EVALUATING TELMISARTAN
The angiotensin II receptor blocker telmisartan has been primarily used in cats, although a few case reports highlight its off-label use in dogs.

FOCUS ON

Telmisartan for Treating Systemic Hypertension

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Telmisartan, an angiotensin II receptor blocker (ARB), was approved by the US Food and Drug Administration in May 2018 to treat hypertension in cats. It is also used off label in dogs.

Since 1995, ARBs have been used to treat primary hypertension in humans and as adjunctive therapy for chronic renal disease and heart failure.[1] Commonly used ARBs in human medicine include losartan, valsartan, and telmisartan. However, their use in veterinary medicine is currently limited. There have been few veterinary studies investigating telmisartan. Therefore, the purpose of this article is to review the mechanism of action of telmisartan and summarize published reports of its use in veterinary medicine to date.

PATHOPHYSIOLOGY OF HYPERTENSION

In dogs and cats, primary hypertension is rare and typically occurs secondary to other disease processes.[2] In cats, systemic hypertension and proteinuria are common sequelae to chronic kidney disease (CKD) and untreated hyperthyroidism.[3,4] In dogs, systemic hypertension and proteinuria can be secondary to CKD[5] but also to other conditions, including acute kidney injury,[6] hyperadrenocorticism,[7] diabetes mellitus,[8] and pheochromocytoma.[9,10] In dogs and cats, systemic hypertension can lead to end organ damage throughout the body, resulting in, but not limited to, decreased renal function, proteinuria, retinopathy, encephalopathies, stroke, and left ventricular concentric hypertrophy.[11] The degree of proteinuria is negatively associated with median survival times in dogs[12] and cats[13,14] with CKD.

Angiotensin II is a peptide hormone that is upregulated in certain disease processes and has multiple effects throughout the body (**BOX 1**).[15] Angiotensin II is produced via the renin-angiotensin-aldosterone system (RAAS). In dogs and cats with CKD[3] and heart disease,[16] angiotensin II production is upregulated in response to chronic stimulation of the RAAS. Chronic RAAS activation ultimately increases angiotensin II and aldosterone production, which can lead to glomerular hypertension and induce glomerular hypertrophy and sclerosis.[17] In addition, angiotensin II and aldosterone cause increased preload and afterload on the heart[16] and induce myocardial inflammation and fibrosis,[18] further exacerbating disease states.

Angiotensin II acts primarily on angiotensin II type 1 and 2 receptors (AT1 and AT2) throughout the body. AT1 mediates production of aldosterone and its detrimental effects.[19] Activation of AT2 receptors can

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lead to renal and cardioprotective effects, including systemic vasodilation, natriuresis, inhibition of renin release, and renal protection from inflammation, ischemia, and fibrosis.[20]

Given the negative effects of AT1 and aldosterone in animals experiencing kidney disease and/or congestive heart failure, decreasing the production of angiotensin II and aldosterone is a therapeutic target.

TELMISARTAN

Pharmacology and Pharmacokinetics

Telmisartan is a selective AT1 receptor antagonist that blocks the effects of angiotensin II.[21] In vitro studies have shown that telmisartan dissociates from AT1 receptors slowly, acting as an insurmountable antagonist.[21] Thus, this receptor antagonism is long lasting.[22]

In humans, after oral administration with food, telmisartan bioavailability is decreased by 20%.[23] In cats, bioavailability after oral administration is 33% and not affected by food. Plasma levels peak at approximately 20 to 30 minutes, and half-life is approximately 8 hours.[24] In dogs, it is unknown whether bioavailability is affected by feeding or fasting, and absolute bioavailability is unknown. Plasma levels peak approximately 45 minutes after oral administration, and half-life is approximately 5.4 hours.[25] Telmisartan is lipophilic and in dogs, more than 98% is bound to plasma proteins,[26] but for cats, this information is not known. Telmisartan is metabolized via glucuronidation, which has been effective in in vitro studies using feline liver microsomes.[27] It is largely excreted unchanged in the feces.

Indications and Uses

Telmisartan has been primarily used in cats, although a few case reports highlight its off-label use in dogs. It is labeled to treat systemic hypertension[24,28] and proteinuria in cats[29] and has been used to treat systemic hypertension and proteinuria in dogs. It can be added to the treatment regimen for chronic heart failure, especially in those animals that cannot tolerate angiotensin-converting enzyme (ACE) inhibitors. Telmisartan also has anticancer properties.[30-33]

Telmisartan as a 10 mg/mL oral solution was recently approved in the United States[28] and European Union[24] for the control of systemic hypertension in cats. In dogs and cats, ACE inhibitors have only mild hypotensive effects.[34] In studies of healthy cats, telmisartan reduced systolic blood pressure.[35] It blocked the systolic pressure response to exogenous angiotensin I more effectively than benazepril, irbesartan, and losartan.[36] In addition, one case report highlighted the effectiveness of using telmisartan to treat systemic hypertension in a cat with gingival hyperplasia secondary to amlodipine administration.[37] In dogs, telmisartan has been used in combination with amlodipine to control systemic hypertension refractory to standard hypertension therapy.[38-40]

The blood pressure of patients receiving telmisartan should be routinely monitored. Indeed, for patients receiving any antihypertensive medication, blood pressure should be rechecked 7 to 10 days after starting or changing the dose and routinely monitored every 1 to 4 months, depending on patient stability and severity of the hypertension.[11]

In addition to treating hypertension, since 2014, telmisartan as a 4 mg/mL oral solution has been approved in the European Union for the treatment of proteinuria secondary to CKD in cats.[29] For dogs and cats, ACE inhibitors have been reported to decrease proteinuria but did not improve survival times.[3,34,41-43] In terms of decreasing proteinuria in cats with CKD, telmisartan was not found to be less effective than benazepril.[3] In one case report, refractory proteinuria in a dog initially treated with benazepril was successfully managed when telmisartan was added to the treatment regimen. The dog's proteinuria was eventually controlled by telmisartan alone when benazepril was discontinued.[44]

BOX 1 Effects of Angiotensin II Throughout the Body[2]

- Increased sympathetic nervous systemic activity
- Vasoconstriction
- Aldosterone production
- Sodium and water retention
- Antidiuretic hormone release
- Increased blood pressure

Chronic heart failure leads to increased production of angiotensin II. Currently, enalapril is the only ACE inhibitor labeled for the treatment of heart disease in dogs.[16] ACE inhibitors, but not ARBs, inhibit the breakdown of bradykinin and consequently result in vasodilation and natriuresis.[45] However, ACE inhibitors may result in incomplete neuroendocrine blockade because the conversion of angiotensin I to angiotensin II can be accomplished by enzymes other than ACE.[16,46] In a study of dogs receiving an ACE inhibitor for heart disease and heart failure, RAAS blockade was incomplete for approximately 30%.[47] Therefore, ARBs like telmisartan may produce a more effective neuroendocrine blockade, although one study in which a small sample of healthy dogs received telmisartan showed incomplete RAAS blockade.[40]

In human medicine, ARBs are recommended only for patients who are intolerant to ACE inhibitors.[48,49] Side effects of ACE inhibitors in humans include cough, hypotension, renal dysfunction,[48] and angioedema (in up to 0.7%).[50] For veterinary patients, cough is rarely reported.[34] Commonly reported side effects of enalapril in dogs include gastrointestinal upset (anorexia, diarrhea, vomiting), lethargy, hypotension, renal dysfunction, and hyperkalemia.[51] Therefore, telmisartan may be useful in those animals that cannot tolerate ACE inhibitors. Combination therapy with ACE inhibitors and ARBs may be beneficial for patients with proteinuria refractory to standard therapy as described above, but studies of humans found that combination therapy decreased glomerular filtration rate and was associated with hypotension, hyperkalemia, and acute renal failure.[52,53] If combination therapy is indicated, routine monitoring of renal values and blood pressure is recommended.

Telmisartan may also have anticancer properties. It is a peroxisome proliferator–activated receptor-gamma (PPARγ) agonist.[30] Activation of PPARγ can induce apoptosis in cancer cells.[54] Telmisartan has shown anticancer properties in both in vitro[31,32] and in vivo studies.[33] Current information is based on human medicine; research is needed to determine the efficacy of telmisartan as an anticancer agent in veterinary medicine.

Side Effects and Precautions

For cats, the telmisartan side effects reported to the Food and Drug Administration included vomiting, hypersalivation, weight loss, diarrhea, lethargy, weight loss, decreased appetite, nonregenerative anemia, dehydration, retinal lesions, and hypotension.[28] Because anemia is a reported side effect, routine monitoring of hematologic parameters is recommended every 3 to 6 months, depending on baseline values. If hypotension is noted, blood pressure should be periodically monitored and dosing adjusted accordingly. In clinical studies, adverse effects of telmisartan included gastrointestinal issues (vomiting, diarrhea, regurgitation) but did not require dosage alterations or study withdrawal.[3,35] Telmisartan has not been evaluated for safety and efficacy in cats younger than 6 months or in pregnant or lactating cats.[24,28] Although no formal studies of safety in dogs have been conducted, no adverse reactions have been reported.[38-40,44,55,56]

In humans, telmisartan increases serum digoxin levels[57]; therefore, if these drugs are administered concurrently, serum digoxin levels should be monitored. In humans, the antihypertensive effects of telmisartan may be diminished by concurrent use of cyclooxygenase-2 (COX-2) inhibitors. Moreover, concurrent administration of COX-2 inhibitors and telmisartan to patients who are volume depleted (including those receiving diuretic therapy) and those with decreased renal function may result in further deterioration of renal function. Periodic monitoring of renal parameters is recommended for human patients[58] and should also be routinely done for veterinary patients. The most serious consequence of overdosing telmisartan is hypotension, which can be managed symptomatically (fluid therapy, inotropes, vasopressors).[22]

SUMMARY

Telmisartan is a selective AT1 receptor antagonist[21] and, as a result, may mitigate the effects of chronic RAAS activation[19] while allowing angiotensin II to act on AT2 receptors to induce their renal and cardioprotective effects.[20] Telmisartan effectively reduces systemic hypertension and proteinuria in cats.[24,28] Isolated case reports or case series have found telmisartan to be effective at reducing proteinuria[39,44] and systemic hypertension[38-40] in dogs. Further research is needed to evaluate its clinical efficacy, safety, and adverse effects in dogs.

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