

Investigation of pulmonary deposition of a nebulized radiopharmaceutical agent in awake cats

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Objective—To determine whether conscious, unседated cats will inhale a nebulized material administered via a facemask and whether this material will reach the lower airways.

Animals—20 healthy adult cats.

Procedure—Technetium Tc 99m-diaminetriaminopentaacetic acid (^{99m}Tc-DTPA) was nebulized into a spacer and administered to the cats via a closely fitting facemask. By use of a gamma camera, images were then immediately obtained to determine the distribution of ^{99m}Tc-DTPA within the lower airways.

Results—Images obtained by use of the gamma camera revealed that all 20 cats had inhaled ^{99m}Tc-DTPA from the facemask. In each cat, deposition of the radiopharmaceutical agent was evident throughout the lung fields.

Conclusions and Clinical Relevance—Awake cats that were not used to the application of a facemask did inhale substances from such a device. Aerosolization of medications may be a feasible route of administration for cats with lower airway disease. (*Am J Vet Res* 2004;65:806–809)

As a route of treatment delivery, inhalation is frequently used in human medicine; in the management of asthma, the use of corticosteroid and bronchodilator inhalants is commonplace. Asthma is a clinical syndrome characterized by reversible airflow obstruction, bronchial hyperresponsiveness, and airway inflammation.¹ Treatment with corticosteroids via inhalation reduces all of these components involved in asthma.²

Feline bronchopulmonary disease (FBPD) encompasses a group of common, but poorly understood, airway diseases. Asthma and acute and chronic bronchitis are different bronchopulmonary diseases that may develop in cats.³ The spectrum of FBPD ranges from acute reversible airway hyperreactivity and bronchoconstriction to chronic inflammatory conditions with airway remodeling and excessive secretions. It is estimated that bronchopulmonary disease affects

1% of the general cat population and > 5% of the Siamese breed.⁴ Affected cats typically have intermittent respiratory distress and may be without clinical signs between episodes. In some cats, FBPD can result in severe, potentially fatal respiratory distress. With time, progressive airway changes can develop that result in more severe clinical disease and diminished quality of life.

At present, treatment of FBPD primarily involves administration of bronchodilators orally and administration of corticosteroids orally or via injection.⁵ These medications have many potential systemic adverse effects. Many bronchodilators including theophylline and terbutaline can cause CNS stimulation and cardiac arrhythmias in certain species, including dogs and humans.⁶ Xanthine derivatives such as theophylline can cause irritation of the gastrointestinal tract, which may result in nausea, inappetence, vomiting, or diarrhea.⁶ Administration of corticosteroids can result in polyphagia, irritation and ulceration of the gastrointestinal tract, and immunosuppression. In addition to adverse effects associated with these medications, many owners have difficulty administering medications to their cats orally, which results in poor compliance and inadequate dosing.

In human medicine, administration of medications via inhalation is a common and preferred practice for maintenance of control of asthma.⁷ Fewer adverse effects develop in association with glucocorticoids administered via inhalation, compared with those associated with glucocorticoids administered via the oral route.² Additionally, rapid-acting β -adrenoceptor agonists administered via inhalation are beneficial during acute episodes of asthma in humans.⁸ Treatment with glucocorticoid inhalants has recently been recommended for cats with lower airway disease,⁹ but the feasibility of inhalation as a method of drug administration to cats requires investigation. Cats are frequently uncooperative patients and often do not tolerate excessive handling. Handling of a cat in respiratory distress may negatively affect the outcome of treatment of the disease episode. The purpose of the study was to determine whether conscious, unседated cats will inhale nebulized material administered via a facemask and whether this material will reach the lower airways.

Materials and Methods

Animals—Healthy adult cats belonging to staff and students of the College of Veterinary Medicine at the University of Illinois were eligible for inclusion in the study. With owner consent, cats that had no history of pulmonary disease and were assessed as clinically normal on the basis of findings of

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physical examination, a CBC, serum biochemical analyses, and thoracic radiography (right lateral, left lateral, and ventrodorsal radiographic views) were included in the study. Cats were excluded from the study if they had clinical findings of pulmonary, cardiovascular, or systemic disease or if they were judged to be too fractious to handle for routine examination and venipuncture.

Administration of the radiopharmaceutical agent—Forty millicuries of technetium Tc 99m-diaminetriaminopentaacetic acid (^{99m}Tc-DTPA) was nebulized by use of a commercially available nebulizer.^a With an oxygen flow rate of 8 L/min, 77% of the particles produced by the nebulizer were ≤ 1.3 μm, according to information provided by the manufacturer. The nebulizer was attached to a spacer,^b a device designed to work with medications delivered via metered dose inhalers. A facemask^c was connected to the spacer for delivery of the radiopharmaceutical agent to the cats (Fig 1). Cats were restrained by use of a cat restraint bag and placed into a biohazard containment unit to minimize contamination of the room with the radiopharmaceutical agent. The delivery system was first primed by nebulizing the ^{99m}Tc-DTPA into the facemask prior to placement on each cat. During the period required to fill the spacer (approx 10 seconds), the open end of the mask was temporarily sealed. After turning off the nebulizer, the facemask was applied to each cat. Cats breathed through the mask for approximately 10 to 15 seconds (ie, taking 10 to 15 breaths). With the cats in ventral, dorsal, and right and left lateral recumbency, scintigraphic images of the thoracic region were then imme-

diately obtained by use of a gamma camera^d and a low-energy, all-purpose parallel hole collimator. The image matrix size was 128 × 128 × 16. Scintigrams were visually examined by an investigator (SSC) to assess distribution of the radiopharmaceutical. Residual radiopharmaceutical agent in the spacer and facemask was not measured. Cats were required to stay in the hospital overnight following the procedure in compliance with health safety standards.

Statistical analyses—For the purpose of statistical analyses, cats for which there was evidence that ^{99m}Tc-DTPA had reached their lungs were considered to have responded positively to the procedure. The proportion of positive cats was calculated as the number of positive cats divided by the

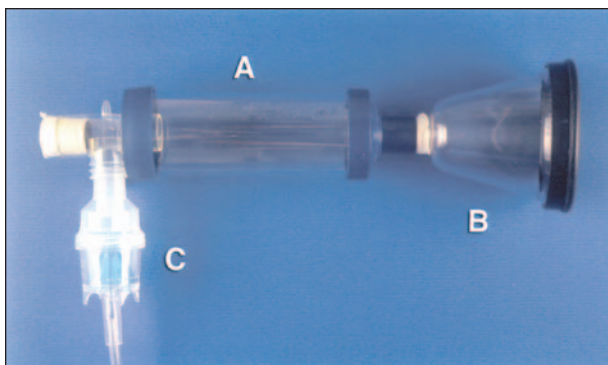


Figure 1—Photograph of the apparatus used to deliver the nebulized radiopharmaceutical agent to awake, unsedated cats. A = Spacer. B = Facemask. C = Nebulizer.

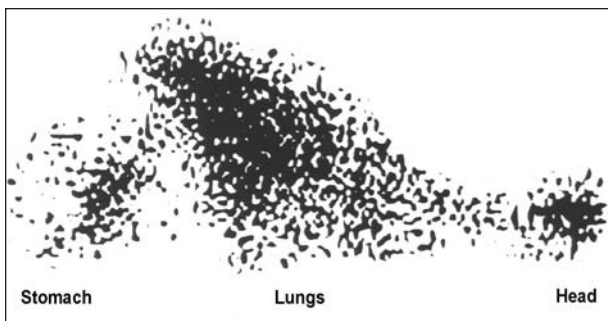


Figure 2—Scintigraphic image (right lateral view) of a cat after administration of a nebulized radiopharmaceutical agent via a facemask. Notice that the greatest uptake of radiopharmaceutical agent is in the area of the lungs; there is fairly uniform distribution of the agent to all areas of the lung. To the left of the image, swallowed radiopharmaceutical agent has accumulated in the stomach. The area of concentration on the right of the image represents accumulation of the radiopharmaceutical agent on the face and within the oral cavity during administration.

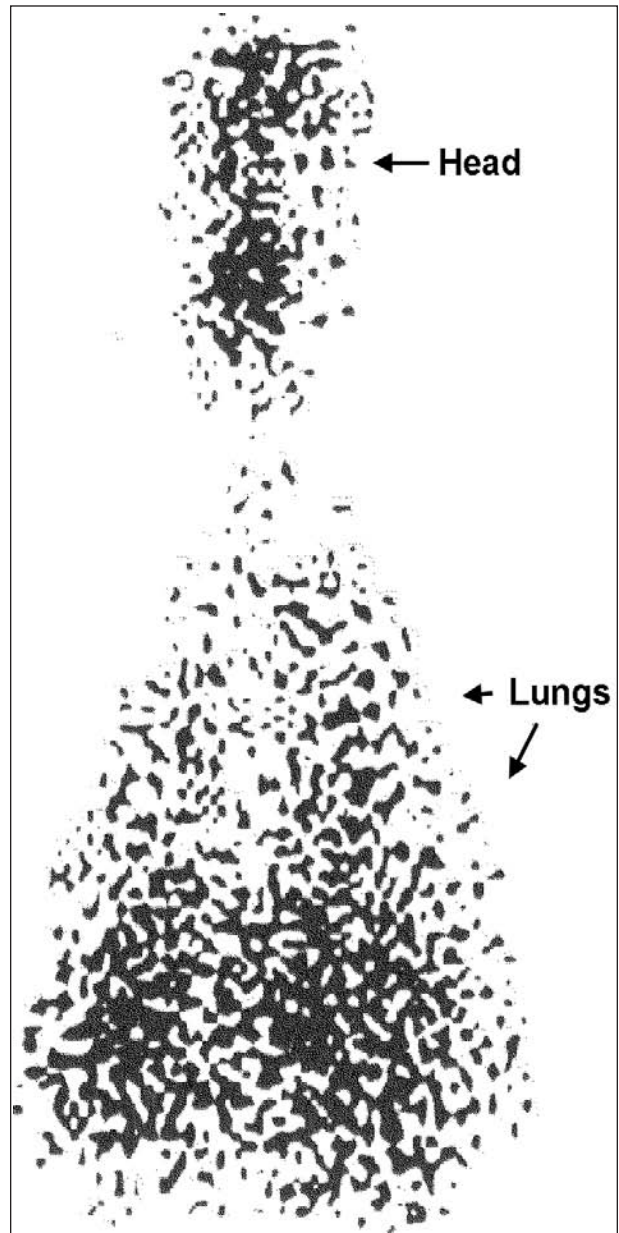


Figure 3—Scintigraphic image (dorsoventral view) of a cat after administration of a nebulized radiopharmaceutical agent via a facemask. Notice that the greatest uptake of radiopharmaceutical agent is in the area of the lungs; there is fairly uniform distribution of the agent to all areas of the lung. The area of concentration on the upper portion of the image represents accumulation on the face and within the oral cavity during administration.

number evaluated. If no cats were positive in a sample of 20 cats, the upper 95% confidence limit bound on the binomial proportion of inhaling cats in the population of all cats would be 0.14.¹⁰ If all 20 cats had ^{99m}Tc-DTPA in their lungs, the lower 95% confidence limit bound on the binomial proportion of positive cats in the population of all cats would be 0.86.

Results

Animals—Sixteen spayed female and 4 castrated male cats were included in the study. The ages of the cats ranged from 1 to 6 years (median age, 2 years). The cats' weights ranged from 1.6 kg to 6.8 kg (median weight, 4 kg). For all cats, results of CBCs and serum biochemical analyses indicated minor deviations from reference ranges. None of these abnormalities were considered clinically important. Thoracic radiography revealed normal bronchial patterns in 9 cats, mild bronchial patterns in 9 cats, and moderate bronchial markings in 2 cats.

Inhalation of the radiopharmaceutical agent—All 20 cats tolerated the procedure; respiratory rate and effort remained normal and no adverse effects were observed. On evaluation of the scintigrams (obtained by use of the gamma camera) of all 20 cats, the radiopharmaceutical agent was detected in the lungs (Fig 2 and 3). On visual inspection of the scintigrams, uniform distribution of the ^{99m}Tc-DTPA to the alveoli was evident in all cats. In 15 of the 20 (75%) cats, the radiopharmaceutical agent was also detected in the stomach.

Discussion

The results of our study indicated that it is feasible to use inhalation as a method of drug delivery to cats. After delivery via inhalation, radiopharmaceutical agent had reached the lower airways in all 20 study cats; from the binomial distribution, the lower 95% confidence limit bound on the positive rate in the population of all cats was 86%. Oral administration of medications is often difficult in cats, resulting in poor owner compliance. Treatment via inhalation was investigated because it has been suggested to be an appropriate method for drug delivery for the treatment of FBPD. Inhalation of medications would allow local application of the drug to the affected organ system. Glucocorticoid and bronchodilator inhalants commonly used in management of human asthma may be beneficial in treatment of lower respiratory tract disease in cats. From experience in human medicine, other clinical applications of drug administration via inhalation that could be explored in small animal practice include the treatment of pulmonary hypertension and administration of chemotherapeutic agents; administration of insulin via inhalation for the management of diabetes mellitus in humans is presently in phase-II trials.

In the study of this report, an unexpected observation was that cats with no known history or physical examination findings to suggest pulmonary disease had mild (9 cats) or moderate (2 cats) bronchial patterns visible on thoracic radiographs. This may represent normal variation or subclinical pulmonary changes. It is possible that some of these study cats had mild airway disease. Further evaluation of these cats

would have required cytologic examination of tracheal or bronchial wash specimens. Although it would have been interesting to assess whether these cats had subclinical inflammation, that endeavor was beyond the scope of this study.

In the study of this report, mild abnormalities in hematologic and serum biochemical variables were detected for each of the 20 cats; however, on the basis of history and physical examination findings, all cats were considered healthy. For each of the 20 cats, none of the hematologic and serum biochemical abnormalities would have altered the response to inhalation of the radiopharmaceutical agent.

Examination of the scintigrams obtained by use of a gamma camera did not reveal differences in the pulmonary deposition of the radiopharmaceutical agent in these cats. In our study, ^{99m}Tc-DTPA was used because it has a short half-life (6 hours) and is easy to obtain.¹¹ For ventilation scintigraphy in animals, ^{99m}Tc-DTPA is one of the most commonly used radioaerosols. To ensure a sufficient quantity of ^{99m}Tc-DTPA had been nebulized so that radiopharmaceutical agent would be detectable via the gamma camera, observation of the filling of the spacer was used as an end point. The appropriate amounts of medications that should be used with spacers remain to be determined.

Our study was not designed to more critically evaluate regional differences in pulmonary distribution of the inhaled radiopharmaceutical agent. Because some of the radiopharmaceutical agent was detected in the stomach of the study cats, it appears that they must have swallowed a portion of the material in addition to inhaling it. In humans, it is estimated that 90% of the inhaled material is actually swallowed.² Presently, many of the glucocorticoid inhalants manufactured have low oral bioavailability, which decreases the risk of development of adverse effects.¹² In the study of this report, we did not calculate the percentage of the radiopharmaceutical agent that reached the lower airways of the study cats. In the treatment of any human with airway disease with medications via inhalation, the proportion of medication that reaches the lower airways is affected by the pharmacokinetics of each individual medication in addition to the patient's profile, including age, concomitant treatments, and the extent of airway inflammation in that individual.² The cats in the study of this report did not have clinical signs of lower airway disease; in cats with airway disease, the pulmonary deposition of materials administered via inhalation may be different.

The nebulized radiopharmaceutical agent was administered to the cats by use of a spacer. Spacers are designed to work with metered dose inhalers and are particularly useful for administration of drugs to children and those individuals who have difficulty coordinating the timing of inhalation with activation of the metered dose inhaler device. These devices enhance the delivery of the medication and may double the amount of medication that reaches the lower airways.¹³ In humans with asthma, the use of spacers appears to reduce the systemic effects of inhaled glucocorticoids.^{2,13,14} Spacers are not typically used with nebulized medications in the management of lower airway dis-

ease in people. To administer a radiopharmaceutical agent via inhalation to the study cats, it was necessary to nebulize the agent. Our study was performed to examine whether facemasks and spacers would be tolerated by cats as a means of delivering medications via inhalation.

In the study of this report, cat restraint bags were used because the safety precautions required for handling radioisotopes necessitated working with the cats inside a biocontainment unit, which made handling of the cats unwieldy. Furthermore, these cats were undergoing a novel experience in a strange setting. In the home environment, owners would be more readily able to hold their cats; if cats did object to the procedure, owners could use either a restraint bag or a towel to facilitate handling.

The results of our study indicated that cats that were not used to the application of a facemask will inhale substances from such a device. Moreover, all of the cats in the study of this report had ^{99m}Tc -DTPA throughout all lung fields. These data suggest that administration of medications via inhalation may be an additional treatment option for cats with respiratory disease. At present, administration of corticosteroid and bronchodilator inhalants is considered the standard of care for humans with asthma. These same drugs have been recommended for use in small animal practice, and results of our study appear to support that delivery of material to the lungs and lower airways of cats via inhalation is possible. However, in the study of this report, the effectiveness or benefit of any specific agent administered via inhalation in cats with lower airway disease was not evaluated, and such conclusions cannot be extrapolated from our data. Nevertheless, in cats with respiratory disease, treatment via inhalation could have several advantages including reaching the target organ specifically, better tolerance of administration of medications by the animal, improved treatment compliance, and fewer

adverse effects, compared with that achieved through administration of medications orally or via injection.

^aNebulizer 8900, Salter Labs, Arvin, Calif.

^bRespironics Inc, Murraysville, Pa.

^cAnesthetic facemask, Rusch Inc, Duluth, Ga.

^dOmega 500, Technicare, Jeffersonville, Ind.

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