200mmHg that did not have evidence of TOD. Initial reductions of 20-30mmHg can be expected with either medication and cats should be re-evaluated after 14 days and dose adjustments made as required. No studies have compared the performance of one drug against the other. At present, there is more data in the literature to support the use of amlodipine when evidence of TOD or severe hypertension (SBP <200mmHg) is present. It is very uncommon that a cat requires polypharmacy to successfully control hypertension.

Table 1: The categories for systolic blood pressure (SBP) interpretation in cats and dogs as outlined by the American College of Veterinary Internal Medicine (ACVIM) consensus statement (Acierno et al. 2018).

Category	SBP (mmHg)	Risk of TOD
Normotensive	140	Minimal
Prehypertensive	140-159	Low
Hypertensive	160-179	Moderate
Severely hypertensive	>180	High

Table 2: A summary of dosing and monitoring information for the licensed medications available to treat feline hypertension in the UK.

	Amlodipine	Telmisartan
Licensed formulation	Amodip® 1.25mg chewable tablets for cats (Ceva Animal Helath Ltd)	Semintra 10mg/kg oral solution for cats (Boehringer Ingelheim Animal Health UK Ltd)
Recommended starting dose	0.125-0.25mg/kg/day *Dose as* Cats 2.5-5.0Kg: half a tablet q24h Cats 5.1-10Kg: one tablet q24h	2mg/kg q24h
Recommended monitoring	After 14 days the dose may be doubled or increase up to 0.5mg/kg q24h if SBP response is not yet adequate	Reduce dose if needed after 4 weeks in 0.5mg/kg increments to target SBP 120-140mmHg
Warning for clients		Pregnant women should avoid contact with ARBs.

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