

## The antihypertensive effect of amlodipine in cats

### Efectul antihipertensiv al amlodipinei la pisici

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#### Abstract

The purpose of the study was to evaluate the effect of amlodipine on blood pressure and renal function in cats with arterial hypertension secondary to chronic renal failure. The research was conducted on 11 cats, aged between 7 and 14.5 years, diagnosed with arterial hypertension secondary to chronic renal failure. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MBP) and pulse rate were determined by oscillometric method, before and after 7, 30 or 120 days of treatment with amlodipine. At the beginning of treatment, all cats were receiving 0.625 mg amlodipine once daily and after 7 days of treatment, in five cats, the dose was increased to 1.25 mg amlodipine, once daily. Before amlodipine administration the mean values of SBP/DBP were  $175 \pm 13.2$  mmHg/ $119 \pm 7.2$  mmHg and after 30 days of treatment, the mean values of the SBP/DBP were reduced by 27.9/25.4 mmHg ( $p < 0.001$ ). After 120 days of treatment with amlodipine mean values of SBP/DBP were lower with 32/31 mmHg compared with baseline values ( $p < 0.001$ ). The treatment with amlodipine did not significantly affect the values of blood biochemical parameters of renal profile.

**Key words:** cats, arterial hypertension, amlodipine

#### Rezumat

Scopul acestui studiu a constat în evaluarea efectului amlodipinei asupra tensiunii arteriale și funcției renale la pisici cu hipertensiune arterială secundară insuficienței renale cronice apărută din cauze naturale. Cercetările au fost efectuate pe 11 pisici, cu vârsta cuprinsă între 7 și 14,5 ani, diagnosticate cu hipertensiune arterială secundară insuficienței renale cronice. Tensiunea arterială sistolică (TAS), tensiunea arterială diastolică (TAD), tensiunea arterială medie (TAM) și frecvența pulsului au fost determinate prin metoda oscilometrică, înainte și după 7, 30 respectiv 120 de zile de tratament cu amlodipină. La începutul tratamentului, amlodipina a fost administrată o dată pe zi, în doză de 0,625 mg/zi, iar după 7 zile de tratament, la 5 dintre pisicile incluse în acest studiu doza a fost mărită la 1,25 mg/zi. Valorile medii ale TAS/TAD înainte de administrarea amlodipinei au fost de  $175 \pm 13,2$  mmHg /  $119 \pm 7,2$  mmHg, iar la evaluarea de la 30 de zile, TAS/TAD s-au redus cu 27,9/25,4 mmHg. După 120 de zile de administrare a amlodipinei valorile medii ale TAS/TAD s-au redus cu 32/31 mmHg, diferențele față de valorile inițiale fiind semnificative ( $p < 0,001$ ) atât la 30 cât și la 120 de zile. Amlodipina nu a influențat semnificativ parametrii biochimici sangvini ai profilului renal.

**Cuvinte cheie:** pisici, hipertensiune arterială, amlodipină

In cats, arterial hypertension (AHT) is frequently associated with chronic kidney disease and hyperthyroidism. AHT following kidney disease is recorded in approximately 90% of the hypertensive cats.

AHT prevalence in cats with chronic renal failure, in the studies conducted so far, varies between 20 and 65% (6, 8, 12, 16).

Sustained AHT can lead to irreversible damage especially in richly vascularized organs, with high oxygen needs, known as *target organs*.

In hypertensive cats have been described ocular, cardiac, kidney or central nervous system lesions following sustained increasing arterial blood pressure (2, 3, 9).

The kidney, as a key regulator of the blood flow and vascular resistance, is equally a cause and a victim of AHT.

The correlation between hypertension, proteinuria and kidney disease progression

has been scientifically proven in studies on dogs and cats experiencing chronic renal failure by natural causes or induced experimentally.

Therefore, controlling arterial blood pressure altogether with diet measures, could slower the progression rate of the kidney disease towards the uraemia ending (6, 11, 15).

In veterinary medicine, the angiotensin converting enzyme inhibitors and calcium channel antagonists represent the main therapeutic agents recommended for their antihypertensive and antiproteinuric effects.

Amlodipine belongs to the calcium channel blockers. It produces vasodilatation by inhibiting L type calcium channels in smooth vascular cells.

Experimental studies and clinical cases on cats with AHT have proven that the vasodilator and hypotensive effect of

amlodipine is also efficient when administrated once a day at a dosage between 0.625-1.25 mg/kg b.w. (3, 6, 11, 13 15).

However, amlodipine, like other dihydropyridine derivatives, have the theoretical disadvantage that preferentially expands the kidney afferent arteriole, which could lead to glomerular hypertension consecutive to direct transmission of hypertension to the glomerular vascular bed (1, 4, 15).

**The purpose** of this study was to evaluate the effect of amlodipine on blood pressure and renal function in cats with naturally occurring chronic renal failure.

### Material and method

The research was performed on 11 cats aged between 7 and 14.5 years, diagnosed with AHT secondary to chronic renal failure at the University Veterinary Clinics, Timisoara.

Diagnosis of chronic renal failure was based on clinical signs and results of laboratory examination of blood and urine.

All cats included in this study had higher serum creatinin concentration of 1.9 mg/dl on two successive determinations, made at an interval of 2-3 weeks.

Blood pressure (BP) was determined by the oscillometric method, using the apparatus *Cardel Veterinary Monitor 9401*, which measured systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse rate.

BP measurement was done at the thoracic member median artery using cuffs with a median width of about 30-40% of the circumference of the forelimb.

To limit the influence of stress on BP, measurements were made in the presence of the owner, after a period of acclimatization (15-20 minutes) with the space, measuring device and after the cats were accustomed to the presence of cuff at the BP measurement site, by inflating and deflating the cuff repeatedly.

Blood pressure measurement was made after the cats were placed in a comfortable position, most often in sterna-abdominal decubitus, while the forelimb was removed from the body slightly forward.

Cats that were too stressed have been kept by the owners, in their arms and the forelimb was held at heart level.

Five measurements were made for each cat, at an interval of 20-30 seconds between two successive measurements.

Finally, was calculated the arithmetic mean of five measurements, which was used in statistical processing.

All cats included in this study had SBP/DBP >150/96 mmHg at least two blood pressure measurement sessions.

At the beginning of treatment, amlodipine was given one daily dose of 0.625 mg/day and after 7 days of treatment, at five of the cats included in this study, the dose was increased to 1.25 mg/day.

To observe the effect of the treatment, BP was measured before and after 7, 30 and 120 days of treatment.

Also, to assess the impact of amlodipine on renal function, blood and urine samples were taken before and after 7, 30 and 120, respectively, days of treatment.

Blood samples were taken from the forearm cephalic vein or jugular vein in lithium-heparin tubes and plasma was separated from red blood cell mass by centrifugation.

Biochemical parameters determined with semiautomatic biochemistry analyzer *Vet-Screen* were:

- albumin (colorimetric method, bromine cresol green);
- total proteins (colorimetric method with biuret);
- creatinine (picric acid colorimetric method - *Jaffe*);
- serum urea (urease colorimetric method);
- phosphorus (colorimetric method with ammonium molybdate);
- potassium (turbidimetric method with sodium tetraphenylborate).

Quantitative estimation of proteinuria was done by calculating the ratio of urinary protein/creatinine.

Urinary creatinine was determined by *Jaffe* method, after a preliminary dilution of 1:49 with saline solution, and the result was multiplied by 50.

Urinary protein was measured by colorimetric method with *red-pyrogallol*. Statistical processing of results was performed with *Anova* tests with *Tukey* and *Mann-Whitney*, and differences were considered significant at  $p < 0.05$ .

### Results and discussions

Treatment with amlodipine resulted in a gradual reduction in blood pressure, without

recording any events of hypotension in none of the cats.

Mean BP measured before and during treatment with amlodipine are shown in fig. 1.

Before taking amlodipine mean SBP/DBP were higher than 160/109 mmHg in all cats in this study.

After 7 days of treatment, although the mean SBP/DBP decreased by 16.1/15.1 mmHg, in 5 cats SBP/DBP was greater than 160/109 mm Hg.

Because, exceeding these values of SBP/DBP, there is increased risk of hypertensive lesions in target organs, the dose of amlodipine was increased to 1.25 mg/day in the cats in question.

At the 30 days evaluation, SBP/DBP decreased by a mean of 27.9/25.4 mmHg, and only two of the cats had SBP/DBP within the moderate risk category.

After 120 days of amlodipine administration, mean SBP/DBP decreased by 32/31 mmHg.

Only one cat had SBP/DBP > 150/100 mmHg, but at this value of hypertensive blood pressure the risk of organ damage is reduced.

It is worth noting that in most cats after 3 months of treatment, mean SBP/DBP were

significantly close to what, today, are the target of antihypertensive therapy in cats, ie, SBP/DBP < 150/90 mmHg.

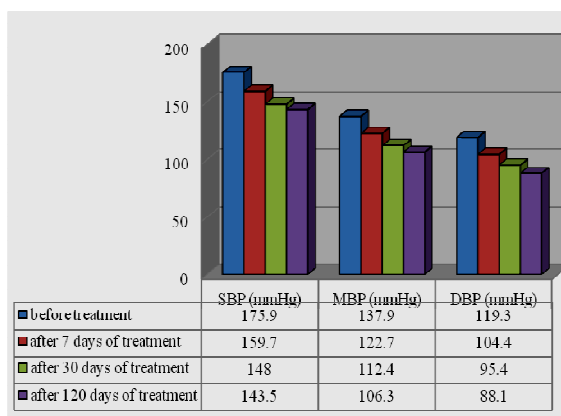


Fig. 1. Dynamics of the mean blood pressure values in cats treated with amlodipine

Comparing the blood pressure values measured before administration of amlodipine with those obtained after 7, 30 and 120 days of therapy significant differences were found ( $p \leq 0.001$ ) for both SBP and the DBP and MBP (table 1).

Table 1

Anova with Tukey test for the comparison of blood pressure mean equality taken before and after administration of amlodipine

Variables	Values measured before treatment	Evaluations during treatment	Mean differences (II-III)	Standard error	Deviation	Confidence Interval (95%)	
						Inferior limit	Superior limit
I	II	III	IV	V	VI	VII	VIII
SBP (mmHg)	1	2	16,17	4,37	0,004	4,38	27,96
		3	27,95	4,37	0,001	16,15	39,74
		4	32,39	4,37	0,001	20,60	44,18
DBP (mmHg)	1	2	14,86	3,16	0,001	6,32	23,41
		3	23,86	3,16	0,001	15,32	32,41
		4	31,20	3,16	0,001	22,65	39,75
MBP (mmHg)	1	2	15,13	3,22	0,001	6,44	23,82
		3	25,46	3,22	0,001	16,77	34,16
		4	31,58	3,22	0,001	22,88	40,27
PULSE (beats/min.)	1	2	5,17	3,82	0,54	-5,14	15,49
		3	3,26	3,82	0,83	-7,06	13,58
		4	2,53	3,82	0,91	-7,79	12,85

Note: 1 = before treatment;  
2 = after 7 days of treatment;  
3 = after 30 days of treatment;  
4 = after 120 days of treatment

In literature, most clinical studies performed on cats with hypertension have shown that amlodipine reduces blood pressure effectively and relatively quickly, to levels where the risk of organ hypertensive injury is negligible.

Thus, in a retrospective study performed on 30 cats with hypertension arising from natural causes, Elliot et al. (3) found SBP reduction from a mean of  $202.5 \pm 16.8$  to  $153.2 \pm 21.6$  mmHg in the first 50 days of treatment with amlodipine.

Similar results are reported by *Snyder et al.* (14), who achieved a reduction from a mean SBP of  $217 \pm 25$ - $142 \pm 27$  mmHg after three months of treatment with amlodipine on 13 cats with spontaneous hypertension.

Likewise, *Henik et al.* (5) reports that in 12 cats with hypertension, treated with amlodipine at a dose of 0.625 mg/kg, SBP was reduced from a mean of 198 mmHg to 155 mmHg.

In this study, the magnitude of blood pressure reduction in the cats treated with amlodipine was lower than that seen in other studies on cats with hypertension (3, 5, 14).

This is not surprising since, in the case of calcium channel blockers, blood pressure reduction is dependent on its level before treatment, respectively, higher BP prior to treatment results in a greater decrease in BP (4, 17).

Thus, in this study, we started from a mean SBP/DBP of 175/119 mmHg when the studies

in the literature mean BP was greater than 200 mmHg at the beginning of treatment.

The effect of amlodipine on the renal function was assessed in the light of changes in blood biochemical parameters of renal profile and that of the urinary protein/creatinin ratio.

Compared to the values recorded before treatment, during the assessments at 30 and 120 days, no significant differences were found for any of the blood biochemical parameters investigated (table 2).

It is noted that there were no significant increases in serum creatinin during treatment.

Because creatinin is an accurate indicator of glomerular filtration rate, we can say that amlodipine, at the dose administered, did not adversely affect the renal function.

**Table 2**

Effect of amlodipine administration on renal biochemical profile in cats

Variables	n	Mean	Standard deviation	Mean standard error	Minimum	Maximum
<b>Creatinine</b> (mg/dl)	1	2,85	0,74	0,22	1,90	4,40
	2	2,94	0,80	0,30	1,80	4,30
	3	2,93	0,87	0,33	2,16	4,50
<b>Urea</b> (mg/dl)	1	81,83	33,01	9,95	32,00	160,20
	2	74,00	18,67	7,05	45,00	97,00
	3	74,14	17,57	6,64	57,00	104,00
<b>Albumin</b> (mg/dl)	1	2,81	0,34	0,10	2,30	2,50
	2	2,70	0,23	0,08	2,40	3,00
	3	2,84	0,24	0,09	2,50	3,20
<b>Total protein</b> (mg/dl)	1	6,79	0,79	0,24	5,60	5,80
	2	6,60	0,51	0,19	5,80	7,40
	3	6,62	0,44	0,17	5,90	7,30
<b>Potassium</b> (mmol/l)	1	4,06	1,06	0,32	2,80	6,20
	2	4,84	0,69	0,26	3,60	5,60
	3	4,68	0,47	0,17	3,90	5,20
<b>Phosphorus</b> (mg/dl)	1	5,89	1,24	0,37	3,80	8,40
	2	5,87	0,85	0,32	4,50	7,20
	3	5,60	0,77	0,29	4,56	6,70
<b>Urinary protein/creatinine ratio</b> (mg/dl)	1	0,53	0,22	0,05	0,21	0,96
	2	0,41	0,10	0,03	0,24	0,56
	3	0,36	0,12	0,04	0,20	0,61

**Note:** 1 – values obtained before amlodipine administration;  
2 – values obtained after 30 days of amlodipine treatment;  
3 – values obtained after 120 days of amlodipine treatment

Proteinuria, assessed by value of the urinary protein/creatinine ratio, expressed a decreasing evolution in cats undergoing amlodipine treatment (fig. 2).

Before amlodipine administration the mean value of the urinary protein/creatinin *ratio* was  $0.53 \pm 0.22$  mg/dl, and after 30 days reduced to  $0.41 \pm 0.10$  mg/dl.

The difference was insignificant ( $p > 0.05$ ).

At the evaluation after 120 days, the ratio protein/creatinin decreased from  $0.36 \pm 0.12$  mg/dl, the difference from the initial value being still insignificant to the ratio ( $p = 0.057$ ), but very close to the threshold of significance 95%.

These results are clinically important for cats, as in human medicine are no holds on the use of calcium channel blocker alone as hypertensive agents.

Calcium channel blockers, particularly dihydropyridine derivatives, preferentially dilate afferent glomerular arteriole, which means that in the absence of adequate control of hypertension, vascular glomerular pressure increases greatly, exacerbating glomerular injury and loss of protein (4, 6, 17).

This effect is significant during inadequate reduced blood pressure under treatment.

Adequate blood pressure control or the implications of inadequate blood pressure control on proteinuria and progression of chronic nephropathies in cats are still insufficiently clarified.

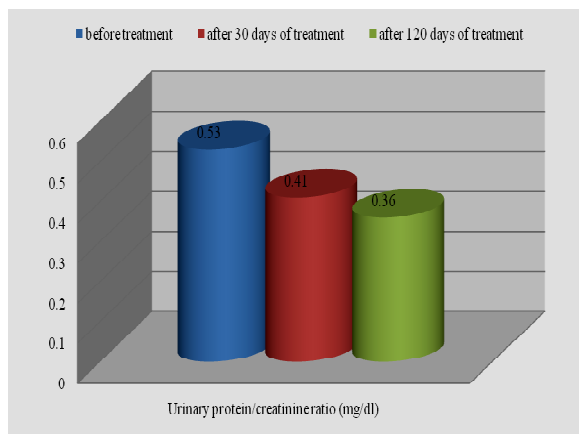


Fig. 2. Urinary protein/creatinine ratio before and during amlodipine treatment in cats

In a study of 141 hypertensive cats undergoing amlodipine treatment significantly reduced proteinuria, which was the only variable significantly associated with the survival time (6).

### Conclusions

1. Amlodipine administration led to a mean of 30 mmHg reduction in blood pressure, which justifies the recommendation of amlodipine to treat hypertension with moderate to severe risk of organ dysfunction.
2. The average time to stabilize blood pressure in cats in this study was approximately 30 days.
3. Amlodipine did not significantly affect blood biochemical parameters of renal profile, so does not adversely affect renal function in cats with chronic renal failure.
4. Treatment with amlodipine, by the antihypertensive effect and reducing proteinuria, could slow down the progression rate of chronic renal insufficiency to end-stage uremia.

### Bibliography

1. Brown, S., Atkins, C., Bagley, R., Carr, A., Cowgill, L., Davidson, M., Egner, Beate., Elliott, J., Henik, R., Labato, M., Littman, M., Polzin, D., Ross, L., Snyder, P., Stepien, R. (2007). *Guidelines for the Identification, Evaluation, and Management of Systemic Hypertension in Dogs and Cats*, *J. Vet. Intern. Med.*; 21:542–558.
2. Brown, S. A (2003). *The kidney as a target organ*. În: *Essential Facts of Blood Pressure in Dogs and Cats - A reference guide*, Ed. Egner Beate., Carr, A., Brown, S., Ed. Vet Verlag, Berlin, 121-128.
3. Elliott, J., Barber, P. J., Syme M. Harriet, Rawlings, J. M., Markwell, P. J. (2001). *Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases*, *Journal of Small Animal Practice*, 42 (3):122-129.
4. Gherasim, L., Dorobanțu Maria (2004). *Hipertensiunea arterială*. În: *Medicina internă, Ediția a-II-a, Bolile cardiovasculare și metabolice vol II*, Editor Gherasim, L., Editura Medicală, Bucuresti, 1058 – 1235.
5. Henik, R., Snyder, P. S., Volk, L. M. (1997). *Treatment of systemic hypertension in cats with amlodipine besylate*, *J. Am. Anim. Hosp. Assoc.*, 33, 3, 226-234.
6. Jepson Rosanne, Elliott, J., Brodbelt, D., Syme M. Harriet (2007). *Effect of Control of Systolic Blood Pressure on Survival in Cats with Systemic Hypertension*, *J. Vet. Intern. Med.*; 21:402–409.
7. Kraft W., Egner Beate (2003). *Causes and Effects of Hypertension*. În: *Essential Facts of Blood Pressure in Dogs and Cats - A reference guide*, Ed. Egner Beate, Carr, A., Brown, S., Ed. Vet Verlag, Berlin, 61-86.
8. Littman, M. P. (1994). *Spontaneous systemic hypertension in 24 cats*, *J. Vet. Intern. Med.*, 8, 2, 79-86.
9. Maggio Federica, Davidson, M.G. (2003). *The eye as a target organ*. În: *Essential Facts of Blood Pressure in Dogs and Cats - A reference guide*, Ed. Egner, B. Carr, A., Brown, S., Ed. Vet. Verlag, Berlin, 112-120.
10. Maggio Federica, Defrancesco, T. C., Atkins, C. E., Pizzirani, S., Gilger, B. C., Davidson, M. G., (2002). *Ocular lesions associated with systemic hypertension in cats (1995-1998)*, *JAVMA*, 217, 5, 695-702.
11. Mathur, S., Sheerin, Syme Harriet, Brown Cathy, Elliot, J., Moore, A. P., Newell, A. M., Munday, S. J., Cartier, M. L., Sheldon Suzanne E., Brown, S. A. (2002). *Effects of the calcium channel antagonist amlodipine in cats with surgically induced hypertensive renal insufficiency*, *American Journal of Veterinary Research*, 63, 6, 833-839.
12. Mishina, M., Watanabe, T., Fujii, K., Maeda, H., Takahashi, W., Takahashi, M. (1998). *Non-invasive blood pressure measurements in cats: clinical significance of hypertension associated with chronic renal failure*, *Journal of Vet. Med. Sci.*, 60, 7, 805-808.



13. **Snyder, P. S., Sadek, D., Jones, G. L. (2001).** *Effect of amlodipine on echocardiographic variables in cats with systemic hypertension, Vet. Intern. Med., 15, 1, 52-56.*
14. **Syme M. Harriet, Markwell, P. J., Pfeiffer, D., Elliot, J. (2006).** *Survival of cats with naturally occurring, chronic renal failure is related to severity of proteinuria, J. Vet. Intern. Med., 20, 3, 528-535.*
15. **Syme M. Harriet (2005).** *Diagnosis and management of the feline hypertension. Waltham Focus, 15:1, 31-37.*
16. **Syme M. Harriet, Barber, P. J., Markwell, P. J., Elliot, J. (2002).** *Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation, J. Am. Vet. Med. Assoc., 220, 12, 1799-1804.*
17. **Tissier, R., Perrot, S., Enriquez Brigitte (2005).** *Amlodipine: One of the main anti-hypertensive drugs in veterinary therapeutics, Journal of Veterinary Cardiology 7, 53-58.*