John Chitty BVetMed CertZooMed MRCVS
JC Exotic Pet Consultancy Ltd.
Wombourne, Allington Track
Allington, Salisbury, Wilts SP4 0DD, UK

INTRODUCTION

Aerosol therapy has been commonly used in the therapy of respiratory disease in avian patients for a long time.(Spink, 1986; Tully and Harrison, 1994; Carpenter, 2005; Boothe, 2000). This form of therapy has been used in human medicine since ancient time though techniques have, obviously, more refined in recent time (Dessanges, 2001). A variety of techniques are now used in human medicine with pressurized metered dose inhalers (PMDI) with or without spacers, dry powder inhalers and nebulisers being used in a variety of conditions (Spiro and MacCochrane, 1999). The basic principle of all these devices is that drugs are put into droplets in the air that are then inspired. Nebulisers tend to be used in cases where patient compliance may be an issue or where larger volumes of liquid are required to be delivered while avoiding gastrointestinal tract deposition (Spiro and MacCochrane, 1999). This mirrors the situation in veterinary medicine and presumably accounts for the use of nebulisation over other techniques although PMDI's with spacers are gaining in popularity in feline medicine (Mason and Rand, 2006). There are two main types of nebuliser used - ultrasonic and jet. The former relies on a vibrating mesh to produce and aerosol of drug while the latter uses a jet of air to draw up liquid through a capillary and atomiser (Spiro and MacCochrane, 1999). Nebulisation of agents is used in a variety of techniques in human medicine (Table 1).

Table 1. Use of Nebulisers in Respiratory Medicine

Category	Use	Condition
Diagnosis	Airway reactivity	Suspected asthma
	Airway reversibility	Asthma
	Sputum induction	*Pneumocystis* pneumonia
Physiology	Ventilation distribution	Pulmonary embolism
	Epithelial permeability	Interstitial lung diseases
Treatment	Bronchodilators	Asthma, COPD
	Antibiotics	Cystic fibrosis
	Corticosteroids	Asthma
	Mucolytics	Asthma, cystic fibrosis, chronic bronchitis
	Local anesthetics	Persistent cough, fibrosing alveolitis
	Opiates	Severe dyspnoea, lymphangitis, carcinomatosa

In avian medicine, nebulisation tends to be used for therapeutic purposes, rather than diagnostic (Spink,1986; Tully and Harrison, 1994; Carpenter, 2005). As in human medicine this may be to deliver drugs to the respiratory system or to provide an expectorant effect or hydrate the mucous membranes (Spink, 1986; Tully and Harrison, 1994; Chitty, 2002).

Reviewing the human literature shows a huge amount of published literature relating to the diverse range of techniques, equipment and purposes.

In contrast, in avian medicine, nebulisation appears to be poorly covered by the literature with most references appearing in conference proceedings or review papers/ chapters. Nonetheless very strong opinions are often held by practitioners relating to the use of particular techniques and agents. The following discussion will attempt to examine some of these opinions in the light of the published research in this field

DISCUSSION

Compliance

It has been shown that the major reason for failure of nebulisation therapy is that of compliance (Everard, 2006). This falls into two parts - regimen compliance and device compliance. The former relies mainly on the actions of the patient and owner. The owner needs to be able to follow the regimen while the action of the device should not cause the bird to change its breathing pattern.

The latter depends more on the machine - the ability to use the machine and the, importantly, the ability to maintain the machine. This appears to be at least as important as choice of nebuliser and drug!

Best practice should be followed with respect to type of machine, patient, drug and condition to be treated British Thoracic Society Standards of Care Committee (1997). It should be borne in mind that a “visible” fog can be a bad thing - if small droplets are required (see below) then the fog should be nearly invisible as the droplets are so small.

Nebuliser Type

It is often proposed in discussion groups or boards (eg www.vin.com) that ultrasonic nebulisers carry advantages over jet nebulisers in terms of particle size with the former producing smaller size droplets than the latter.

In fact, the converse appears to be true (Spiro and MacCochrane, 1999; Rau, 2002).

In general jet nebulisers are cheaper, more robust and more readily available than ultrasonic models. However, they may not have as high an output rate (Rau, 2002).

It is more relevant to select nebuliser type based on the drug to be nebulised as the output and aerosolisation of drug is greatly influenced by nebuliser. In general, it is stated that ultrasonic nebulisers should not be used to aerosolize suspensions as they are very inefficient with these formulations (Rau, 2002, O’Riordan, 2002). However, both types have been shown to damage certain drugs in nebulisation (O’Riordan, 2002). It is also important to note that huge differences have been shown in the aerosolisation of the same drug by different nebulisers in the same class! Barry and O’Callaghan (1999).

Physical environmental effects also exert significant effects on nebuliser output, eg relative humidity (Zhou et al., 2005).

Particle Size
This is often proposed as being the most important factor in achieving proper drug penetration.

Certainly it has been shown that particle size does have relevance in penetration to different parts of the respiratory tree. In general particles of around 5µm have the greatest penetration to the alveoli. Particles larger than this tend to deposit in the oropharynx or trachea/ bronchi. Particles smaller than 0.5-1.0µm tend to penetrate well but not settle onto respiratory membranes (Spiro and MacCochrane, 1999; Boe et al., 2001; Aerosol Research laboratory of Alberta). Reviewing references it is easy to find slight variances in these figures. However, there appear to be variations according to the type of drug used during each study - presumably this will affect mass of the droplet and liquid viscosity.

It is also important to remember that these are based on probability. Droplets of all sizes will penetrate to the lungs. Droplets of all sizes will be deposited in the oropharynx. However, there is variance in likelihood as to where they will be deposited.

Other factors, too, affect this especially flow rate – the faster the air flow the more likely the drug is to penetrate deeper. Similarly deeper breathing will enable deeper penetration compared to rapid shallow breathing.

Anatomical differences in airway also have an effect with patients with more tortuous upper airways not achieving the same particle deposition. Bronchoconstriction and airway obstruction similarly reduce particle deposition in the lungs (O'Callaghan and Barry, 1997).

It is important to consider that nebulisers do not produce monomorphic particles. A range of particle sizes is produced that depends on machine, method and drug used. This results in a figure being produced - the Mass Median Aerodynamic Diameter (MMAD) describing the diameter of a sphere of unit density that has the same aerodynamic properties as a particle of median mass from the aerosol. The Geometric Standard Deviation (GSD) describes the spread of particle size. A GSD of 1 means that all particles produced are the same size (O'Callaghan and Barry, 1997).

The MMAD/GSD is appropriate for an individual model of nebuliser using a particular drug formulation.

As in any technique the method used to measure aerosol particle size will affect results .

Drug Use
In human medicine small particle sizes are used to deposit drugs in the alveoli for local action and systemic absorption. This has been shown to occur for a number of drugs.

However, some drugs are not intended to be absorbed nor to act at this level. Therefore larger particle sizes may be appropriate for drugs acting, for example, as bronchodilators Boe et al., 2001). Some drugs have been shown to cause unwanted side-effects - eg amphotericin-B has been associated with bronchospasm to the extent that it is not recommended to be used by nebulisation (Boe et al., 2001).

WHAT DOES THIS MEAN FOR AVIAN MEDICINE?

It is apparent from the human field that there is a lot of specific information for specific uses of nebulisation.

Presently, this simply doesn't exist in avian medicine and much of the current literature is based on experience and clinical observation with nebulisation often a part of a clinical regimen rather than the whole.

Recommendations for its use in avian medicine are often, therefore, unsound without looking at the following:

1. In the human field it is shown that anatomical variations cause changes in particle deposition during nebulisation. Consider the very different anatomy of the respiratory system in the bird and the great variation between species and it is clear that human nebulisation models are unlikely to apply to birds (Maina, 2005). Few studies have been done to show penetration of aerosolised droplets in birds. A rare exception is Corbanei et al (2006). This study, having initially characterised the aerosolisation method and effect of relative humidity, showed that particles of 10µm diameter or more were unlikely to penetrate the lower airways of 4 week old chickens. Particles of 5µm or more were unlikely to penetrate in 2 week old chickens. It should however, be considered that this study utilised dry powder nebulisation and there may be some differences in particle behaviour between this technique and droplet nebulisation. Alveolar diameter in humans is approx 0.3mm. Bird air capillaries are considerably smaller (3-15µm diameter, though there is considerable variation between species – to some extent, the larger the species, the wider the capillaries (Maina, 2005). This may influence particle size selection though particles this size have been shown to be less likely to settle on respiratory membranes. Certainly Corbanei et al. (2006) did appear to demonstrate this effect though this study also demonstrated differences attributable to breathing pattern.

2. Consider where the drug is desired to penetrate. To enter the air sacs caudal to the lung the particles do not need to enter air capillaries. This may well impact on the size of particle required. After all, *Aspergllus* spores are 2-5µm in diameter (Girling, 2005).

3. Consider the disease process - congestion of the lungs and encapsulation of abscessated material will reduce or even prevent penetration of nebulised drugs.

4. Consider the drug formulation and nebuliser type/ model. Even if the liquid is disappearing from the machine, this does not mean that the drug is entering the aerosol and certainly does not mean that the drug is entering the bird. As stated earlier, seeing a "fog" is likely to indicate that the MMAD is quite large.

5. Consider drug toxicity. It is often proposed that nebulisation enables use of drugs that may otherwise be toxic if used systemically. It is unclear whether nebulised drugs are, in fact, absorbed from the lungs/ air sacs of birds as so few studies have been performed. Gentamycin has been shown not to be absorbed in a study that demonstrated its presence in the lungs and airsacs (Spink, 1986). Lincomycin and oxytetracycline have been shown to be absorbed well and achieve effective plasma concentrations after nebulisation (Chaleva et al., 1994; Dyer and van Alstine, 1987). Ceftriaxone was shown not to achieve detectable plasma

concentrations after nebulisation (Junge et al., 1994) - however this paper did not assess lung, airsac or even airborne levels of the drug so it is unclear whether it represents failure to absorb drug or failure to nebulise. One bird did show some transient tissue levels which may indicate the drug was nebulised, but may also show ingestion by another route (see below). Tylosin has also been shown to be absorbed following nebulisation especially after addition of DMSO to the nebulised mixture (Locke and Bush, 1984). However, use of potentially toxic or irritant drugs should be discouraged until their internal effects are more widely known. Even if a drug is not absorbed via the respiratory system, it must be considered that after standing in a nebulisation chamber the bird's plumage will be covered in droplets from the nebuliser. This represents an opportunity for the bird to ingest drug during preening. Irritation to the respiratory system also has to be considered – as described earlier amphotericin-B has been shown to cause such complications through bronchospasm in humans with little proven clinical benefit that it is no longer recommended in human aspergillosis and has entirely been replaced by systemic drug use (Boe et al., 2001). Overall, use of antibacterials via nebulisation rather than by systemic routes remains controversial in human medicine (Smith and Ramsay, 1995). Certainly drugs used should be the forms designed for nebulisation rather than intravenous preparations used off-label.

6. Consider toxicity to humans. While the bird may not absorb drug, it is possible that the owner (or veterinary staff) can. When removing the bird from the chamber the handler is likely to inhale residual droplets. This could impact on their health.

7. Nebuliser care. Where used, nebulisers should be maintained in good order in accordance with manufacturer guidelines. To ensure compliance good communication with clients and staff is essential throughout the treatment period.

8. Studies. Most nebulisation regimes described have been based on clinical use and observation and not following clinical trial. While the observer may see apparent clinical improvement following use of the nebulised drug, aerosolisation and drug uptake (with or without systemic absorption) are rarely demonstrated. Effects, therefore, are hard to assess especially if nebulisation is used concurrently with other therapies (Chitty, 2002; Joseph et al., 1994). It is important that those citing such "doses" distinguish between these regimes and more formal clinical trials.

While clinical studies provide much in the way of "circumstantial" evidence more clinical trials are needed that follow best practice guidelines (Boe et al., 2001) to produce nebulisation data that shows aerosolisation of the drug, particle size produced, penetration of the drug (and, ideally, absorption studies) and reports of side-effects (both systemic and localized) as well as clinical benefit.

This can then result in a recommendation to use a particular drug formulation in a particular nebuliser model for a particular length of time.

Until more of these studies are performed, nebulisation must be regarded as more of a supportive therapy providing hydration of mucous membranes and, possibly, expectorant effects and not a means of drug delivery.

SO, WHERE DOES F10 FIT INTO THIS?

F10 Super Concentrate Disinfectant ("F10") is produced by Health and Hygiene (Pty) Ltd in South

Africa. It was originally developed for disinfection within pharmaceutical plants particularly aseptic fill areas (eg. intravenous drips). It is a complete spectrum virucidal, bactericidal, fungicidal and sporicidal aldehyde-free compound of six main active ingredients. The product contains quaternary ammonium (0-10%) and biguanide compounds (5.8%); 10-30% nonylphenol ethylene oxide condensate; and 10-30% tetrasodium EDTA. Reports of its clinical effects, however, are largely anecdotal (Chitty (2002), http://www.f10biocare.co.uk/articles.html). For the clinician this is not helped by the potential difficulties in assessing its activity *in vitro* in commercial laboratories (Monks et al., 2005). However, there is product data showing a very wide range of activity and effectiveness in fogging regimes (especially against *Aspergillus* spp - Verwoerd (2001).

Considering the points above:

1. F10SC has been designed for use via fogging systems – to all intents and purposes these are jet nebulisers. Product data therefore tells us that F10SC will survive the nebulisation process and is aerosolised from such devices. However, there is no data readily available on MMAD/ GSD in different conditions, nor is there evidence to show its performance when used in ultrasonic nebulisers. As described above there may also be differences between different models of jet nebulisers.

2. F10SC used at the correct concentration is non-irritant to mucous membrane and has very good human safety data - it can therefore be considered "safe" for use by staff and owners. As ever, though, compliance is all-important so owner education in terms of mixing the agent and use of the nebulisers is vital. There is a tendency for this agent to clog jet nebulisers, so device care is particularly important and foaming from the aerosolisation chamber should be taken as evidence of a problem.

3. There is anecdotal evidence of its penetration into the avian lung/ airsac system (Temperley, personal communication). However, no data appears available on whether all components penetrate equally.

4. Evidence of reduced incidence of aspergillosis in poultry houses following fogging is clear - however, whether this is via effects within the bird or effects on the environment is not clear. Therefore, such data may be taken as evidence only that the agent is aerosolised and that it has activity against *Aspergillus* species.

5. Nebulisation is useful in hydration of mucous membranes and in exerting an expectorant effect – the inclusion of surfactants in F10SC may be helpful in these effects. Certainly it appears pleasant-smelling and is very well tolerated by patients – the behaviour of patients in the nebulisation chamber is very interesting as many will actively move toward the aerosolisation chamber and even stand over it. Some falcons in a raptor hospital have been observed to move to a lower perch to stand in the mist from a fogging unit. While it is easy to anthropomorphise, this does at least show that patients do not find the experience unpleasant and may even "feel better" - an important factor in therapy, and in inducing owner compliance.

In summary, F10SC has more data available on its performance in nebulisation than, probably, any other veterinary product – the clinician can, at least, be confident that they are aerosolising a potentially antimicrobial agent. Certainly there is good evidence to show F10SC does no harm and weak evidence that it actively does good.

However, particularly, when dealing with aspergillosis, clinicans must be aware of what they are expecting of a nebulised agent – many of the lesions are well-encapsulated and contain caseous material: lungs are often congested. Therefore, any nebulised therapy is likely only to be adjunctive and not curative.

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