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Efficient nebulisation of powdered antibiotics

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Summary

Antibiotic aerosols have a role to play in the treatment of certain respiratory tract infections, but relatively viscous antibiotic solutions may be difficult to nebulise efficiently. Solutions of ceftazidime and colistin, made up by adding 3 ml diluent to powder, have been nebulised in vitro by 4 combinations of jet nebuliser and compressor in order to determine the most efficient apparatus for use with each substance. Nebulisation time, droplet size and drug output were determined. Droplet mass median diameters varied according to the type of nebuliser and compressor, but were confined to the range 3.2–5.0 μm throughout the studies. For colistin, DeVilbiss and Turret were both efficient nebulisers, and the use of the more powerful Maxi compressor reduced nebulisation time. For ceftazidime, Turret nebuliser with Maxi compressor was the most efficient system, while the "dead" solution volume retained within the DeVilbiss nebuliser was unacceptably high. These results emphasize the need for careful choice of nebuliser and compressor for use with antibiotic aerosols.

Introduction

Nebulisers are the most versatile type of device for delivery of therapeutic aerosols, since they can be used with virtually any drug solution or suspension. The beneficial effects of antibiotic aerosols were first demonstrated more than 40 years ago (Mutch, 1944; Southwell, 1946) in a variety of respiratory tract infections. Despite some unsuccessful clinical experience subsequently (Williams, 1974), recent studies have shown that there is a role for antibiotic aerosol therapy with gentamicin and carbenicillin (Hodson et al., 1981) ticarcillin and tobramycin (Wall et al., 1983), ceftazidime (Stead et al., 1985), amoxycillin (Stockley et al., 1985) and colistin (Burns, 1974; Littlewood et al., 1985), particularly in the management of *Pseudomonas* infection in patients with cystic fibrosis. Erythromycin, rifampicin and ciprofloxacin aerosols are effective in treating experimental Legionnaires' disease in an animal model (Gibson et al., 1983; Fitzgeorge et al., 1986).

Successful aerosol therapy is, however, likely to depend upon delivering an adequate amount of respirable aerosol to the patient's lungs in a relatively short treatment period. These goals may sometimes be achieved only by correct selection of apparatus; we have shown in previous studies that both nebulisation time and the quantity of gentamicin or carbenicillin contained within droplets < 5 μm diameter (Newman et al., 1985; Newman et al., 1986a) can vary widely according to the type of nebuliser and compressor employed.

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Antibiotic solutions made up by adding diluents to powders may pose special problems since they may be relatively viscous and hence difficult to nebulise quickly and efficiently. In this study we have assessed in vitro the nebulisation times, droplet sizes and drug outputs of two such solutions, a cephalosporin (ceftazidime) and a polymixin (colistin). Four combinations of nebuliser and compressor were used in order to determine the best delivery system for use with each drug solution.

Materials and Methods

The two powdered antibiotics tested were 1 g ceftazidime (Fortum, Glaxo) and 1 MU (80 mg) colistin (Colomycin, Pharmax). A diluent volume of 3 ml water for injection was added to the drug powder, and the contents of the vial were subsequently transferred by syringe to the nebuliser. The viscosities of the solutions at 20°C were 2.67 mPas and 1.04 mPas, respectively.

The drug solutions were nebulised by 8 individual samples of each of the DeVilbiss 646 nebuliser (DeVilbiss Health Care, U.K.) and the Turret nebuliser (Medic-Aid): a Maxi mark I compressor (Medix) and a PortaNeb 50 compressor (Medic-Aid), chosen as representatives of relatively powerful and relatively weak compressors (Newman et al., 1986a), were used as sources of compressed air. With the Maxi the pressures upstream of DeVilbiss and Turret nebulisers were 155 kPa (22 psi) and 190 kPa (27 psi) respectively; with the PortaNeb these pressures were 70 kPa (10 psi) and 105 kPa (15 psi).

The nebulisers were fitted with mouthpieces, and were clamped in a fume cupboard. The drug solutions were nebulised to "dryness", i.e. until no further aerosol could be released, and nebulisation time was defined as the point 30 s after the last visible aerosol release. The "dead" mass of solution, retained in the nebuliser after completion of nebulisation, was determined by weighing. Owing to preferential evaporation of solvents, solutions became more concentrated in the nebuliser reservoir with time (Ferron et al., 1976; Davis, 1978; Wood et al., 1986). In this study, the ratio of "dead" to initial drug concentrations was determined by comparing the osmolarity of the "dead" solution volume with that of the initial drug solution (Advanced Instruments). Pilot studies showed that osmolarity was linearly related to drug concentration. The solution weights and concentrations were used to calculate the "dead" mass of drug retained in the nebuliser, and hence the mass of drug released as aerosol (Newman et al., 1985; Newman et al., 1986a).

Aerosol droplet size was measured for each nebuliser/compressor combination using a Malvern Instruments 2600 HSD laser analyser (Malvern, U.K.), with the beam passing 2.5 cm from the tip of the mouthpiece (Newman et al., 1986b). The spray was drawn through the beam to a filter by means of a suction pump. A dedicated microprocessor connected on-line to the laser was used to calculate the mass of aerosol in 15 size bands on a logarithmic scale between 1.2 and 120 μm. The parameters determined were the aerosol mass median diameter (MMD), and the percentage of the aerosol mass contained in droplets < 5 μm diameter.

Statistical significance of data was assessed using the Wilcoxon Rank Sum Test for Paired Data, and the Friedman Two-Way Analysis of Variance by Ranks (Siegel, 1956).

Results

Nebulisation times, droplet sizes and drug outputs are summarised for the two solutions in Tables I and II. The initial solution volumes created by adding 3 ml diluent to the drug powders were 3.8–4.0 ml for ceftazidime but only 2.9–3.2 ml for colistin; the corresponding initial solution masses were 4.2–4.4 g and 3.0–3.3 g.

For both drug solutions, nebulisation times were shorter ($P < 0.05$), droplet MMDs were smaller ($P < 0.01$) and the percentages of the aerosol mass contained in droplets < 5 μm diameter were higher ($P < 0.01$) for the Maxi compressor than for the PortaNeb. Droplet MMDs for both ceftazidime and colistin were smaller when the Turret nebuliser was used ($P < 0.05$); however, MMDs were confined to the range 3.2–5.0 μm and varied little

TABLE I

Nebulisation of ceftazidime

	Nebuliser + compressor			
	DeVilbiss + Maxi	DeVilbiss + PortaNeb	Turret + Maxi	Turret + PortaNeb
Mean (S.E.M.) nebulisation time, min	15.3 (1.4)	19.3 (1.6)	23.3 (1.8)	34.4 (2.1)
Mean (S.E.M.) MMD, μm	3.9 (0.2)	5.0 (0.3)	3.3 (0.2)	3.9 (0.1)
Mean (S.E.M.) percentage of aerosol mass $< 5\ \mu$m	66 (4)	50 (4)	72 (5)	68 (3)
Range of initial solution masses, g	4.29–4.38	4.32–4.38	4.30–4.38	4.22–4.40
Range of "dead" solution masses, g	2.18–2.77	2.17–2.76	0.88–1.08	0.98–1.45
Range of "dead"/initial solution concentration ratios	1.22–1.34	1.22–1.35	1.59–1.73	1.52–1.58
Mean (S.E.M.) "dead" mass of ceftazidime, mg	705 (17)	685 (10)	353 (11)	421 (20)
Mean (S.E.M.) mass of ceftazidime released as aerosol, mg	295 (17)	315 (10)	647 (11)	579 (20)

between the two drug solutions.

The Turret nebuliser had a smaller "dead" solution mass than the DeVilbiss for both antibiotics, and consequently released more drug as aerosol ($P < 0.02$), this effect being very marked for ceftazidime. With the DeVilbiss, nebulisation of ceftazidime was completed relatively quickly ($P = 0.01$), and this was associated with dead

TABLE II

Nebulisation of colistin

	Nebuliser + compressor			
	DeVilbiss + Maxi	DeVilbiss + PortaNeb	Turret + Maxi	Turret + PortaNeb
Mean (S.E.M.) nebulisation time, min	13.3 (0.8)	16.4 (1.0)	12.6 (0.8)	22.6 (1.4)
Mean (S.E.M.) MMD, μm	3.6 (0.1)	5.0 (0.3)	3.2 (0.1)	3.6 (0.1)
Mean (S.E.M.) percentage of aerosol mass $< 5\ \mu$m	72 (3)	51 (4)	81 (1)	73 (1)
Range of initial solution masses, g	3.12–3.21	2.99–3.13	2.95–3.15	3.12–3.23
Range of "dead" solution masses, g	0.67–1.07	1.00–1.37	0.53–0.95	0.46–0.81
Range of "dead"/initial solution concentration ratios	1.70–1.95	1.70–1.76	1.30–1.68	1.86–2.05
Mean (S.E.M.) "dead" mass of colistin, MU	0.44 (0.02)	0.59 (0.02)	0.33 (0.02)	0.31 (0.02)
Mean (S.E.M.) mass of colistin released as aerosol, MU	0.56 (0.02)	0.41 (0.02)	0.67 (0.02)	0.69 (0.02)

solution masses approximately double those for the Turret. Although the increase in ceftazidime concentration during nebulisation was less for DeVilbiss than for Turret, the "dead" mass of ceftazidime was increased for DeVilbiss and the mass of ceftazidime released as aerosol consequently reduced ($P < 0.02$).

Discussion

Nebulisation time, droplet size and the mass of drug released as aerosol are all important in the assessment of nebuliser performance since these parameters determine the quantity of drug aerosol available to the patient and its distribution within the respiratory tract. Our findings support those of earlier studies using various drug solutions including gentamicin and carbenicillin (Newman et al., 1985, 1986a; Davis, 1978; Sterk et al., 1984) confirming that nebuliser characteristics can vary according to the type of nebuliser, its mode of operation and the properties of the fluid being nebulised. Such information is seldom available from nebuliser manufacturers, even for the most commonly used solutions such as bronchodilators. The inappropriate choice of apparatus may result in nebulisation times which are too long for patient convenience, droplet sizes too large for adequate penetration to the bronchial tree, and drug output which is insufficient for effective therapy. The value of aerosol antibiotic therapy has been questioned on the basis that insufficient aerosol is delivered to the site of infection within the bronchial tree (Gough and Jordan, 1982), and poor clinical results obtained in some trials with antibiotic aerosols (Williams, 1974) may have resulted in part from the incorrect selection of nebuliser and compressor. The use of efficient apparatus should, on the other hand, help to ensure successful therapy, and might also improve the reproducibility of aerosol delivery in experimental laboratory procedures. The potential importance of using specific nebulisers and gas flow rates with aerosol antibiotics was recognised several decades ago (Schwartz and Oteen, 1952), although this knowledge seems to have been forgotten subsequently.

Nebulisation times were lower for the Maxi compressor than for the PortaNeb, reflecting the higher flow rates and air pressures with the former compressor model. This observation is in agreement with previous assessments of nebulisation time using either fixed air flow rates (Newman et al., 1985; Clay et al., 1983) or electric compressors (Newman et al., 1986a). Colistin was nebulised more rapidly than ceftazidime, reflecting two factors, firstly the relatively small solution volume produced by adding 3 ml diluent to 1 MU (80 mg) powder, and secondly the lower viscosity of colistin solution compared to ceftazidime. Viscous solutions nebulise relatively slowly (Newman et al., 1986a), and hence it is virtually essential to use a powerful compressor such as the Maxi for antibiotic aerosol therapy if treatment times are not to become unacceptably prolonged. Treatment times can sometimes approach 1 h in duration when carbenicillin is nebulised by a relatively weak compressor such as the PortaNeb (Newman et al., 1986a).

Aerosol droplets < 5 μm diameter are sometimes said to comprise the "respirable range" since they are likely to escape deposition by inertial impaction in the oropharynx and central airways of the lungs, and can penetrate to the more peripheral lung regions (Newman and Clarke, 1983). In the present study, mass median diameter was smaller for the Maxi compressor than for the PortaNeb, while more drug was released in droplets < 5 μm diameter with the former compressor. A reduction in aerosol droplet size with increasing gas flow rate or driving pressure has been observed previously with a variety of nebuliser solutions (Newman et al., 1985, 1986a and b). However, it should be noted that the mean value of MMD was confined to a relatively narrow range throughout the present study (3.2–5.0 μm) and it remains to be demonstrated whether changes in MMD within this size band are of major clinical importance for aerosol antibiotic therapy.

The Turret nebuliser had a smaller "dead" volume than the DeVilbiss, and hence released a greater quantity of drug as aerosol. Nebulisation times were, however, correspondingly shorter for DeVilbiss. The reduced efficiency of the DeVilbiss was probably caused by high adhesion of drug

droplets to the baffles and other internal surfaces of this nebuliser, while the higher efficiency of the Turret probably reflects the relative ease with which droplets were able to coalesce and run back into the fluid reservoir for re-nebulisation. This effect was very marked for ceftazidime where Turret doubled the mass of drug released; this increased drug delivery would more than compensate for the longer nebulisation time required, providing that a powerful compressor was used. The percentage of the initial drug doses nebulised for ceftazidime and for colistin are compared in Fig. 1 with those for carbenicillin (1 g plus 3 ml diluent) determined in a previous study using the same nebulisers and compressors (Newman et al., 1986a). While the efficiency of DeVilbiss approaches that of Turret for carbenicillin and for colistin, the low efficiency of DeVilbiss with ceftazidime probably makes this combination of nebuliser and solution unsuitable for delivering high drug doses to the respiratory tract.

A single diluent volume of 3 ml was tested in these studies. Nebulisers generally work more efficiently when the fluid volume is increased (Kradjan and Lakshminarayan, 1985) although for carbenicillin the mass of drug contained in droplets $< 5\ \mu m$ diameter was little changed when the diluent volume was raised from 3 to 4 ml, while nebulisation times were longer (Newman et al., 1986a). A reduction in diluent volume from 3 to 2 ml would predictably reduce nebulisation times, but the solutions would be very viscous and difficult to handle. A diluent volume of 3 ml for powdered antibiotics may thus constitute a satisfactory compromise between the conflicting needs of efficient nebulisation and short treatment times.

In conclusion, we would make the following practical recommendations: for colistin, either DeVilbiss or Turrett are acceptable nebulisers, coupled to a Maxi compressor of to another model of comparable power. For ceftazidime, the reduction in drug output with the DeVilbiss was sufficiently high for us to be unable to recommend this nebuliser, and the Turret should be used, again coupled to a powerful compressor. Many other nebuliser models are available, but our results suggest that each nebuliser brand should be tested with each drug solution in order to ensure that drug delivery is acceptable.

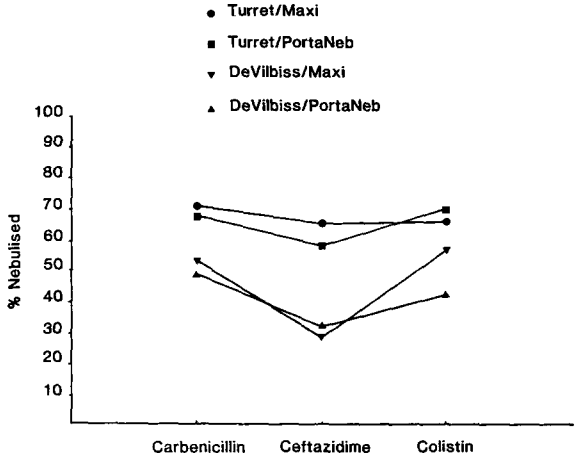

Fig. 1. Mean percentage of initial drug masses delivered as aerosol for carbenicillin, ceftazidime and colistin using DeVilbiss and Turret nebulisers with Maxi and PortaNeb compressors. Data for carbenicillin taken from Newman et al. (1986a).

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