An In-Depth Look:

FELINE BRONCHIAL ASTHMA

Feline Bronchial Asthma: Treatment*

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ABSTRACT:

Treatment of feline bronchial asthma is directed toward promoting bronchodilation, reducing inflammation, and restoring normal mucus clearance. Therefore, determining and subsequently eliminating the inciting cause(s) of feline bronchial asthma should be the therapeutic priority of veterinary practitioners. Emergency treatment, including supplemental oxygen therapy, glucocorticoids, β_2-adrenergic agonists, and methylxanthines, is often indicated. Long-term therapy is aimed at further reducing inflammatory cell infiltration into the tracheobronchial tree and may be accomplished with inhalant glucocorticoids and antileukotriene medications.

Feline bronchial asthma is a reversible respiratory condition of the lower airways characterized by altered airway immunosensitivity. Many medications, including β_2-adrenergic agonists and glucocorticoids, are available for treating acute and chronic feline bronchial asthma (see boxes on page 427; Table 1). In addition, novel therapies, most notably adjuvant magnesium and leukotriene modifiers, are currently being intensely investigated as therapeutic adjuncts in managing feline bronchial asthma.

β_2-ADRENERGIC AGONISTS

β_2-adrenergic agonists are used extensively in treating acute asthmatic patients in veterinary and human medicine; these drugs are the rapid stimulators of β_2-adrenergic receptors, producing almost immediate relaxation of airway smooth muscle.[1–3] Albuterol sulfate and terbutaline sulfate are oral β_2-adrenergic agonists used in veterinary medicine for their speedy and beneficial effects, including bronchodilation, inhibition of acetylcholine release, stabilization of mast cell membranes, reduction of vascular permeability, and promotion of mucociliary clearance.[3] Terbutaline sulfate is also avail-

*A companion article on pathophysiology and diagnosis appears on page 418.

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Drugs Contraindicated for Use with β_2-Adrenergic Agonists in Treating Feline Bronchial Asthma

Sympathomimetic amines
- Isoproterenol (Isuprel, Sanofi Winthrop)
- Epinephrine (AmVet Epinephrine 1:1,000, Neogen)
- Dopamine (Intropin, Faulding)
- Dobutamine (Dobutrex, Lilly)

Tricyclic antidepressants
- Imipramine hydrochloride (Tofranil, Novartis)
- Imipramine pamoate (Tofranil-PM, Novartis)
- Amitriptyline (Elavil, Zeneca)
- Clomipramine (Clomicalm, Novartis)
- Doxepin (Sinequan, Roerig)

Monoamine oxidase inhibitors
- Selegiline hydrochloride (Anipryl, Pfizer)

Treatment Protocols for Cats with Acute Bronchial Asthma[2,6]

Intermittent clinical signs
- Albuterol sulfate inhaler (108 µg as needed)

Mild to moderate clinical signs
- Supplemental oxygen therapy
- Albuterol sulfate inhaler (108 µg as needed) or terbutaline sulfate (0.325–0.625 mg [total dose/cat] PO bid or tid)
- Theophylline extended release (25 mg/kg PO in the evening) or aminophylline (6.6 mg/kg PO bid)
- Prednisolone (1 mg/kg PO bid for 5 days, then 1 mg/kg PO sid for 5 days, then 1 mg/kg PO every other day for 5 days)
- Fluticasone propionate inhaler (110–220 µg bid)

Initial treatment for severe clinical signs
- Supplemental oxygen therapy
- Albuterol sulfate inhaler (108 µg q30–60min until respiratory distress resolves) or terbutaline sulfate (0.01 mg/kg SC or IM up to q4h)
- Dexamethasone sodium phosphate (1 mg/kg IV or IM)
- Consider adjuvant magnesium administration

After stabilization
- Prednisolone (1 mg/kg PO bid for 5 days, then 1 mg/kg PO sid for 5 days, then 1 mg/kg PO every other day for 5 days)
- Fluticasone propionate inhaler (220 µg bid; wean to lowest possible dose)
- Albuterol sulfate inhaler (108 µg as needed)

able as an injectable medication and may be administered subcutaneously or intramuscularly. Administration of these medications is contraindicated if a patient is receiving concurrent sympathomimetic amines, tricyclic antidepressants, or monoamine oxidase inhibitors because these medications may perpetuate various cardiac dysrhythmias (see box on this page). Furthermore, administration of β_2-adrenergic agonists should be avoided in patients being treated for cardiac disease because these medications have a minimal effect on β_1 receptors in the heart.[4] Stimulation of cardiac β_1 receptors may evoke tachyarrhythmias; thus all patients receiving β_2-adrenergic agonists should be closely monitored for evidence of tachycardia, tremors, central nervous system (CNS) excitement, hypertension, vomiting, mydriasis, and dizziness.[4]

METHYLXANTHINES

Human and veterinary pharmacology studies have demonstrated that methylxanthines inhibit phosphodiesterase—the enzyme responsible for cAMP degradation.[5,6] This class of bronchodilators is the most widely used and studied in cats with acute asthma, and although the effects of the drugs are rapid, the mechanism of action in feline bronchial asthma remains unclear because methylxanthines do not inhibit phosphodiesterase at therapeutic levels.[3,7,8] Aminophylline and theophylline promote swift bronchodilation, stabilize mast cells, increase frequency of ciliary beating, and enhance diaphragmatic contractile strength, possibly by depressing the rate of cAMP degradation.[3] Methylxanthines should be cautiously administered to patients with cardiac disease because these medications have inotropic and chronotropic effects.[4] Tachyarrhythmia may also develop following methylxanthine administration. These medications also increase gastric acid secretion, and signs of nausea and vomiting may manifest. Other potential signs of methylxanthine intoxication are the results of profound CNS excitation, including nervousness, excitability, tremors, ataxia, and/or seizures. Both nonsustained and sustained release products are available for prescription. The bioavailability of orally administered nonsustained release products is reportedly 100%, whereas that of sustained-release products is significantly lower.[4–7] However, the duration of effect of the sustained-release medications is longer, allowing lower doses and/or reduced dosing frequencies.

Table 1. Drugs Commonly Used in Treating Feline Bronchial Asthma[4]

Drug	Brand, Manufacturer	Dose
Terbutaline sulfate	Brethine, Geigy	0.312–0.625 mg (total dose/cat) PO q24h
Albuterol sulfate	Proventil, Schering	108 µg inhaled as needed
Prednisolone	Prelone, Muro	1–2 mg/kg/day PO
Theophylline extended release	Slo-bid, Rhône-Poulenc Rorer	25 mg/kg PO q24h in the evening
Theophylline	Theolair, 3M Pharmaceuticals	6–8 mg/kg PO bid
Fluticasone propionate	Flovent, GlaxoSmithKline	44–220 µg inhaled bid
Zafirlukast	Accolate, AstraZeneca	1–2 mg/kg PO q24h bid
Montelukast sodium	Singulair, Merck	0.25–0.50 mg/kg/day PO
Dexamethasone sodium phosphate	Dexaject SP, Vetus	1 mg/kg IV
Cyproheptadine hydrochloride	Periactin, Merck	1–2 mg PO bid

GLUCOCORTICOIDS

Glucocorticoids are essential in treating bronchial asthma patients in critical condition. These drugs bind to cytosolic receptors, and the glucocorticoid-receptor complexes move to an intranuclear position to alter gene transcription. Specifically, glucocorticoids are thought to inhibit transcription of proinflammatory mediators, most notably interleukin (IL)-5, released in cats with bronchial asthma. These drugs also markedly reduce the number of macrophages, lymphocytes, neutrophils, eosinophils, and mast cells involved in airway inflammation because they decrease the rate of inflammatory cell diapedesis and migration, promote apoptosis of these cells, and decrease mucus production. The results of one human study documented that glucocorticoids indirectly augment bronchodilation by increasing the number of β_2-adrenergic receptors and acting synergistically with methylxanthines.[9] Glucocorticoids do not have an onset of action as rapid as β_2-adrenergic agonists and/or methylxanthines; thus the benefits of altered gene transcription and reduced cellular infiltration are not immediately apparent. The oral glucocorticoids of choice in treating cats with bronchial asthma are prednisolone and prednisone. Prednisone is reduced in the liver via glutathione metabolism to form the active hydroxyl form—prednisolone; a relatively recent study documented reduced glutathione levels in both dogs and cats with naturally occurring liver disease.[10,11] Thus cats suspected of having any level of glutathione depletion and/or significant underlying hepatic disease may benefit more from prednisolone therapy. The effects of chronic, oral steroid treatment in cats may include insulin resistance, polyuria, cystitis, and inappropriate urination. Therefore, inhaled steroids that do not cause profound systemic effects are gaining popularity.

Acute therapeutic intervention for feline bronchial asthma may involve administration of β_2-adrenergic agonists, glucocorticoids, methylxanthines, and magnesium therapy.

Glucocorticoids and bronchodilators may be given effectively by inhalation to cats experiencing acute episodes of bronchial asthma; each class of drug is available as a metered-dose inhaler[12] (see boxes on page 429). Albuterol sulfate is a β_2-adrenergic agonist used as a metered-dose aerosol medication. Fluticasone propionate and beclomethasone dipropionate are more common inhalant glucocorticoids available at various doses per actuation. Multiple human studies have demonstrated a

Veterinary Spacers

- Opti Chamber (Respironics HealthScan Asthma and Allergy Products, Cedar Grove, NJ)
- Aero Chamber (Forest Pharmaceuticals, St. Louis, MO)
- Aerokat (Trudell Medical International, London, ON, Canada)

Instructions for Using a Metered-Dose Inhaler for Cats with Asthma

- Insert the metered-dose inhaler into the back of the spacer chamber, and shake it for 15–20 sec.
- Apply the mask securely to the cat's face.[a]
- Depress the metered-dose inhaler, and hold the mask in place for at least five breaths.

[a]We recommend periodically placing the mask on the cat's face during asymptomatic periods to help acclimate it to the device.

significant ability to reduce oral glucocorticoid doses with the addition of inhaled glucocorticoid therapy, thus significantly reducing the likelihood of severe systemic side effects.[13,14] Bronchodilators should be administered before glucocorticoids to help maximize lung distribution of glucocorticoids.

Humans must coordinate inhalation with actuation (i.e., pressing) of the device, and this harmonization is profoundly difficult when medicating infants and cats. Therefore, scientists developed a spacer—a cylindrical device into which an metered-dose inhaler fits at one end (see box on this page); at the other end of the spacer is an attachment for a face mask. At the end of a human-modeled spacer, there is a one-way valve connected to a face mask, allowing medication within the spacer to leave only during inhalation[12] (Figure 1). Spacers come in many different shapes and sizes, and veterinary studies have used small-volume or pediatric spacers when evaluating cats.[12,15] Specific feline models have recently been developed to conform to feline facial structures (Figure 2).

Long-term therapy for feline bronchial asthma may include glucocorticoids and antileukotriene medications.

MAGNESIUM

Magnesium can also be used in treating acute feline bronchial asthma. Administering adjuvant magnesium to patients experiencing acute asthmatic attacks is being actively researched in both human and veterinary medicine because initial human reports indicated that intravenous administration of magnesium in patients with acute bronchospasm significantly improved airway function.[16,17] The mechanism of action of magnesium has not been definitively elucidated in veterinary medicine, and to our knowledge, no current scientific studies have investigated adjuvant magnesium administration in cats with asthma. Some human research has focused on the ability of the magnesium cation to antagonize calcium, thereby inhibiting calcium-mediated muscle contraction. Other proposed mechanisms from human studies include interference with parasympathetic stimulation, potentiation of β_2-adrenergic agonist effects, and influence on sodium–potassium–ATPase.[16–19] Because no parenteral formulation of magnesium has been approved for use in animals, research into the veterinary pharmacokinetics and efficacy of this drug in treating feline bronchial asthma is needed. Furthermore, veterinarians should be aware of the potential side effects of adjuvant magnesium administration, including CNS depression, hypotension, bradyarrhythmias, and muscular weakness.[4]

LEUKOTRIENE MODIFIERS

Leukotriene modifiers are a promising group of novel antiinflammatory agents being used to combat feline bronchial asthma. Arachidonic acid is converted to leukotrienes by lipoxygenases. Furthermore, these proinflammatory mediators cause significant bronchoconstriction; therefore, leukotriene-receptor antagonists and specific inhibitors of the lipoxygenase pathway show great promise as new therapies for feline bronchial asthma. Currently, two types of antileukotrienes are available for prescription. Zafirlukast and montelukast sodium obstruct the receptor sites for leukotrienes, thus blocking their ability to contract bronchial smooth muscle. Zileuton inhibits 5-lipoxygenase, an enzyme in the

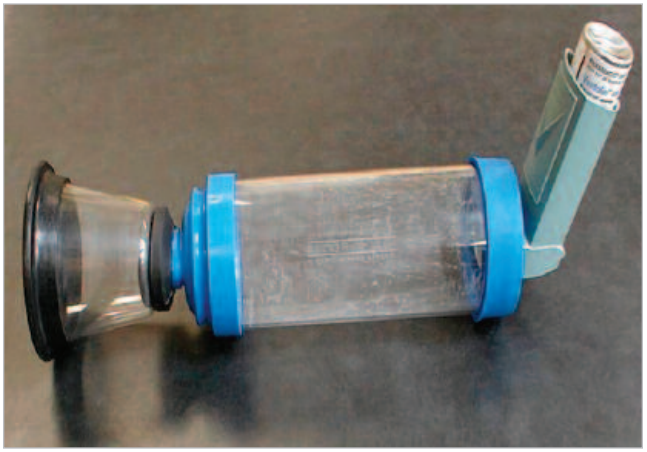

Figure 1. An alternate inhalant medication delivery device composed of a human pediatric spacer and a small inhalant anesthesia delivery face mask.

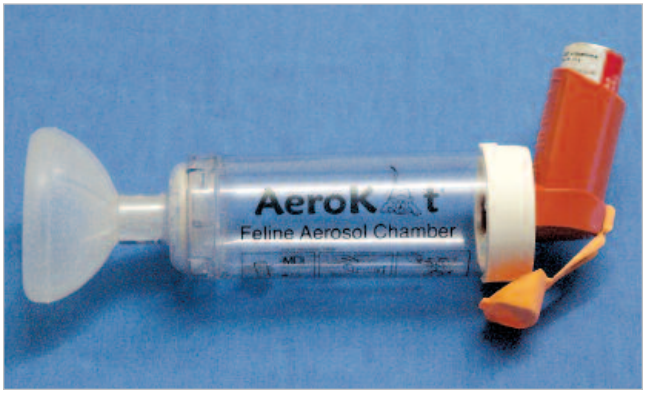

Figure 2. Many companies, including Aerokat (www.aerokat.com), have developed devices to facilitate delivery of inhalant medications to cats with bronchial asthma. This cat-specific design does not have a one-way valve connecting the face mask to the spacer chamber. (Courtesy of Trudell Medical International, London, Ontario, Canada)

lipoxygenase pathway.[3,20] This drug is available for use, but initial results of a recent study documented no significant benefit in reducing airway eosinophilia.[12,21,22] Leukotriene modifiers are not effective for use in acute episodes of feline bronchial asthma because their effects are not rapidly observed in patients. Some human studies and anecdotal veterinary evidence have indicated that these drugs can minimize the dose of administered steroids (i.e., steroid-reducing effect), possibly indicating that leukotriene modifiers may be helpful in treating mild cases of feline bronchial asthma.[23] Additional investigation is needed to definitively determine the effectiveness of these medications as standard components of feline bronchial asthma management.

Inhaled corticosteroids and β_2-adrenergic agonists have shown promise in treating cats with acute and chronic bronchial asthma.

CYPROHEPTADINE

Cyproheptadine hydrochloride is a histamine antagonist commonly administered as an appetite stimulant in cats. In addition, this medication has potent antiserotonin activity—a facet of its pharmacology that may prove clinically useful in cats with bronchial asthma.[3] Clinical research has shown that serotonin may cause airway smooth muscle contraction, and a recent study demonstrated measurable serotonin levels in mast cells of feline airways in vitro.[24] Potential side effects of cyproheptadine administration include CNS depression and dry mucus membranes. Paradoxical excitation may also be seen.[4] Although the theoretical use of cyproheptadine hydrochloride may prove to be an important therapeutic adjunct in treating feline bronchial asthma, further clinical research is needed to determine the effectiveness of this medication in vivo.

CYCLOSPORIN A

Cyclosporin A is an immunosuppressant agent with efficacy primarily against cell-mediated immune responses. Pharmacologic investigation of this medication determined that cyclosporin A acts through reversible inhibition of helper T cells.[4] Potential side effects of cyclosporin A administration include vomiting, diarrhea, anorexia, increased hair growth, nephrotoxicity, and hepatotoxicity. A recent study documented that cyclosporin A inhibited production of immune cells responsible for the development of airway hyperrespon-

siveness and inflammation in cats.[25] However, administration of this medication is typically reserved for patients unresponsive to more traditional therapies.

CONCLUSION

Feline bronchial asthma is an inflammatory disease of the lower airways characterized by increased responsiveness of the tracheobronchial tree to various stimuli. The classic presentation of cats with bronchial asthma is distress, orthopnea, tachypnea, and dyspnea with pronounced expiratory effort. Oral and inhaled β_2-adrenergic agonists and glucocorticoids are the cornerstone of therapy for acute asthmatic patients. Newer therapies, including adjuvant magnesium and leukotriene modifiers, may prove to be effective therapeutic adjuncts, and continued research will enhance effective management of feline bronchial asthma.

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1. Which of the following is an action of β_2-adrenergic agonists?

a. promotion of acetylcholine release
b. bronchoconstriction
c. inhibition of mucociliary elevation
d. reduction of vascular permeability

2. With which medication is concurrent use of β_2-adrenergic agonists not contraindicated?

a. sympathomimetic amines
b. prednisone
c. tricyclic antidepressants
d. monoamine oxidase inhibitors

3. Which statement regarding methylxanthines is true?

a. Theophylline inhibits acetylcholinesterase.
b. Methylxanthines promote swift bronchodilation.
c. Mast cells degranulate in response to methylxanthine administration.
d. Theophylline reduces the frequency of ciliary beating.

4. The most notable inflammatory mediator inhibited by glucocorticoids is
a. IL-2
b. tumor necrosis factor–α
c. IL-5
d. IL-8

5. Which statement regarding glucocorticoids is true?
a. Glucocorticoids have a more rapid onset of action than do methylxanthines.
b. The oral glucocorticoid of choice is cromolyn.
c. Fluticasone propionate is a glucocorticosteroid delivered by a metered-dose inhaler.
d. A short course of oral glucocorticosteroids is not needed if prescribing inhalant glucocorticosteroids.

6. Which of the following is not a potential side effect of oral glucocorticoids in cats?
a. inappropriate urination
b. insulin resistance
c. hirsutism
d. cystitis

7. Which medication is not indicated in treating cats with acute bronchial asthma?
a. montelukast sodium
b. theophylline
c. prednisolone
d. albuterol sulfate

8. Which of the following is a proposed mechanism of adjuvant magnesium in feline bronchial asthma?
a. inhibition of calcium-mediated muscle contraction
b. sympathetic stimulation
c. suppression of β_2-adrenergic agonist effects
d. parasympathetic suppression

9. Which of the following is not a proposed mechanism of magnesium in feline bronchial asthma?
a. calcium antagonism
b. parasympathetic inhibition
c. β_2-adrenergic agonist inhibition
d. modulation of sodium–potassium–ATPase

10. Zileuton inhibits
a. methyljasmonate.
b. hydroxymethylglutaryl coenzyme A reductase.
c. 5-lipoxygenase.
d. phosphodiesterase.

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