PRACTICAL PHARMACOLOGY

Antitussive Medications for Dogs and Cats

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The cough reflex is an essential protective mechanism for clearing the airways, preventing aspiration of foreign or noxious inhaled substances, enhancing the clearance of mucociliary material, and preserving a healthy respiratory system.[1] However, despite being an evolutionary beneficial reflex, a persistent cough can significantly affect quality of life by interfering with sleep, activity, eating, drinking, and exercise. Occasionally, a profound cough can lead to syncope, urinary and fecal incontinence, muscle pain, and respiratory exhaustion.[1,2]

Among veterinary patients, coughing can be associated with diseases of the lower airway and pulmonary parenchyma, upper airway disorders, pleural space diseases, pharyngeal/laryngeal disorders, and occasionally sinonasal disorders. Nonrespiratory conditions (e.g., cardiac disease leading to congestive heart failure, masses exerting external pressure on the airways) can also cause coughing. Successful management of coughing generally requires identification and treatment of the underlying cause. However, when an underlying cause cannot be determined, or if coughing persists despite therapy, antitussive therapy is indicated to minimize cough,

Abstract

Although coughing serves as a protective airway reflex, chronic coughing can significantly impair quality of life for dogs and cats. Effective management involves treating the underlying cause, which can involve respiratory, cardiac, or extrathoracic structures. However, when the etiology is unclear or coughing persists despite therapy, antitussive treatment is needed to mitigate airway irritation and improve patient comfort. The first-line options for dogs are centrally acting agents (e.g., opioid derivatives); use of other opioids is more limited by adverse effects and regulatory constraints. Effectiveness of dextromethorphan is limited due to poor bioavailability. Peripheral antitussives are potentially useful although veterinary data are sparse. Animal studies have shown minimal evidence-based success for Chinese botanicals. Novel drug classes under investigation include P2X3 receptor antagonists, neurokinin-1 receptor antagonists, and neuromodulators. Further veterinary-specific research is needed to validate current therapies and refine dosing strategies for newly developing drugs.

Take-Home Points

- Coughing is a normal, protective, physiologic reflex that protects the respiratory tract from foreign material and infectious agents; thus, beneficial coughing should not be suppressed.
- Coughing should be addressed by finding the underlying cause, treating the specific disease state, and prescribing antitussive therapy as needed.
- Among centrally acting antitussives, opioids should be the first line of therapy for cough suppression; dose adjustments can be escalated provided they do not lead to mental suppression/sedation or constipation.
- Although optimal dosing requires further research, developments in use of δ-opioid receptor antagonists, P2X3 antagonists, and neuromodulating drugs show promise as non-narcotic alternatives to opioid drug therapy.
- Dextromethorphan, diphenoxylate, and Chinese herbal remedies have been used as antitussives with little anecdotal benefit or clear scientific proof of efficacy and thus should be used with skepticism.

ameliorate progressive airway inflammation, and restore an acceptable quality of life for the patient and client.[3,4]

PATHOPHYSIOLOGY OF COUGHING

A cough is a sudden and involuntary reflex induced by mechanical, chemical, or inflammatory stimuli within the respiratory tract and can be divided into 3 mechanistic phases: inspiratory (deep inhalation), compressive (forceful expiratory effort against a closed glottis), and expulsive (forceful expulsion of air through the mouth). The cough reflex is often accompanied by the characteristic sound produced by vibration of the vocal cords and should be distinguished from a gag or retch because their etiologies differ.[1,5]

Similar to all neurophysiologic reflexes, the cough reflex consists of an afferent sensory input, a central neurologic integration, and efferent motor pathways that complete the reflex. The afferent pathway involves branches of the vagus nerve and sensory nerve fibers within the ciliated epithelium of the airways and lower respiratory tract that enter the central nervous system (CNS). Peripheral triggers of the cough reflex typically involve activation of C-fibers and cough receptors, which include rapidly adapting stretch receptors, slowly adapting stretch receptors, and Aδ fibers.[5] The central nerve pathway coordinates these signals within the cough center located in the pons and upper brainstem, where 2 main excitatory neurotransmitters (glutamate and neurokinins, particularly neurokinin A) mediate the cough reflex. Antitussive medications act either peripherally (by inhibiting cough receptors) or centrally (by acting within the nucleus tractus solitarius [NTS]) to inhibit the propagation of the neural input.

ANTITUSSIVE DRUGS

Antitussive drugs are broadly divided into centrally acting and peripherally acting agents. The most commonly used antitussive drugs in small animals are opiate derivatives, which reduce cough by decreasing the responsiveness of the NTS cough center to afferent stimuli and by diminishing the perception of peripheral irritation, primarily via μ-opioid receptors.[1,5] Opioids are thought to act on the CNS via opioid receptor modulation (μ, δ, κ) and calcium channel regulation.[5,6] Antitussive drug dosages can be found in **TABLE 1**.

Centrally Acting Antitussives

Hydrocodone

Hydrocodone, a μ-opioid receptor agonist partially metabolized to hydromorphone, is a U.S. Drug Enforcement Agency (DEA) Schedule II controlled opioid commercially available in the United States for off-label use as Hycodan, Tussigon, and Hydromet.[6] Hydrocodone directly suppresses the cough center within the medulla and may reduce respiratory mucosal secretions by unknown mechanisms. Hydrocodone is usually formulated with an anticholinergic, homatropine, to make the taste undesirable and reduce the potential for human abuse. Veterinarians should be cautious when prescribing hydrocodone because other preparations (e.g., Vicodin) are often combined with acetaminophen and are contraindicated in cats.

Because of its measurable and reliable antitussive effects, hydrocodone is often the first-choice opioid antitussive prescribed for dogs.[1] The initial maintenance dose is usually low (0.25 mg/kg PO q6h

to q8h[6,7]) but may need to be increased after chronic use due to μ-receptor downregulation in the NTS; patients experiencing significant tracheal collapse/tracheobronchomalacia may need substantially higher doses. The goal of therapy is to control cough without excessive sedation or constipation. Commercially available syrups (5 mg/5 mL or 1.5 mg/5 mL) or compounded liquid suspensions (formulated to 1 mg/mL) are often preferred for easier dose adjustments, especially for small dogs.

Butorphanol

Butorphanol (Torbutrol, Torbugesic; Zoetis, zoetisus.com]) is an agonist-antagonist opioid that works at μ and κ receptors, leading to analgesic and antitussive effects.[8] In dogs, it is reportedly a more potent antitussive than codeine or morphine.[9] Although butorphanol is well absorbed orally, it undergoes significant first-pass metabolism, reducing its effective antitussive action in the CNS. Its antitussive actions last about 4 hours in dogs.[8] Similar to hydrocodone, chronic use may necessitate higher doses due to receptor downregulation.

Although butorphanol administration can be intravenous, intramuscular, subcutaneous, or oral, the oral tablet form (Torbutrol) has become harder to obtain, limiting its widespread use. Compounded butorphanol tartrate is still being sold as capsules, tablets, and chewable treats by national or local compounding pharmacies; however, the efficacy of the compounded products has not been evaluated against that of the original commercial product and may not be similar. Antitussive dosing ranges are 0.005 to 0.1 mg/kg IV or SC and 0.5 to 1 mg/kg PO, q6h to q12h.[7] Butorphanol is classified as a DEA Schedule IV controlled substance, which allows for less restrictive prescription.

Diphenoxylate

Diphenoxylate, a μ-opioid agonist of the phenylpiperidine series primarily used to treat nonspecific diarrhea, has also been proposed for off-label used as an antitussive. Co-phenotrope and Lomotil are commercially available combinations of diphenoxylate (an opioid antitussive) and atropine (a mucolytic and antimuscarinic bronchodilator).

TABLE 1 Antitussive Medication Dosages for Dogs and Cats

CATEGORY, DRUG	DOSE	ROUTE	FREQUENCY
OPIOID			
Hydrocodone	▪ Starting dose 0.25 mg/kg 25%, escalated to effect	PO	q6–12h
Butorphanol	▪ 0.05–0.1 mg/kg	IV, SC	PRN
	▪ 0.55–1.1 mg/kg	PO	q6–12h
Diphenoxylate	▪ 0.25–0.5 mg/kg	PO	q12h
Codeine	▪ 1–2 mg/kg	PO	q6–12h
NMDA RECEPTOR ANTAGONIST			
Dextromethorphan	▪ **Dogs:** 0.5–1 mg/kg	PO	q8–12h
	▪ **Cats:** 2–4 mg/kg	PO	
PERIPHERALLY ACTING ANTITUSSIVE			
Benzonanate	▪ **Dogs:** 100 mg	PO	q8–12h
P2X3 RECEPTOR ANTAGONIST			
Gefapixant	▪ Undetermined	Not applicable	Not applicable
NK-1 RECEPTOR INHIBITOR			
Maropitant	▪ 2 mg/kg	PO	q24h for 5 days; q48h thereafter
NEUROMODULATOR			
Gabapentin	▪ Starting dose 10–15 mg/kg, escalated to effect	PO	q8h
Amitriptyline	▪ **Dogs:** Starting dose 1–2 mg/kg	PO	q24h
	▪ **Cats:** 0.50–1 mg/kg, escalated to effect		

NK-1 = neurokinin-1; NMDA = N-methyl-D-aspartate

Diphenoxylate use in dogs is empirical, based on extrapolated human doses; suggested dosing is 0.25 to 0.5 mg/kg PO q12h. Despite its theoretical benefits, excessive use of diphenoxylate can lead to constipation and other gastrointestinal disturbances (e.g., vomiting, abdominal cramping, xerostomia, weakness). Because diphenoxylate is a DEA Schedule V narcotic,[10] when combined with atropine it is readily available by prescription with little regulatory restrictions.

Codeine

Codeine phosphate and codeine sulfate are contained in many analgesic preparations of oral tablets, syrups, and liquids. Although codeine has weaker analgesic properties than other opioids, the antitussive properties of codeine are more similar to those of morphine.[3,11] However, codeine is often formulated concurrently with acetaminophen and other compounds that create an unfavorable treatment profile for veterinary patients. In addition, because of the adverse effects of constipation and sedation and the potent addictive properties and abuse potential associated with inappropriate client use, codeine use in veterinary medicine is broadly discouraged.[7] However, single-ingredient codeine preparations are available in Canada and can be prescribed for antitussive use at 1 to 2 mg/kg PO q6h to q12h.[1,7]

Dextromethorphan

Dextromethorphan is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been widely used in human medicine as both an over-the-counter and prescription antitussive.[11,12] The clinical usefulness of dextromethorphan for cough suppression in children has been questioned, and little information about its efficacy in small animals is available.[1,3,7,11,13] Despite its availability in veterinary-labeled products such as Cough Tablets by Creative Science (creative.science), its short half-life, rapid clearance, poor bioavailability, and questionable efficacy limit its usefulness in small animal medicine. Controlled prospective studies involving dextromethorphan are sparse, and the authors' anecdotal experience has been disappointing. Despite the limitations of dextromethorphan, the literature describes doses of 0.50 to 1 mg/kg q8h to q12h for dogs and 2 to 4 mg/kg PO q8h to q12h for cats.[1]

Peripherally Acting Antitussives

Benzonatate

Benzonatate (e.g., Tessalon Perles) is a non-narcotic, peripherally acting antitussive that works by anesthetizing the stretch receptors and sensory input on the bronchial walls, pulmonary tissues, and visceral pleura.[12] As a local anesthetic, it minimizes the secondary sedative effects of opioids. In humans, it has provided symptomatic relief for cancer patients with opioid-resistant cough.[14] Therapeutic use of benzonatate has not been shown to be associated with adverse effects, although sporadic cases of seizure and cardiac arrest in humans after high-dose or toxic ingestion have been reported. Clinical data on the use of benzonatate in veterinary medicine are lacking. Because this orally administered non-narcotic antitussive significantly reduces cough, benzonatate shows promise as symptomatic therapy.[15] The dose of benzonatate is 100 mg PO q8h to q12h; however, because benzonatate is not based on body weight, it should be used with caution in dogs that weigh less than 4.5 kg (10 lb) and is contraindicated for use in cats.

Drugs Under Investigation for Antitussive Use

P2X3 Receptor Antagonists

P2X3 receptor antagonists (e.g., gefapixant, previously known as AF-219 and MK-7264) inhibit adenosine triphosphate (ATP)–mediated sensory nerve activation. ATP released from non-neuronal pulmonary epithelial cells during inflammation has been associated with sensitization and activation of purinergic receptors within the respiratory tract. ATP actively binds to the P2X3 receptor found primarily on the afferent sensory C-fibers of the lung and vagal sensory nerves and is a potent inducer of the cough reflex.[16] Gefapixant is a first-in-class, non-narcotic, selective P2X3 receptor antagonist shown to have potent antitussive activity in humans with chronic refractory cough.[12,17] Gefapixant has been evaluated in canine patients with no reported adverse effects at lower doses. In human and canine trials, reports of ageusia (loss of taste), nephrotoxicosis, and dietary inappetence were noted only at higher doses compared with the initial proof-of-concept trial. In December 2023, the FDA rejected the application for gefapixant marketing in the United States, requiring additional efficacy studies. However, this category of antitussives holds great promise for veterinary medicine.

Gabapentin is believed to block specific centrally located voltage-gaited calcium channels, thus modulating NMDA receptors and preventing the release of excitatory cough-inducing neurotransmitters.

Maropitant

Maropitant (Cerenia; Zoetis, zoetisus.com]) is a neurokinin-1 (NK-1) receptor antagonist that the FDA has approved for treatment of acute vomiting in dogs and cats. Substance P, acting via gefapixant receptors, has been linked as a neurotransmitter in the NTS during the cough reflex as well as a peripheral sensitizer of afferent nerve receptors locally in the respiratory tract.[18] Substance P has also been shown to be a proinflammatory agent in airways and pulmonary tissue.[18] NK-1 receptor antagonists have been reported to suppress coughing induced by mechanical stimulation, indicating that they may have a mechanism of action other than chemical.[19] However, evidence supporting the antitussive efficacy of maropitant remains controversial.[18,20] Nevertheless, because of its broad availability and ease of administration as a non-DEA controlled substance, maropitant remains a viable, although arguably weak, antitussive option in clinical practice.

Historically, the brand name drug Cerenia was considered cost prohibitive for use in large-breed dogs; however, other generic maropitant options approved under the Abbreviated New Animal Drug Application in the United States market (e.g., Emeprev [Dechra, dechra-us.com], Ceritant [Pivetal, animalhealthinternational.com]) may enable more economical use of these products in patients with chronic bronchitis and other long-term inflammatory airway diseases. Although optimal dosing has not been established, in its initial study maropitant was administered at 2 mg/kg PO q48h.[18]

δ-Opioid Receptor Antagonists

δ-Opioid receptor antagonists (e.g., naltrindole, naltriben) have demonstrated antitussive effects through inhibition of intracellular calcium levels within the CNS. This category of antitussives shows great promise due to their unique mechanism of action and lack of DEA regulatory restrictions. However, no clinical trials investigating their use in veterinary patients have been published.[21]

Neuromodulators

Chronic cough is commonly associated with central hypersensitivity similar to that of neuropathic pain. Neuromodulators (e.g., gabapentin, amitriptyline) have been assessed as management strategies for refractory chronic cough.

Gabapentin

Gabapentin is commonly used for anxiolysis and neuropathic pain in dogs and cats. It has shown positive effects on cough-specific quality of life in humans and is recommended as a therapeutic trial for chronic unexplained cough in humans.[12,22] Gabapentin is believed to block specific centrally located voltage-gaited calcium channels, thus modulating NMDA receptors and preventing the release of excitatory cough-inducing neurotransmitters. In human trials, escalating doses of gabapentin were often needed to achieve the desired effect while risking sedation and other neurologic adverse effects.[12,22,23] Although use as an antitussive is promising, gabapentin has not been evaluated for such use and determination of proper dosing is needed. Currently, gabapentin is started at 10 to 15 mg/kg PO q8h and sequentially increased to the desired effect.

Amitriptyline

Amitriptyline is a tricyclic antidepressant with a broad range of pharmaceutical actions on multiple neurotransmitter receptors (e.g., serotonergic, muscarinic, histaminergic, adrenergic). In veterinary medicine, amitriptyline has been used to treat behavior disorders, neuropathic pain, pruritus, and lower urinary tract diseases. In human medicine, amitriptyline has been used for decades to treat suspected postviral vagal neuropathic cough, although its exact mechanism remains unclear.[22] In human trials, the initial dose of amitriptyline has been relatively low and then escalated to effect. As with gabapentin, proof-of-concept trials

with dose escalation studies are lacking. However, an initial dose of 1 to 2 mg/kg PO q12h in dogs and 0.5 to 1 mg/kg PO q24h in cats can be initiated with similar biweekly dose increases of 25% to 50% until desired cough suppression without sedation.

Herbals

Traditional herbal remedies (e.g., menthol, peppermint, Chinese cough remedies such as luo han guo [Chinese: monk fruit] and ma huang [Chinese: *Ephedra sinica*]) have been anecdotally reported to ease coughing. Nonetheless, clinical trials supporting the efficacy of herbal therapies in human and veterinary medicine are scarce.[24]

Oral supplementation with honey has been evaluated in children with nocturnal cough secondary to sinonasal discharge and oropharyngeal disease.[25] Honey has been shown to have demulcent actions in the oral cavity, antibacterial properties topically, and antioxidative and cytokine-releasing actions within tissues. When evaluated for nighttime cough in children, cough frequency scores indicated that 2.5 mL of honey administered orally performed better than dextromethorphan or diphenhydramine.[25] Whether the effects of honey on veterinary patients result strictly from the demulcent actions in the oral cavity or any local effects in the lower respiratory tract remains to be established.

SUMMARY

Coughing is common among veterinary patients. The primary clinical directive is to identify the underlying disease process and address it therapeutically. Early intervention and treatment of the primary disease represent the best antitussive strategy. However, many respiratory diseases are chronic, and for these cases, cough management becomes a valuable part of the therapeutic plan along with treatment of the underlying condition. Rigorous clinical trials evaluating antitussive therapies in veterinary medicine are currently limited. Further research to improve knowledge of the cough reflex and to develop novel and effective antitussives for veterinary patients is needed. TVP

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Zenalpha®
(medetomidine and vatinoxan hydrochlorides injection)
Sedative, Analgesic
For Use in Dogs Only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

BRIEF SUMMARY: (for full prescribing information, see package insert)

DESCRIPTION: Zenalpha is a combination of medetomidine and vatinoxan hydrochlorides. Each mL of Zenalpha contains 0.5 mg medetomidine hydrochloride, 10 mg vatinoxan hydrochloride, 32.5 mg mannitol (USP), 4.16 mg citric acid monohydrate (USP), 1.8 mg methylparaben (NF), 0.2 mg propylparaben (NF).

INDICATION: Zenalpha is indicated for use as a sedative and analgesic in dogs to facilitate clinical examination, clinical procedures and minor surgical procedures.

CONTRAINDICATIONS: Do not use Zenalpha in dogs with cardiac disease, respiratory disorders, shock, severe debilitation, that have hypoglycemia or are at risk of developing hypoglycemia, or are stressed due to extreme heat, cold or fatigue.

Zenalpha is contraindicated in dogs with a known sensitivity to medetomidine or vatinoxan.

WARNINGS:
Human User Safety Warnings
Not for use in humans. Keep this and all medications out of reach of children and pets.

Avoid skin, eye or mucosal contact. Use caution while handling and using filled syringes. Absorption of the active ingredients is possible following exposure via the skin, eye or mucosa. In case of accidental eye exposure, flush eyes with water for 15 minutes, remove contact lenses then continue to flush. In case of accidental skin exposure, wash with soap and water and remove contaminated clothing. If symptoms occur, seek the advice of a physician.

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician. DO NOT DRIVE as sedation, loss of consciousness, and changes in blood pressure may occur.

Persons with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid any exposure to this product.

Pregnant women should exercise special caution to avoid exposure. Uterine contractions and decreased fetal blood pressure may occur after accidental systemic exposure.

Persons with known hypersensitivity to any of the ingredients should avoid contact with Zenalpha.

Caution should be exercised when handling sedated animals. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

Note to physician: Zenalpha contains medetomidine, an alpha$_2$-adrenoceptor agonist, in combination with vatinoxan, a peripherally selective alpha$_2$-adrenoceptor antagonist. Symptoms after absorption or accidental self-injection may include dose-dependent sedation, respiratory depression, bradycardia, tachycardia, and hypotension.

Animal Safety Warnings
Zenalpha should not be administered in the presence of pre-existing hypotension, hypoxia or bradycardia. Due to the pronounced cardiovascular effects of alpha$_2$-adrenoceptor agonists, only clinically healthy dogs (American Society of Anesthesiologists [ASA] classes I and II) should be administered Zenalpha. Dogs should be monitored frequently for cardiovascular function and body temperature during sedation.

Zenalpha is not intended for use in cats. The use of Zenalpha in cats has been associated with hypotension.

PRECAUTIONS: Dogs should be monitored frequently during sedation for changes in heart rate, blood pressure, respiratory rate and body temperature. Tachycardia may occur in some dogs after recovery from sedation.

In the event of hypoxia or apnea, supplemental oxygen should be administered.

Following administration of Zenalpha, a decrease in body temperature may occur and an external heat source may be needed to maintain body temperature. Hypothermia may persist longer than sedation and analgesia.

The analgesic effect of Zenalpha will not last longer than the sedative effects. Additional analgesic(s) should be administered as needed.

Nervous, excited or agitated dogs with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to Zenalpha (ineffectiveness). The onset of sedative/analgesic effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. Therefore, allow the dog to rest quietly for 10 to 15 minutes after injection.

With the alpha$_2$-adrenoceptor agonist drug class, including Zenalpha, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation) exists.

Repeat dosing with Zenalpha has not been evaluated.

Zenalpha has only been evaluated in fasted dogs; therefore, the effects on fed dogs (for example occurrence of vomiting) have not been characterized.

The concurrent use of anticholinergic medications and Zenalpha has not been evaluated.

Zenalpha may decrease serum glucose in healthy dogs and this effect may persist longer than sedation.

The safe use of Zenalpha has not been evaluated in dogs with hepatic or renal impairment, dogs younger than 4.5 months old, or dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS: The most common adverse reactions observed in the field study were decreased body temperature (not requiring external heat support), reduced respiratory rate, diarrhea, muscle tremor, signs of colitis, hypothermia (requiring external heat support).

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Dechra Veterinary Products at (866) 933-2472. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

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Dechra

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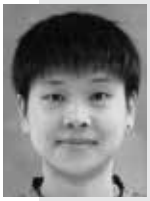

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