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SMALL ANIMAL PRACTICE

Advances in Respiratory Therapy

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Therapy in pulmonology, as in all subspecialties, is most effective when a specific recognized therapy is available for a precise diagnosis. For example, it is more rewarding to treat an *Escherichia coli* pneumonia susceptible to enrofloxacin than it is to treat a "chronic snuffling sound, with a little clear nasal discharge" in a dog. Many respiratory diseases can be effectively treated or cured with antibiotics, anti-inflammatory agents, or chemotherapeutic drugs; however, chronic inflammatory diseases and those with undefined causes remain difficult to manage. As in all fields, advancing knowledge may lead to improved outcome and quality of life. Recent advances in pulmonary therapeutics can be divided into new pharmaceutics (drugs) and new methods of drug delivery.

NEW PHARMACEUTICS

Use of new drugs and development of new applications for established drugs are common in veterinary medicine. The astute clinician should recognize that the best use of a new drug follows positive results from at least a single if not multiple placebo-controlled double-blind studies. That said, use of most drugs in veterinary medicine does not follow those guidelines; thus, the decision to use or not to use a drug in a specific patient should be based on careful evaluation of the risk-to-benefit ratio, objective monitoring, and informed client consent. In some cases, different but closely related drugs may have different efficacies. It is also important to remember that cats have unique metabolic pathways that influence efficacy and toxicity.

Recent additions to the respiratory armamentarium include the fluoroquinolones, azithromycin (Zitromax), sildenafil (Viagra), and leukotriene receptor antagonists. Additionally, the pharmacokinetic properties of theophylline have recently been re-evaluated in dogs and in cats, and the use of doxapram for evaluation of laryngeal function has been incorporated into the mainstream

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[1–3]. Finally, in cats with experimentally created asthma, rush immunotherapy has been explored as a therapeutic option [4].

Fluoroquinolones

The fluoroquinolone class of antibiotics was originally introduced in the late 1980s with the prototypical drugs ciprofloxacin and enrofloxacin (Baytril). Since that time, several other fluoroquinolones have been introduced for the veterinary market, including difloxacin (Dicural), marbofloxacin (Zeniquin), and orbifloxacin (Orbax). The mechanism of action is primarily by inhibition of bacterial replication through an effect on DNA gyrase. Interestingly, similar to the penicillins, the activity of fluoroquinolones is bacteriostatic at low doses, although at therapeutic doses, it is bactericidal [5]. At extremely high doses, bactericidal activity may actually be impaired, perhaps because of inhibition of protein synthesis [5]. Fluoroquinolones are particularly appealing for use in respiratory disease for many reasons, including excellent penetration into the respiratory system, accumulation in the epithelial lining fluid and in macrophages, and a broad spectrum of activity against most gram-negative organisms and *Mycoplasma*. As a rule, fluoroquinolones are not effective in vivo against *Streptococcus* species or against anaerobes. Therefore, before obtaining sensitivity data on a sample, a fluoroquinolone should be combined with another antibiotic, such as amoxicillin, to achieve broad-spectrum coverage. Additionally, when evaluating bacterial sensitivity data, the actual fluoroquinolone intended for use should be evaluated, because despite similar mechanisms of action, variations in sensitivities exist [6]. Generic ciprofloxacin has recently become available and may represent a significant cost savings to patients being treated long term, although the bioavailability of ciprofloxacin in veterinary patients is far less than that of enrofloxacin. As of this writing (December 2006), at the Tufts Cummings School of Veterinary Medicine, a 250-mg tablet of generic ciprofloxacin costs $0.17 per tablet, whereas a 136-mg tablet of enrofloxacin is $2.39, a 100-mg tablet of marbofloxacin is $2.67, and a 68-mg tablet of orbifloxacin is $3.59.

An important consideration for the clinical use of fluoroquinolones includes the recognized side effects of the drug class, including blindness, which has been reported in cats in association with use of enrofloxacin, and the potential for abnormalities associated with cartilage in growing animals. Importantly, fluoroquinolones, like most antimicrobials, have poor penetration into tracheal and bronchial secretions. Consequently, systemic use for kennel cough complex does not hasten resolution of disease and may contribute to bacterial resistance. Finally, in respiratory patients in particular, if theophylline is administered in conjunction with ciprofloxacin or enrofloxacin, the metabolism of theophylline (a methylxanthine) is decreased, which may potentially lead to toxicity by increasing plasma theophylline concentration.

Azithromycin

Azithromycin has gained popularity over the past decade as a respiratory antibiotic [7]. It should be noted that azithromycin is generally grouped with the macrolide class of antibiotics because it shares many of the properties of

a macrolide, although it is technically an azalide [7]. Macrolides represent a large group of similar compounds that are products of *Streptomyces* spp. Biochemically, they are characterized by a macrocyclic lactone ring attached to one or more sugar moieties. Macrolides with the greatest clinical efficacy are generally derived from erythromycin.

Azithromycin acts by reversibly binding to the 50S ribosome [7] and suppressing RNA-dependent protein synthesis. Azithromycin is bacteriostatic at clinical concentrations. It is particularly effective against gram-positive organisms and *Mycoplasma* spp, although it has some activity against gram-negative organisms as well. In addition, it has fair efficacy against anaerobic organisms.

Azithromycin is stable in acid and, as a result, has high oral bioavailability [7]. Azithromycin seems to be rapidly taken up by tissues and then slowly released. Tissue concentrations are generally 10 to 100 times those achieved in serum, and the drug can be concentrated 200 to 500 times in macrophages. This high level of drug in macrophages may not always be advantageous because it can suppress phagocytic activity. Azithromycin does not exhibit any effect on gastrointestinal smooth muscle; as a result, gastrointestinal side effects are uncommon.

Azithromycin is commonly used by veterinarians to treat severe respiratory infections. It can be highly effective in resolving chronic persistent pneumonia, particularly that secondary to *Bordetella* infection [8]. Care should be taken when using azithromycin as a sole agent because of the limitations of its gram-negative spectrum and the fact that resistance is a growing problem. In addition, one study found azithromycin to be ineffective in clearing chlamydophilosis in a clinical trial, although clinical signs were improved [9]. Azithromycin is commonly administered at 5 to 10 mg/kg once a day for 5 to 7 days, although other schemes exist as well.

Sildenafil

Pulmonary hypertension (PHT) is a devastating condition in dogs that is typically associated with a poor outcome [10]. Sildenafil (Viagra), which was first introduced into human medicine as therapy for erectile dysfunction (ED), has been shown to be useful in reducing pulmonary artery pressure and decreasing clinical signs in people and dogs with PHT [11,12]. Sildenafil is a phosphodiesterase (PDE) type V inhibitor that results in increased concentrations of cyclic guanosine monophosphate (GMP) in vascular smooth muscle cells and subsequent nitric oxide–mediated vasodilation of the pulmonary vasculature. A recent retrospective study reported on the use of sildenafil in 13 dogs with naturally occurring PHT [11]. This report described mild to moderate improvements in pulmonary arterial pressures and quality of life after addition of sildenafil as therapy. Further studies are needed to validate this finding and to determine an optimal dosing strategy. The published dose is 0.5 mg to 2.7 mg/kg every 8 to 24 hours. The authors start sildenafil therapy at approximately 1 mg/kg administered orally every 8 hours and titrate upward if needed. Sildenafil therapy can result in systemic hypotension and must not

be combined with nitrates, such as nitroglycerin, or profound hypotension may result. Sildenafil is marketed as an oral PHT therapy under the trade name of Revatio in 20-mg tablets. Because one of the main limitations to widespread use of sildenafil is its high cost, however, it is much more cost-effective to divide 100 mg tablets of Viagra for use in veterinary patients. A longer acting PDE-5 inhibitor (tadalafil) might prove useful in therapy. Other oral ED drugs, such as vardenafil (Levitra), are only now being evaluated in people with PHT but may ultimately be useful in dogs as well [13].

Leukotriene Receptor Antagonists

Although prednisone remains the primary therapy for airway inflammation in human asthmatic patients, the high rate of side effects associated with chronic therapy has led to development of alternative modulators of inflammation, including leukotriene receptor antagonists, such as zafirlukast (Accolate) and montelukast (Singulair). The only controlled study in the literature that examined the role of leukotriene blockers was performed in cats with experimentally created asthma and found no benefit to therapy with zafirlukast [14]. Therefore, such therapy is not likely to be effective, although additional studies are perhaps needed in naturally affected cats. In a small blind study of dogs with atopy, zafirlukast was beneficial in 11% (2 of 18) of dogs, which actually compared favorably with the clinical response to commonly used antihistamines [15]. The role, if any, of leukotriene receptor antagonists remains to be determined in veterinary pulmonology.

Extended-Release Theophylline

Theophylline is a methylxanthine, similar to caffeine, and this drug has been widely used in respiratory medicine as a bronchodilator. The specific mechanism of action responsible for bronchodilatory properties seems to be multifactorial [1]. Theophylline is a nonspecific phosphodiesterase inhibitor and may lead to bronchodilation by means of increased concentrations of cyclic adenosine monophosphate (cAMP). Theophylline also acts as an antagonist of adenosine, one of the proposed mediators involved in asthma. Theophylline has nonspecific effects, such as decreasing diaphragmatic fatigue and increasing mucociliary clearance (in dogs), that may result in clinical improvement in respiratory patients.

It is well established that various extended-release formulations of theophylline available in human pharmacies do not result in similar plasma concentrations [16]. Pharmacokinetic studies had established dosages for products available in 2001; however, these drugs were withdrawn from the market, and re-evaluation of bioavailability and pharmacokinetics of currently available products was required. In a recent study, dogs that were dosed at 10 mg/kg orally every 12 hours using the product manufactured by Inwood Laboratories, Inc. (Commack, New York) developed plasma theophylline concentrations within the therapeutic range described for human beings [1]. In cats, using the same Inwood Laboratories, Inc. product, a dose of 15 mg/kg for the tablets and 19 mg/kg for the capsules administered orally once daily was

found to provide an acceptable plasma concentration [3]. Previously, evening administration of theophylline has been recommended in cats because of improved chronopharmacokinetics.

Doxapram

Doxapram hydrochloride (Dopram-V) is a centrally acting respiratory stimulant. Doxapram's original clinical use was for the treatment of apnea or hypoventilation, although intubation and manual ventilation are far more effective and should supersede the use of doxapram for these conditions. In 2002, Miller and colleagues [2] introduced the use of doxapram into clinical medicine for evaluation of laryngeal dysfunction. In small animals, laryngeal examination requires sedation, and although some agents have more or less effect on intrinsic motion, in all cases, the examiner may be confounded by the degree of sedation required to visualize the larynx (Fig. 1) [17]. Doxapram is administered intravenously at a dose of 1 mg/lb (2.2 mg/kg), and the observed effect is almost immediate in animals with normal laryngeal function, with an increase in opening of the rima glottis. Tobias and colleagues [18] validated the utility of doxapram hydrochloride for detecting laryngeal paralysis in 2004.

Rush Immunotherapy

Rush immunotherapy is a technique pioneered 50 years ago by which an individual is rapidly hyposensitized to a specific allergen over a period of hours to days rather than over the more typical period of weeks to months. The appeal of rush immunotherapy is the opportunity to cure the individual of an allergy within a short time [19]. Rush immunotherapy is particularly popular for desensitizing individuals with severe insect (eg, bee and wasp) allergies [20]. Rush immunotherapy was evaluated in a group of cats with experimentally induced asthma by Reinero and colleagues [4]. This study documented a decrease in eosinophilic airway inflammation in treated cats compared with untreated cats, and relatively few side effects were encountered. The current limitation of rush immunotherapy in cats is the lack of knowledge or ability to identify a specific allergen responsible for the syndrome of feline asthma.

Intraluminal Tracheal Stents

Tracheal collapse is a progressive degenerative condition that most often affects middle-aged to older toy and miniature breed dogs. Medical management has included antitussives, anxiolytics, avoiding neck leashes, weight loss, and, occasionally, corticosteroids. Surgical options have used extraluminal polypropylene stabilization for dogs with cervical tracheal collapse. Recently the use of self-expanding intraluminal stents has gained further acceptance, and success has been shown in alleviating life-threatening clinical signs associated with airway obstruction and unrelenting cough [21]. Placement of such stents requires specialized equipment (eg, fluoroscopy, tracheoscopy). Complications, including stent migration, pneumothorax, stent compression, and infection, seem to

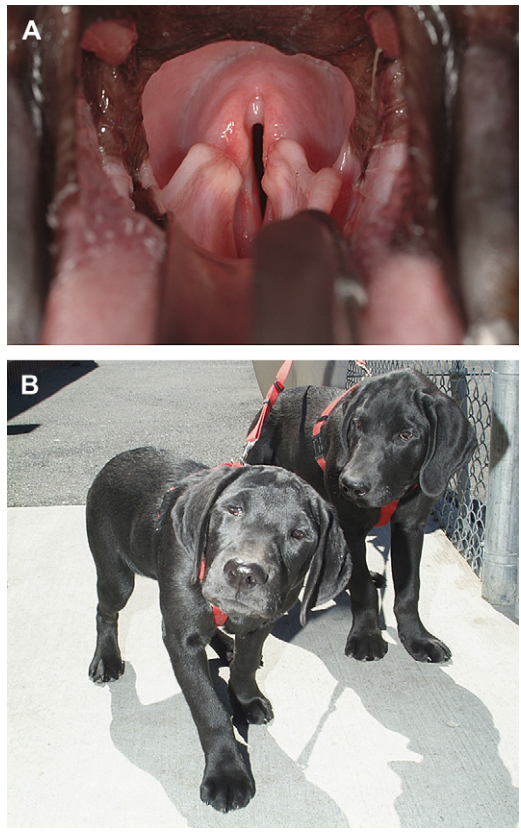

Fig. 1. An excellent knowledge of normal anatomy and function of the larynx is required for the pulmonologist. (*A*) Image illustrates the larynx of a Labrador Retriever puppy affected with congenital laryngeal paralysis. (*B*) This defect, which was associated with a progressive neurodegenerative disorder, was also accompanied by microphthalmia.

occur less frequently with the newer products that are specifically measured for the individual dog and with increased familiarity with the procedure [22].

Propofol

Finally, no discussion of advances in respiratory therapy would be complete without mention of the anesthetic agent propofol. The widespread availability and overall safety profile of propofol have led to increased opportunities to perform short invasive respiratory procedures and transoral tracheal aspirates in patients with respiratory compromise. It is crucial to remember that the use of propofol is not without risk, because apnea and hypotension are often seen with its use, similar to thiopental. The most appealing characteristics of propofol are its rapid metabolic rate and limited period of recovery, which makes it clinically useful for outpatient procedures and for rapid recovery of inpatients.

NEW METHODS OF DRUG DELIVERY

The two major novel methods of pulmonary drug delivery include aerosol therapy for parenchymal and lower airway disease and intracavitary therapy for pleural space diseases.

Aerosol Therapy

Aerosol therapy is commonly used in human medicine to provide local delivery of a variety of medications to the airways. Aerosol therapy has also been used with good success in horses [23,24]. Because of equipment challenges and an inherent lack of cooperation in companion animals, aerosols have not been widely used in cats or dogs. Recently, however, there has been renewed interest and enthusiasm for the development of face mask equipment for use in the dog and cat. The two companies that have been the most proactive in the field of small animal aerosol therapy are Trudell Medical (London, Ontario, Canada) [25] and IVX Animal Health (Fort Dodge, Iowa).

To understand aerosol therapy, it is important to review the technical aspects of aerosol delivery and the normal physical response to particulate inhalation. Deposition of aerosol particles within the respiratory tract depends on their size as well as on the patient's tidal volume, inspiratory flow rate, and ability to breath hold. Optimal particle size for delivery to the trachea is 2 to 10 μm and is 0.5 to 5 μm in the peripheral airways. Particle size depends on the type of nebulizer or metered dose inhaler (MDI) used. In dogs and cats, aerosols are usually delivered by means of an ultrasonic or compressed air nebulizer. The drug to be nebulized is placed within a medication cup, and the nebulizer unit is connected to a baffle that generates the particles. The patient is typically placed within a cage or carrier and receives the nebulization treatment for a specific length of time. It is important to differentiate a medical-grade nebulizer from a "humidifier" that merely generates water vapor.

Aerosol therapy is considered desirable as a method of drug delivery to limit systemic absorption and to direct therapy at the site of the problem. Diseases that are considered particularly amenable to aerosol therapy include feline lower airway disease, canine chronic bronchitis, and kennel cough complex in puppies [26]. Aerosol treatment with a bronchodilator has also been used as a preventive therapy against bronchoconstriction during bronchoscopic bronchoalveolar lavage. A study in cats with experimentally induced lower airway disease documented a beneficial effect of pretreatment with an aerosolized bronchodilator in preventing bronchoconstriction associated with the lavage procedure [27].

Agents that are considered potentially beneficial when administered by means of the aerosol route include physiologic saline; some antibiotics (particularly aminoglycosides); glucocorticoids (through commercially available MDIs); and bronchodilators, including β_2 agonists, such as albuterol, and anticholinergics, such as ipratropium [28]. Doses that are currently recommended for use in veterinary patients are somewhat arbitrary, because human dosing is based on cooperation with instructions to inhale deeply and to momentarily hold one's breath.

Feline bronchitis is a common airway disease with clinical signs that range from mild and intermittent to severe and life threatening. Most cats respond extremely well to oral anti-inflammatory treatment with prednisone or prednisolone, and some clinicians advocate concurrent use of oral bronchodilators, such as theophylline or terbutaline. Aerosol therapy has been proposed as a method for limiting complications of systemic glucocorticoids by local treatment with inhaled glucocorticoids or use of an inhaled β_2 agonist for immediate relief of bronchoconstriction. Rational initial treatment of asthmatic cats should be directed at controlling the crisis with oral or injectable glucocorticoids before considering a transition to inhaled glucocorticoids. It is prudent to warn clients that inhaled glucocorticoids are expensive ($100 every 1–2 months), particularly when contrasted with the costs associated with oral prednisolone. Some cats do well with intermittent treatment with an inhaled β_2 agonist during a crisis; however, it is not appropriate to treat cats with inhaled β_2 agonists on a regular basis because this approach has been shown to increase the likelihood of complications in people as a result of uncontrolled and progressive airway inflammation. Most cats do tolerate inhaled therapy, particularly in a home environment, but some cats are quite challenging to treat.

Canine chronic bronchitis is another common inflammatory airway disease that responds well to oral prednisone. Infection may occasionally complicate chronic bronchitis as well as tracheal collapse [29], and dogs with acute flare-up of disease may benefit from the addition of oral antibiotics. Because the presence of infection is a relative contraindication to the use of oral prednisone, addition of inhaled steroids may be useful in these instances. Although dogs are more intrinsically cooperative than cats, they may resent application of the face mask and aerosol spacer, and this may lead to treatment failure. Dogs have not been documented to experience bronchoconstriction in association with chronic bronchitis, and a benefit for aerosolized bronchodilators has not been established. Eosinophilic bronchopneumopathy is a second inflammatory disease of the airways and lung parenchyma that may be controlled with the use of inhaled steroids. Because affected dogs often require long-term steroid therapy, inhaled drugs can be beneficial in limiting systemic side effects.

Kennel cough complex is common in puppies, particularly those from "puppy mills." Most cases of kennel cough are rapidly self-limiting; however, some severely affected puppies may benefit from nebulized antibiotics in addition to systemic therapy for pneumonia. Aminoglycosides are particularly amenable to delivery by nebulization, and this treatment modality can hasten recovery from infection as well as limit the potential for side effects from systemic administration, such as nephrotoxicity. A recent abstract documented the clinical utility of this treatment for affected puppies in clinical practice [26].

Addition of aerosolized or nebulized drugs into the therapeutic regimen for the pet with respiratory disease can aid in control of clinical signs and reduce systemic side effects. The use of nebulized aminoglycosides for kennel cough complex and inhaled steroids for treatment of chronic inflammatory airway disease is particularly exciting. Use of other medications should be considered

adjuvant to conventional therapy rather than as a replacement for systemic medications.

Intracavitary Therapy

Pleural effusion represents a common clinical condition in cats and dogs. In most cases, the underlying cause of the effusion can be rapidly determined and treated. A malignant pleural effusion may be primary, caused by pleural mesothelioma or other local neoplasms, or secondary to metastatic disease, most commonly, carcinoma. In human medicine, when malignant pleural effusion accompanies a lung mass, the tumor is often considered inoperable and the course of care may transition from curative to palliative. In people with lung cancer, identification of neoplastic pleural lavage cytology has been associated with a poor prognosis, and there is growing interest in the use of intraoperative pleural lavage to look for evidence of metastatic disease [30]. Therefore, the presence of a lung mass with malignant pleural effusion could be considered likely to represent metastatic disease in veterinary medicine, and it might be wise to pursue a course of therapy designed to control local disease.

Intracavitary therapy is pursued by infusing a chemotherapeutic agent directly into the pleural space. Local infusion of chemotherapy should be considered in animals with diffuse involvement of the pleural space. The chemotherapeutic agent is able to penetrate 1 to 3 mm into the pleura, thus exposing neoplastic cells to a high local concentration of drug. Cisplatin has been used most frequently for this purpose in dogs at a dose of 50 mg/m^2 every 3 to 6 weeks. Cisplatin is associated with renal toxicity; thus, a standard diuresis protocol should be employed before use. Intracavitary carboplatin (180–300 mg/m^2) has also been used in dogs and cats and has the advantage of not requiring diuresis before use as well as reduced gastrointestinal toxicity. Mitoxantrone has also been used at a dose of 5 to 5.5 mg/m^2. In a retrospective study of intracavitary chemotherapy of four dogs treated for malignant pleural effusion, survival times ranged from 18 days to 299 days after treatment with carboplatin or mitoxantrone [31].

The ultimate role of intracavitary chemotherapy remains to be determined, but it seems to be a viable option in some patients because it is associated with limited morbidity. Animals with rapid fluid reaccumulation may be much harder to manage because of dilution of the chemotherapeutic agent by pleural fluid. Technically, the procedure is performed as outlined in Fig. 2. Preexisting pleural effusion should be removed, and the chemotherapeutic agent should be slowly infused over several minutes. In small or compromised pets, thoracostomy tubes may be replaced by a butterfly catheter or an over-the-needle catheter. The patient should be rolled from side to side to assist with distribution of the agent throughout the thoracic cavity and then monitored for 5 to 15 minutes before discharge. In dogs with long-standing large-volume effusion (eg, 2–3 L), cough is commonly reported during the 24 hours after treatment. Reinfusion of chemotherapy may be pursued on an as-needed basis or every 4 to 6 weeks.

Fig. 2. Treatment of an intrathoracic malignancy can be achieved with intracavitary infusion of chemotherapeutic agents, including cisplatin or carboplatin. (*A, B*) Small-bore chest tube is placed for evacuation of fluid. (*C*) Chemotherapy agent is then infused, and the patient is rolled to help distribute the drug.

SUMMARY

Advances in pharmaceutics and in drug delivery have occurred over the past 10 to 15 years in veterinary pulmonology. Clinicians should look for evidence-based studies evaluating the efficacies of these newer therapies to help establish their role in clinical practice.

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