



Losartan

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Losartan is an oral angiotensin II type 1 (AT₁) receptor antagonist that is rapidly absorbed in dogs but has low oral bioavailability. Losartan therapy in veterinary patients with renal, heart, or liver disease is likely beneficial, but its use is limited due to lack of clinical data.

MECHANISMS OF ACTION

Once absorbed by the GI tract, losartan undergoes enterohepatic recirculation and biliary excretion.¹

- ▶ Recent human and veterinary studies have indicated that AT₁ receptor antagonists may be useful for treating patients with chronic disease, either in combination with angiotensin-converting enzyme (ACE) inhibitors or as replacement therapy for ACE inhibitors.^{2,3}
- ▶ ACE inhibitors (eg, enalapril, benazepril) are commonly used to inhibit the negative effects of the renin-angiotensin-aldosterone system (RAAS) on cardiac² and proteinuric renal³ diseases, with an emerging role in treating hepatic fibrosis (see **The Renin-Angiotensin-Aldosterone System**, page 48).
 - Despite ACE-inhibitor therapy, angiotensin II and aldoste-

rone can still be produced by alternate pathways, a phenomenon called *RAAS escape (or aldosterone escape)*.^{4,5}

- Despite the appropriate use of ACE-inhibitor therapy, patients with chronic disease can show negative effects of RAAS activation.

By blocking the actions of angiotensin II at its receptor, losartan leads to decreased aldosterone production, as well as decreased inflammation, fibrosis, hypertrophy, and vascular remodeling.⁶

- ▶ Because losartan is specific for AT₁ receptors, angiotensin II type 2 (AT₂) receptors are spared and continue to provide counter-regulatory effects.

CLINICAL APPLICATIONS

To date, losartan is well studied in experimental veterinary models and in human medicine, but few clinical trials exist in cats and dogs.

- ▶ Although fewer clinical veterinary studies have been published, current data and anecdotal evidence have indicated that patients with severe renal disease, proteinuria, systemic hypertension, cardiac remodeling, or hepatic fibrosis may benefit from cautious losartan therapy.^{3,7,8}

Losartan is most commonly used in cats and dogs with hypertensive or proteinuric renal disease.

Losartan is not typically recommended as a first-line therapy.

- ▶ It can be considered if proteinuria or systemic hypertension is not adequately controlled by treating as recommended by the International Renal Interest Society (ie, diet change, ACE inhibitors, traditional antihypertensive therapies [eg, amlodipine]).⁹
 - The recommended dose in azotemic patients is 0.125 mg/kg q24h.^{10,11}
 - Nonazotemic patients may be started on losartan therapy at a higher dose of 0.25 mg/kg q24h.¹²

Animal models of congestive heart failure have indicated that angiotensin II and aldosterone can promote adverse structural remodeling, which suggests therapies such as losartan may help prevent excessive collagen accumulation.¹³

- ▶ Experimental studies evaluating dogs with heart failure have indicated losartan decreases pre- and afterload and improves fractional shortening and stroke volume.¹⁴
- ▶ Cats and dogs with heart disease should be treated as indicated based on underlying disease processes and clinical signs with medications such as diuretics, positive inotropes, ACE inhibitors, and afterload reducers.
 - Losartan added to standard therapies may be of some benefit, but appropriate doses have not been determined.
 - Specific doses when used in veterinary patients with cardiac disease have not been established.
 - When extrapolating from other resources, the dose may range from 0.25-1 mg/kg PO q24h.
 - When considering losartan therapy in cardiac patients, clinicians should consider comorbidities and adjust the dose appropriately to minimize the risk for adverse events.

No clinical studies have evaluated losartan use in cats or dogs with fibrotic liver disease.

- ▶ Despite the lack of hard data, extrapolations from human medicine and animal models of liver disease have suggested the addition of losartan to standard hepatic support therapies may help improve long-term outcome.
 - Specifically, losartan offers anti-inflammatory and antioxidative actions that lessen the degree of hepatic fibrosis and promote healing.^{8,15}

– In these cases, losartan can be used at 0.25-0.5 mg/kg q24h.^{8,15,16}

MONITORING, ADVERSE EVENTS, & EFFICACY

Regardless of the system being treated, the primary goal of losartan therapy is to improve clinical signs and limit disease progression; it should also result in improved diagnostic parameters.

- ▶ Patients with renal disease should show stable or improved blood urea nitrogen (BUN) and creatinine and decreased urine protein:creatinine ratio (UP:C) and systemic blood pressure values.
- ▶ Patients with heart disease may demonstrate improved echocardiographic estimates of diastolic and systolic performance and delayed onset or recurrence of congestive heart failure.
- ▶ Patients with hepatic disease should have improved liver values and, if possible to complete a repeat biopsy, decreased fibrosis.

Caution and thorough recheck evaluation are recommended in all cats and dogs treated with losartan.

Common adverse events reported in humans and in experimental animal models include hypotension, azotemia, and hepatopathy.¹⁰

- ▶ The profile of adverse events of losartan has not been well documented in veterinary medicine; information is extrapolated from human medicine and from laboratory animal studies (mainly in rats).¹⁷
- ▶ Before initiating losartan therapy, patient blood pressure, BUN, creatinine, UP:C (when applicable), and liver values should be evaluated.
 - The dose should be reduced in patients with azotemia and moderate-to-severe liver dysfunction.
 - Recheck of these parameters should be completed 7 to 10 days after therapy is started, as well as after each dose adjustment.

ACE = angiotensin-converting enzyme
AT₁ = angiotensin II type 1
AT₂ = angiotensin II type 2
BUN = blood urea nitrogen
RAAS = renin-angiotensin-aldosterone system
UP:C = urine protein:creatinine ratio

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

OVERVIEW

The renin-angiotensin-aldosterone system (RAAS) is a complex hormone pathway that is essential in maintaining blood pressure, mediating inflammation, and regulating tissue fibrosis and proliferation.

- ▶ Factors such as β -adrenergic activity, decreased renal perfusion, and decreased renal sodium resorption can lead to renin release from the renal arterioles.
- ▶ The liver secretes angiotensinogen, which is cleaved in circulation by renin into the inactive peptide angiotensin I.
 - Inactive angiotensin I is converted to active angiotensin II and angiotensin III by angiotensin-converting enzyme (ACE).
 - Angiotensin II can also be produced via other pathways and enzymes.
 - Angiotensin II activates 2 receptors: angiotensin II type I (AT_1) receptors and angiotensin II type 2 (AT_2) receptors.
 - AT_1 receptors are found in the blood vessels, kidneys, adrenal glands, heart, liver, and brain.²¹
 - Activation of AT_1 receptors leads to adrenal gland production of aldosterone, which, when released, is associated with sodium resorption, potassium homeostasis, vasopressin release, vasoconstriction, inflammation, fibrosis, myocyte hypertrophy, and vascular remodeling.
 - AT_2 receptors are found in the adult adrenal gland, uterus, ovary, blood vessels, and brain.
 - Activation of AT_2 receptors has a counter-regulatory effect and leads to vasodilation as well as inhibition of inflammation and tissue proliferation.

RAAS INVOLVEMENT IN RENAL DISEASE

RAAS is activated and plays a protective role in early stages of renal disease by helping maintain blood pressure and perfusion.

- ▶ Patients display such clinical signs as polyuria/polydipsia, poor appetite, and weight loss.
- ▶ Diagnostic tests may reveal decreased urine specific gravity; elevations in SDMA, BUN, and creatinine; proteinuria; and elevated systemic blood pressure.
- ▶ Chronic stimulation of RAAS can result in glomerular vasoconstriction, increased glomerular permeability, ischemia, sclerosis, fibrosis, and inflammation.²¹

RAAS INVOLVEMENT IN CARDIAC DISEASE

Cardiac disease is often associated with decreased systemic blood pressure and decreased cardiac stroke volume, which leads to sympathetic stimulation and RAAS activation.²²

- ▶ Patients with advanced heart disease and heart failure often demonstrate decreased energy, weakness, collapse, tachypnea and dyspnea, and cough.
- ▶ Diagnostic tests may reveal cardiomegaly, poor systolic or diastolic function, and radiographic and/or ultrasonographic evidence of congestive heart failure.
- ▶ As with renal disease, RAAS activation is initially protective and leads to improved blood pressure and cardiac performance.
- ▶ Chronic stimulation of the RAAS in cardiac patients is detrimental and can result in myocardial and vascular hypertrophy and fibrosis.
 - These changes ultimately irreversibly compromise cardiac function and can contribute to heart failure.²²

RAAS INVOLVEMENT IN HEPATIC DISEASE

Acute liver injuries are associated with inflammation and tissue repair, both of which may lead to fibrosis over time; the RAAS is activated in patients with liver disease and is considered a key contributor to fibrosis.¹⁵

- ▶ Patients with severe hepatic fibrosis often demonstrate vague clinical signs (eg, lethargy, vomiting, inappetence).
 - In end-stage cases, patients may develop icterus, ascites, coagulopathy, or hepatic encephalopathy.
- ▶ Hepatic insult is associated with elevations in liver enzymes (eg, AST, ALT, ALP, GGT) as well as elevated total bilirubin concentrations.
 - Hepatic failure can lead to decreases in glucose, BUN, cholesterol, and albumin and increased total bilirubin, bile acids, and/or ammonia; derangements in coagulation factors may also be present.
 - Hepatic fibrosis is a histologic diagnosis and can be confirmed with special stains.
- ▶ Although hepatic fibrosis may be reversible, in some cases it is associated with significant chronic hepatic dysfunction and/or failure.

ACE = angiotensin-converting enzyme

AT_2 = angiotensin II type 2

RAAS = renin-angiotensin-aldosterone system

AT_1 = angiotensin II type 1

BUN = blood urea nitrogen

SDMA = symmetric dimethylarginine

- ▶ Losartan therapy should be discontinued if the patient develops new or progressive clinical signs or if laboratory values worsen.

Although losartan is the most commonly used AT₁ receptor antagonist blocker in veterinary medicine, some studies indicate it may not be the most effective.^{1,18,19}

- ▶ Recent publications have identified telmisartan as a potentially more effective AT₁ receptor antagonist because of increased bioavailability and suggest it may more effectively treat some chronic health conditions; in addition, recent and ongoing studies have evaluated the safety and usefulness of telmisartan in cats.²⁰
- ▶ Future veterinary studies evaluating losartan and related medications (eg, telmisartan, irbesartan) will likely help clarify the role of AT₁ receptor antagonist in dogs and cats. ■■■

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