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Amlodipine, a calcium channel blocker, has recently been licensed for the treatment of hypertension in cats. The drug produces arterial vasodilation by a direct effect on vascular smooth muscle and indirectly by the release of vascular nitric oxide. It may also have an anti-hypertrophic effect on the heart and vessels. It undergoes hepatic metabolism and has been demonstrated to be very efficacious and well tolerated in cats.

**Key words:** Feline hypertension, amlodipine, calcium channel blocker, systolic blood pressure, vasodilation, cardiac remodelling

### Introduction

Amlodipine is a second-generation dihydropyridine and a mixture of two enantiomers, S- and R+, which give the drug a dual anti-hypertensive mechanism of action (Tissier et al. 2005):

**S- enantiomer**  
- a calcium channel blocker

Calcium entry, (via L-type channels) into vascular smooth muscle cells results in vascular contraction. Calcium channel blockers inhibit the opening of L-type calcium channels thereby producing arterial vasodilation. There is minimal venodilation at therapeutic doses. Calcium entry into cardiomyocytes not only results in their contraction but also a positive dromotropy (increase in the speed of atrioventricular AV nerve fibre conduction) and a positive chronotropy effect. Depolarisation of nodal tissue during diastole is also dependent on calcium entry into cells. Therefore calcium channel blockers can potentially cause negative inotropic and chronotropic effects on the heart. However, amlodipine is considered relatively selective for vascular smooth muscle. Its main effect is vasodilation, cardiac effects are only slight and are considered negligible at low doses (Ramsey 2011).

**R+ enantiomer**  
- a nitric oxide inducer

The R+ enantiomer has about one thousand times weaker activity than the S- enantiomer (Zhang et al. 2002). In-vitro dog and human studies have demonstrated that the R+ enantiomer of amlodipine activates nitric oxide (NO) synthase in coronary vessel endothelial cells, which will further enhance vasodilation (Zhang et al. 1999). Furthermore, NO has also been demonstrated to reduce myocardial oxygen consumption and increase oxygen consumption efficiency (Loker et al 1999). This could be of further benefit in patients with cardiovascular disease. Other work in normal canine hearts and failing human hearts has found there is a synergy between the NO induced release by ACE inhibitors and amlodipine when the drugs are used concurrently (Mital et al. 1999).

Drug Focus: amlodipine

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A small study (n=32) in human patients being treated for hypertension (with left ventricular (LV) hypertrophy) investigated the effects of amlodipine treatment on LV function and morphology (Motoki et al 2014). Measurements were taken at baseline and then regularly over the following year. A significant drop in systolic blood pressure was seen by one month after treatment started. Interventricular septum thickness and LV mass index were reduced by six months. Transmural flow, tissue Doppler and LV longitudinal strain were also improved.

A larger long-term human study (n=1006) following patients for up to 3.5 years also found that amlodipine treatment resulted in the regression of LV hypertrophy but this was not associated with an improvement in diastolic function (Barron et al 2014).

There is a published study looking at the effects of amlodipine treatment on the echocardiographic parameters of hypertensive cats (Snyder et al 2001). LV free wall thickness, interventricular septum thickness and left atrium size were measured (systolic and diastolic) in 19 hypertensive cats. All three measurements were significantly higher than published normal values and 74% of the cats had LV hypertrophy. Fourteen cats were treated with amlodipine for a minimum of three months. After treatment their mean systolic BP had decreased from 217 +/- 25mmHg to 142 +/- 27mmHg. No differences were found between the echocardiographic parameters of the treated and untreated cats. However, fewer of the cats in the treated group had ventricular hypertrophy after treatment than before the amlodipine, 6/14 compared to 11/14 (p=0.006). This study found ventricular hypertrophy is common in hypertensive cats and the results suggested that it could resolve after amlodipine therapy.

More recently, studies in SHR treated with amlodipine for six months, have demonstrated regression in cardiac remodelling, which persisted three months after the end of treatment (Sevilla et al 2014). There was a reduction in left ventricular hypertrophy and cardiac fibrosis. Amlodipine reduced systolic blood pressure (BP) in a dose dependent way and although it then increased progressively after treatment was withdrawn, systolic blood pressure did not reach the values of the untreated SHR control group.

Metabolism
Amlodipine undergoes hepatic metabolism and none of the main metabolites appear to show any significant pharmacological activity (Tissier et al 2005). Doses should therefore be reduced in patients with liver dysfunction and a risk benefit assessment made in each case (Ramsey 2011). Half the parent drug and its metabolites are excreted in urine and half via faeces (Tissier et al 2005).

Efficacy for hypertension in cats
According to the literature, amlodipine is safe and efficacious for the long-term control of feline systemic hypertension. Table 1 summarises the key published studies looking at amlodipine in hypertensive cats. Figures 2-4 show examples of the ocular manifestations of systemic hypertension in cats.

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