ADMINISTRATION OF AEROSOLIZED ANTIBIOTICS TO REPTILES

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Abstract:The administration of aerosolized antibiotics to mammals, birds and reptiles has been extrapolated from human medicine. Anatomy and physiology of reptile lungs are unique and research has been restricted to only a few species. Currently, there is only one antibiotic that has been manufactured and approved for aerosolization. It is an inhalable solution of tobramycin, which is indicated for the management of cystic fibrosis patients with Pseudomonas aeruginosa pneumonia. All other antibiotics that are nebulized are derived from intravenous preparations. These drugs contain preservatives which impart a bad taste to the aerosol leading to voluntary apnea. Additionally, preservatives cause bronchospasm and bronchoconstriction. Nevertheless, nebulization of antibiotics is considered a useful tool in the treatment of respiratory tract disease in reptiles.

Key words: aerosolization, faveoli, ediculi, trabeculae, nebulization, tobramycin for inhalation, lower respiratory tract disease.

Anatomy of the Reptile Lung

It is estimated that ninety percent of research in reptile pulmonary physiology has been done in less than one percent of all species of reptiles. Reptiles have 10-20% functional respiratory area, as do mammals of comparable mass; however, reptiles possess larger lung volumes (Wang, *et al*, 1998). Reptile lungs also possess thicker blood-air barriers than mammals. There are significant structural differences among reptile lungs. Lungs vary from single chambered (present in lacertids, geckos, terrestrial snakes) to multi chambered (present in iguanids, varanids, helodermatids, chameleons, chelonians and aquatic snakes) (Perry, 1998). More active reptiles possess multi-chambered lungs. Pulmonary parenchyma has been classified as to type. Faveoli (honeycomb shaped) are air spaces that are deeper than wide (present in snakes, iguanids, agamids). In snakes, lungs consist of at least three layers of faveoli which decrease in diameter toward the pleural surface of the lung (Perry, 1998). Ediculi are air spaces that are as wide as deep (present in tortoises, varanids, chameleons, geckos) (Perry, 1998). Trabeculae (present in *Testudo spp*) are air spaces that are flat because they are fused with the lung wall (Perry, 1998).

Reptile lungs, particularly of chelonians, periodically have large influxes of plasma into the air spaces (Wang, *et al*, 1998). This is due to increases in pulmonary arterial pressure caused by intracardiac shunting. To accommodate for this phenomenon pulmonary capillaries have increased permeability. Reptiles possess six to thirty times the amount of pulmonary surfactant as mammals (Wang, *et al*, 1998). Surfactant is composed of phospholipids. In

mammals, surfactant increases lung compliance. In reptiles, surfactant prevents pulmonary epithelial surfaces from adhering to each other during expiration and inhibits excessive pulmonary edema (Wang, *et al*, 1998). Surfactant also prevents exudate from adhering to the mucociliary apparatus and bathes and nourishes ciliated epithelial cells. There is a larger amount of smooth muscle in reptile lungs than in mammalian lungs. During periods of hypoxia, serotonin is secreted which causes pulmonary smooth muscle contraction (Wang, *et al*, 1998). This in turn elevates and exposes the capillaries to inspired air. Hypoxia increases the respiratory rate. Hypercapnia causes an increase in tidal volume and respiratory rate (Wang, *et al*, 1998). Respiration is also affected by temperature. As temperature increases from 26 to 30 degrees Centigrade (78 to 86 degrees Fahrenheit), green iguanas (*Iguana iguana*) increase the rate and depth of respiration thus facilitating gaseous exchange. Temperature changes also affect blood viscosity, blood pressure and organ perfusion. In the green iguana, respiration is inhibited during locomotion. Savannah monitors (*Varanus exanthematicus*) actively breathe during locomotion.

Reptiles tend to have irregular distributions of parenchyma in their lungs. Generally, parenchyma is most dense near the hilus (Wallach, 1998). In snakes, the cranial third of the lung participates in gas exchange while the caudal two thirds (air sac) functions in gas storage. The lungs of sea turtles are structurally similar to those of diving mammals. Reptiles possess intracoelomic septae and pulmonary ligaments effectively dividing the body into pleuro-pericardial and hepato-visceral cavities. These structures prevent free movement of organs during locomotion and assist in active inspiration. Reptiles are capable of exhaling violently to remove exudate from the glottis; however, they are not capable of coughing to remove sputum from the lower respiratory tract (LRT).

Nebulization of Antibiotics

An aerosol is a solution of a drug that can be atomized (nebulized) into a fine mist for inhalation therapy. The advantages of nebulization are the direct application of antibiotics to the targeted site and reduction of systemic toxicities associated with parenteral administration of antibiotics (Smith and Ramsey, 1995). In humans, particles of 1.0 –5.0 um are deposited in the trachea and proximal bronchi. Particles less than 0.5 um reach the alveoli (Smith and Ramsey, 1995). There are several factors that affect the delivery of aerosolized antibiotics to the LRT. One is the drug's physiochemical properties. An antibiotic with a low surface tension tends to foam excessively, which decreases aerosolization. Conversely, drugs with a high surface tension (beta-lactam antibiotics) are refractory to aerosolization (Smith and Ramsey, 1995). Aerosolized antibiotics tend to absorb water in the upper respiratory tract thus increasing their size and preventing them from reaching the targeted sites. Other factors that affect drug deposition are respiratory frequency, tidal volume, duration of breath holding, type of lung disease and flow rates of nebulizers (Smith and Ramsey, 1995). In humans, particles of 5.0 um require up to two

seconds to deposit in the bronchi. Collapsed and consolidated lung lobes are refractory to nebulization because they are not ventilated. Overall, the percent of drug initially placed in the nebulizer which ultimately reaches the alveoli has been shown to range from 2-10% (Smith and Ramsey, 1995).

Currently, there is only one antibiotic that has been manufactured and approved for aerosolization. It is an inhalable solution of tobramycin (TOBI, 300 mg/ 5 ml ampules, Chiron, Emeryville, CA, USA) which is indicated for the management of cystic fibrosis (CF) patients with Pseudomonas aeruginosa pneumonia. CF patients develop copious amounts of bronchial mucus that acts as an excellent medium for Pseudomonas colonization and causes obstructive lung disease. The traditional use of intravenous (IV) aminoglycosides presented certain problems such as poor penetration into mucus, and systemic toxicities (ototoxicity and nephrotoxicity) (Fiel, 1998). TOBI administration causes an improvement in lung function and decreased bacterial counts in sputum. During aerosolization TOBI cannot be mixed with any other drugs in the nebulizer. It crosses the blood-air barrier to reach serum concentrations that exceed minimum inhibitory concentrations. TOBI is administered bid in alternating periods of 28 days ($2800 for one 28 day course). Except for TOBI, all aerosolized antibiotics are derived from IV preparations. This presents significant inherent problems. For example, all IV antibiotics contain preservatives such as phenol, bisulfites, methyl parabens or EDTA. These substances impart a disagreeable taste and odor to the medication that causes voluntary apnea and swallowing of the antibiotic (Fiel, 1998). Additionally, preservatives cause airway irritation, bronchospasm and bronchoconstriction.

Notwithstanding the limitations of aerosolizing IV antibiotics, the author makes the following observations and recommendations. Snakes, because of their unique linear pulmonary anatomy, are poorly responsive to nebulization. Lower respiratory tract disease (LRTD) appears to be relatively uncommon in lizards. LRTD is most commonly seen in chelonians, particularly newly imported individuals. Candidates for nebulization should receive a thorough physical exam, fecal exam for parasites, blood/plasma biochemistry profile and radiography. Underlying diseases such as renal failure, parenchymatous granulomas, obstructive lesions of airways, or overwhelming parasite loads should be identified if possible prior to nebulization. Many wild-caught chelonians have multiple disease processes, which significantly increases morbidity and mortality. Typically, these reptiles appear to respond initially to nebulization therapy and then several weeks to months later will have expired. Necropsy/histopathology findings commonly identify sepsis, pulmonary and hepatic granulomas, amoebic hepatitis, inflammatory bowel disease (nematodes) and herpes virus.

Nebulization of antibiotics appears to be most efficacious in chelonians with upper respiratory tract disease (URTD) or acute LRTD (less than two weeks duration). Antibiotic selection should be based upon culture and sensitivity (C/S)

results. Amikacin (Amiglyde V, 50 mg/ml, Fort Dodge Laboratories, Fort Dodge, IA, USA) and gentamicin (GentaVed, 50 mg/ml, Vedco, St. Joseph, MO, USA) are the most commonly aersolized antibiotics used by the author. Typically, 25 mg (1.0 ml) of aminophylline (250 mg/10 ml, American Regent Laboratories, Shirley, NY) is mixed with 9.0 ml of sterile saline in the nebulizer. After administration of the bronchodilator, 50 mg (1.0 ml) of amikacin or gentamicin is mixed with 9.0 ml of sterile saline and is nebulized. These treatments can be repeated every 12 hours (Drew, *et al*, 1999). Although data is lacking concerning absorption of aerosolized antibiotics across the reptilian blood-air barrier, it would be prudent not to administer the same antibiotic parenterally in order to prevent overdosing. Likewise it would be safer not to nebulize an aminoglycoside to a reptile with compromised renal function. A second antibiotic such as a fluroquinalone or cephalosporin (also based upon C/S results) should be administered to decrease the chances of bacterial resistance. After several minutes of therapy, responsive chelonians are observed to extend and retract their necks followed by oral expulsion of viscous fluid. Other antibiotics that have been nebulized are piperacillin (100 mg) (Lederle, Carolina, PR), and cefotaxime (100 mg) (Hoechst-Roussel, Somerville, NJ, USA) also bid (Murray, 1996; Rupley, 1998). Nebulization with normal saline can be used as an aid in rehydrating reptiles. Saline also nourishes and stimulates epithelial cells of the pulmonary mucociliary elevator (Antinoff, 1998). Additionally, amikacin and saline can be used to treat ophthalmic conditions particularly when there is an exudate sealing the eyelids such as with hypovitaminosis A.

In chronic cases of LRTD where there is buildup of viscous exudate, physical removal of exudate via coprage and suction (large snakes) or carapace osteotomy (Divers, 2000) may be warranted. These reptiles carry a guarded prognosis at best. Response to nebulization therapy is determined by abatement of clinical symptoms and evaluation of serial radiographs. The author uses the portable PulmoAide Compressor/Nebulizer (DeVILBISS Health Care, Somerset, PA, USA).

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