Second-Generation H_1 Antihistamines

Lluís Ferrer, DVM, PhD, DECVD
Tufts Cummings School of Veterinary Medicine

Second-generation H_1 antihistamines can be effective tools in the treatment of canine chronic urticaria. Anecdotal reports have also found them to be useful in the control of pruritus in some dogs with atopic dermatitis (AD) and in cats with allergic skin disease.

CLINICAL APPLICATIONS

Cetirizine (active metabolite of hydroxyzine), loratadine, and fexofenadine (active metabolite of terfenadine) are the most commonly used second-generation H_1 antihistamines in veterinary medicine.[1-4]

- Recommended dose protocols
  - Cetirizine
    - **Dogs:** 1 mg/kg PO once a day[1,3,5]
    - **Cats:** 5 mg/cat PO once a day[6,7]
  - Loratadine[1]
    - **Dogs:** 1 mg/kg PO 1-2 times a day
    - **Cats:** 2.5-5 mg/cat PO once a day
  - Fexofenadine (anecdotal)
    - **Dogs:** 5-10 mg/kg PO once a day
    - **Cats:** 15-30 mg/cat PO once a day
- All 3 medications are affordably priced.
  - One month of treatment costs <$60.

In dogs, the primary indications for use of second-generation H_1 antihistamines are chronic urticaria and AD.

- Acute and severe cases of urticaria have been treated with epinephrine and glucocorticoids (PO, IM, IV).[2]
  - In chronic or relapsing cases, all H_1 antihistamines can be effective in preventing development of new lesions, although they appear to have limited efficacy on existing lesions.[2]
- Clinical efficacy of any H_1 antihistamine treatment of canine AD is controversial, primarily because of the scarce number of well-designed randomized controlled trials.[8]
  - In a single-blinded placebo-controlled study, only 18% of dogs showed satisfactory pruritus control when treated with cetirizine at 1 mg/kg PO once a day.[3]
  - One double-blinded placebo-controlled study could not detect efficacy of terfenadine as an antipruritic agent in atopic dogs.[9]

- However, several open studies have shown acceptable results, especially in mildly pruritic dogs without chronic skin lesions.
  - In 1 study of 30 dogs, >60% had at least partial reduction of clinical signs when treated with 1 of 6 different antihistamines (ie, hydroxyzine, trimeprazine, chlorpheniramine, clemastine, promethazine, cyproheptadine), with hydroxyzine being the most effective.[10]
  - In a comparative study involving 30 dogs, fexofenadine at a high dose of 18 mg/kg PO once a day demonstrated the same efficacy as did methylprednisolone at 0.5 mg/kg PO once a day.[4]
  - A retrospective study showed that 25% of clients administering oral antihistamines to their atopic dogs reported high efficacy in controlling clinical signs.[11]

Despite varied study results, many dermatologists agree that all H_1 antihistamines have a place in the management of canine AD.[1,8]

- Prescribing an antihistamine for a minimum of 2 weeks before evaluating its effectiveness has been recommended.[1] The beneficial effect, if any, occurs within the first 7 to 14 days of treatment.
- Drugs of this class are best used as preventives before a flare occurs and should be given on a continuous daily basis to prevent or reduce severity of AD flares.[8]
- When using any H_1 antihistamine in the treatment of canine AD, recommended strategy is based on clinical observations and patient response.[12]
  - Efficacy appears to be variable among individuals.[1,8]
  - All H_1 antihistamines may be additive or synergistic in their effects when used with other medications (eg, supplemental essential fatty acids, corticosteroids) and are therefore considered steroid-sparing agents (ie, they may allow for steroid dose reduction).[13]
  - Sedative actions may be partly responsible for clinical benefit.[8]
    - In some patients, first-generation antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine, amitriptyline) may be more effective than second-generation antihistamines.[8]

Very few reports have been published on the efficacy of second-generation H_1 antihistamine treatment of allergic skin disease in cats.

- In 1 study, cetirizine administered at 5 mg/cat PO once a day was effective in controlling pruritus in 13 of 32 (41% of) cats with allergic skin disease.[7]
- Because of the steroid-sparing effect of antihistamines, they are usually given to allergic cats in combination with steroids.[2]

H_1 antihistamines, best used as preventives before a flare occurs, should be given on a continuous daily basis.[8]

PHARMACOLOGY

All H_1 antihistamines down-regulate allergic inflammation directly, acting as inverse agonists that combine with and stabilize inactive conformation of the H_1 receptor on sensory neurons and small blood vessels.[14,15]

- They also appear to decrease histamine release from basophils and mast cells in vitro.[16]
- Hydroxyzine and its metabolite cetirizine have demonstrable antihistaminic action in dogs and according to some authors should be the preferred antihistamines used in that species.[5,8]

Second-generation H_1 antihistamines were developed to avoid the sedation (considered a main side effect) of first-generation H_1 antihistamines.[15]

- Because of their lipid solubility, relatively high molecular weight, and affinity for the P-glycoprotein efflux pump, second-generation H_1 antihistamines penetrate poorly into the CNS.[17]
  - They also appear to have low potential of crossing the blood-brain barrier. P-glycoprotein further reduces the accumulation of cetirizine and fexofenadine in the CNS.[17]
- *Third-generation antihistamine* is occasionally used to define the newest members of this antihistamine family (ie, levocetirizine, desloratadine, fexofenadine).
  - However, the pharmacologic characteristics of both second- and third- generation antihistamines are essentially the same and, therefore, have been grouped together.[14]

AD = atopic dermatitis
CNS = central nervous system
H_1 = histamine 1 receptor

There may be some basis for the belief that second-generation H_1 antihistamines may not be as effective as their first-generation counterparts.

- However, good head-to-head comparisons of the pharmacologic actions of first- vs second-generation antihistamines are lacking.
- An advantage of second-generation H_1 antihistamines is their relatively minimal sedative effect as compared with their first-generation counterparts.[15]
  - Second-generation drugs are considered a good alternative for patients that respond to antihistamines but present with unwanted side effects (eg, drowsiness, behavioral changes).[12]
    - However, as noted earlier, the sedative actions of first-generation antihistamines may have clinical benefits in some patients.[8]
- Another main advantage is the longer half-life of second-generation antihistamines and once- or twice-daily administration.
  - In dogs, the terminal half-life of cetirizine is 10 to 11 hours.[5]
    - In comparison, first-generation antihistamines require more frequent administration (ie, 2-3 times a day).[5]

DRUG INTERACTIONS & ADVERSE EVENTS

No known contraindications are associated with second-generation H_1 antihistamines.

- Substances that act as inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme (eg, ketoconazole, erythromycin, cimetidine) can lead to increased plasma levels of loratadine.[15]
- In the author's experience, cetirizine, loratadine, and fexofenadine appear to be well tolerated in dogs and cats.
  - Vomiting, loss of appetite, or drowsiness has occasionally been reported.[3,4]

Terfenadine, a second-generation H_1 antihistamine, has shown cardiotoxic effects (ie, arrhythmia, prolonged QT interval) in humans, especially at high doses.[15]

- This product has been removed from the market in the United States, Canada, and most European countries.
- Cardiotoxicity has not been detected in canine or feline patients receiving cetirizine, loratadine, or fexofenadine.

LLUÍS FERRER, DVM, PhD, DECVD, is professor of veterinary dermatology at Tufts Cummings School of Veterinary Medicine. Dr. Ferrer's research focuses on canine leishmaniasis, canine AD, canine demodicosis, and the use of stem cells as a therapy in veterinary dermatology. He earned his DVM and PhD at the University of Zaragoza (Spain).

AD = atopic dermatitis
CYP3A4 = cytochrome P450 3A4

References appear online at **plumbstherapeuticsbrief.com**

References

1. Bloom P. Nonsteroidal, nonimmunosuppressive therapies for pruritus. *Vet Clin North Am Small Anim Pract*. 2013;43(1):173-187.
2. Miller WH Jr, Griffin CE, Campbell KL. *Muller & Kirk's Small Animal Dermatology*. 7th ed. St. Louis, MO: Mosby Elsevier; 2013.
3. Cook CP, Scott DW, Miller WH, Kirker JE, Cobb SM. Treatment of canine atopic dermatitis with cetirizine, a second generation antihistamine: a single-blinded, placebo-controlled study. *Can Vet J*. 2004;45(5):414-417.
4. Plevnik A, Kobal S, Domanjko-Petric A, Kotnik T. The efficacy of antihistamine fexofenadine versus methylprednisolone in the treatment of atopic dermatitis in dogs. *Slov Vet Res*. 2009;46(1):5-12.
5. Bizikova P, Papich MG, Olivry T. Hydroxyzine and cetirizine pharmacokinetics and pharmacodynamics after oral and intravenous administration of hydroxyzine to healthy dogs. *Vet Dermatol*. 2008;19(6):348-357.
6. Papich M, Schooley EK, Reinero CR. Pharmacokinetics of cetirizine in healthy cats. *Am J Vet Res*. 2008;69(5):670-674.
7. Griffin JS, Scott DW, Miller WH Jr, Tranchina MM. An open clinical trial on the efficacy of cetirizine hydrochloride in the management of allergic pruritus in cats. *Can Vet J*. 2012;53(1):47-50.
8. Olivry T, DeBoer D, Favrot C, et al. Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA). *BMC Vet Res*. 2015;11:210.
9. Scott DW, Miller WH Jr, Cayatte SM, Decker GA. Failure of terfenadine as an antipruritic agent in atopic dogs: results of a double-blinded, placebocontrolled study. *Can Vet J*. 1994;35(5):286-288.
10. Paterson S. Use of antihistamines to control pruritus in atopic dogs. *J Small Anim Pract*. 1994;35(8):415-419.
11. Dell DL, Griffin CE, Thompson LA, Griffies JD. Owner assessment of therapeutic interventions for canine atopic dermatitis: a long-term retrospective analysis. *Vet Dermatol*. 2012;23(3):228-e47.
12. Ferrer L. Unpublished data and clinical observations. Tufts Cummings School of Veterinary Medicine; cited as of November 2015.
13. Zur G, Ihrke PJ, White SD, Kass PH. Antihistamines in the management of canine atopic dermatitis: a retrospective study of 171 dogs (1992-1998). *Vet Ther*. 2002;3(1):88-96.
14. Mahdy AM, Webster NR. Histamine and antihistamines. *Anaesth Intensive Care Med*. 2011;12(7):324-329.
15. Simons FE, Simons KJ. Histamine and H_1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*. 2011;128(6):1139-1150.
16. García G, DeMora F, Ferrer L, Puigdemont A. Effect of H_1-antihistamines on histamine release from dispersed canine cutaneous mast cells. *Am J Vet Res*. 1997;58(3):293-297.
17. Obradovic T, Dobson GG, Shingaki T, Kungu T, Hidalgo IJ. Assessment of the first and second generation antihistamines brain penetration and role of P-glycoprotein. *Pharm Res*. 2007;24(2):318-327.