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Ultrasonic nebulisation of pentamidine isethionate

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Summary

The properties of pentamidine isethionate aerosols produced by an ultrasonic nebuliser frequently used in clinical practice have been investigated. The mass median diameter of the aerosols was initially 5.1–5.6 μm, depending on the volume of solution atomized and the output setting of the nebuliser. The aerosol size tended to decrease, and the solution temperature increase with time. Between 57 and 74% of drug placed in the nebuliser was delivered during use, the remainder being associated with the device.

Introduction

Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection associated with the human immunodeficiency virus. Inhaled pentamidine is effective in the prophylaxis and treatment of PCP.

In the many reported studies of inhaled pentamidine therapy, the nebuliser system, dose of pentamidine, solution concentration and nebuliser fill volume employed have varied considerably. Consequently, it is possible that reports of treatment failure (Godfrey-Faussett et al., 1988) and the occurrence of apical *P. carinii* infection in patients receiving prophylactic inhaled pentamidine (Abd et al., 1988; Conces et al., 1989) may result from inadequate delivery of pentamidine to the required pulmonary sites, rather than failure of the drug itself.

PCP is an infection associated with type I alveolar epithelial cells (Long et al., 1986). Consequently, as a strategy to effectively target pentamidine, jet and ultrasonic nebulisers have been developed capable of delivering aerosols in the size range predicted to deposit efficiently in the alveoli, i.e., less than 5 μm and preferably less than 2 μm (Stahlhofen et al., 1980).

Many studies of pentamidine aerosols have determined the size of aerosols generated, this may give a false measure of efficiency of drug delivery or likely clinical efficacy if the amount delivered from the nebuliser is not also taken into account. A study of two jet nebulisers commonly used for pentamidine therapy has also indicated that the median size of aerosols produced in-

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creased with time, and that blockages frequently occurred in the nebulisers (Taylor et al., 1992). This was due to large temperature decreases occurring in the nebuliser solution during use of jet nebulisers and the marked temperature dependence of the aqueous solubility of pentamidine isethionate, the salt of pentamidine used clinically.

In this study we have characterised the aerosols produced from solutions of pentamidine isethionate by the Medix Electronic Nebulizer over the time taken to atomize solutions to dryness.

Materials and Methods

3, 5 or 6 ml of solutions containing 300 mg pentamidine isethionate in deionised water were placed in the Medix Electronic Nebulizer (Medix Ltd, U.K.). Two output/flow settings were used to atomize the solutions: 'maximum' and a setting midway between the minimum and maximum settings, we designated 'median'.

Aerosol size analysis was performed with a Malvern 2600c laser diffraction analyser (Malvern, U.K.), and was continued until no aerosol was detectable with the instrument. Following atomization, any drug remaining in the nebuliser was assayed for pentamidine isethionate by UV analysis at 262 nm. The time required to atomize solutions to dryness was measured with a stop watch.

In some experiments a temperature probe (RS Components Ltd, U.K.) was inserted into the nebuliser chamber, allowing temperature measurements to be made during nebulisation of some solutions.

Results and Discussion

At the maximum setting, the median diameter of the aerosols produced were initially between 5.1 and 5.6 μm (Fig. 1). The Medix Electronic Nebulizer is also marketed as the Fisoneb (Fisons plc) and is commonly used for pentamidine therapy, particularly for prophylaxis against PCP. The sizes measured were similar to the median droplet

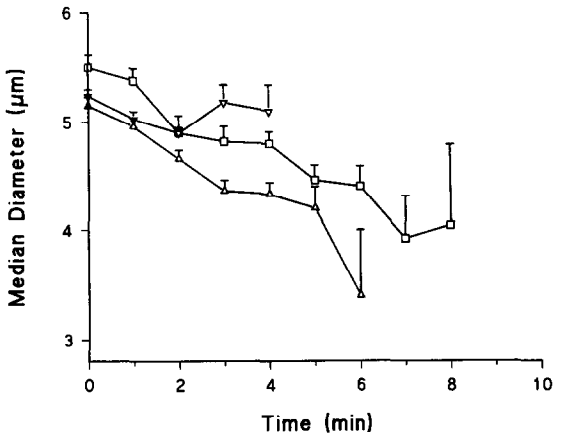

Fig. 1. Median droplet size produced by nebulizing 300 mg pentamidine isethionate in (▽) 3 ml, (△) 5 ml and (□) 6 ml water at maximum setting. Each point is the mean (±SE) of three experiments.

sizes of between 4.7 and 6.13 μm reported in previous studies where laser diffraction was used to measure the size of pentamidine aerosols produced by Fisoneb nebulisers (Dolovich et al., 1990; Simonds et al., 1990; Smith et al., 1992).

The median size of aerosols generally decreased with time. The aerosol droplet size was not log-normally distributed, so a geometric standard deviation is not given. The distribution of sizes may, however, be expressed by the size below which were 90% of the aerosol droplets. This size decreased with time, so that the proportion of droplets in the 'ideal' size range increased (Fig. 2). The variability in the median size and size distribution increased towards the end of nebulisation.

Similar results were obtained when the nebuliser was operated at the median setting (Figs 3 and 4). The measured sizes were generally greater than those produced by the nebuliser operated at maximum setting.

Operating the nebuliser at maximum setting decreased the time required to nebulise pentamidine isethionate solutions to dryness, whilst the smaller the initial fill volume, the shorter the time to atomize to dryness. At the maximum and median settings, the time taken to nebulise solutions to dryness was: for 3 ml, 6.3 and 6.4 min; 5 ml, 7.9 and 8.3 min; and 6 ml, 8.7 and 9.3 min,

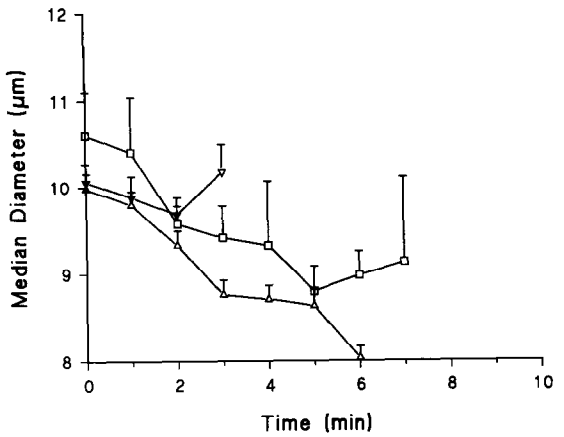

Fig. 2. Size below which are 90% of aerosol droplets produced by nebulizing 300 mg pentamidine isethionate in (▽) 3 ml, (△) 5 ml and (□) 6 ml water at maximum setting. Each point is the mean (±SE) of three experiments.

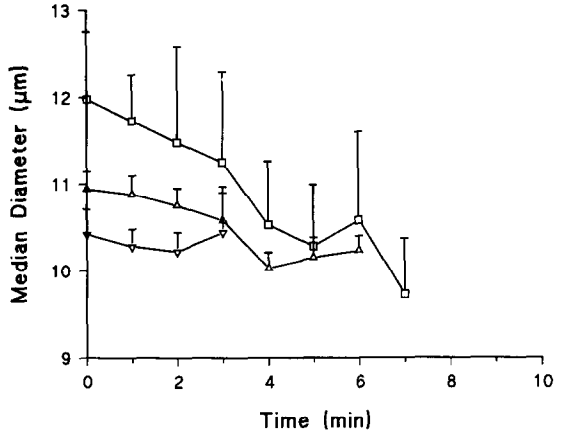

Fig. 4. Size below which are 90% of aerosol droplets produced by nebulizing 300 mg pentamidine isethionate in (▽) 3 ml, (△) 5 ml and (□) 6 ml water at median setting. Each point is the mean (±SE) of three experiments.

respectively. Decreasing the duration of atomization is advantageous in terms of hospital staff time and patient acceptability, since the drug has an unpleasant taste and may cause bronchospasm when inhaled (O'Doherty et al., 1988; Corkery et al., 1990).

During nebulisation the temperature of the solution remaining in the nebuliser increased (Fig. 5). At both maximum and median output settings the solution temperature increased to approx. 20°C above ambient. Such a dramatic increase in temperature may produce changes in the surface tension and viscosity of the liquid being atomized. This may in turn affect the aerosol characteristics of the generated aerosol (Davis, 1978), and may be the cause of the changes in the size characteristics of the pentamidine aerosols produced by the Medix with time.

The temperature solubility profile of pentamidine isethionate indicates that the aqueous solu-

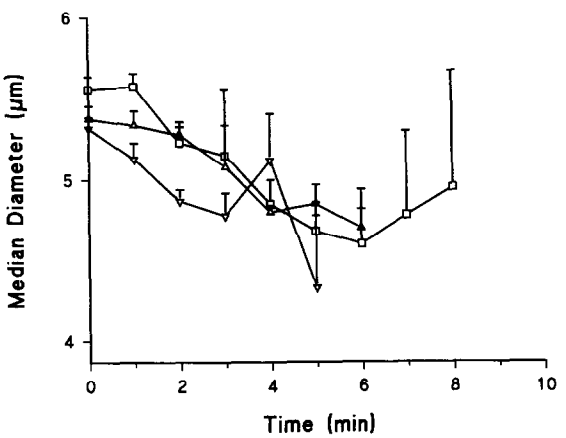

Fig. 3. Median droplet size produced by nebulizing 300 mg pentamidine isethionate in (▽) 3 ml, (△) 5 ml and (□) 6 ml water at median setting. Each point is the mean (±SE) of three experiments.

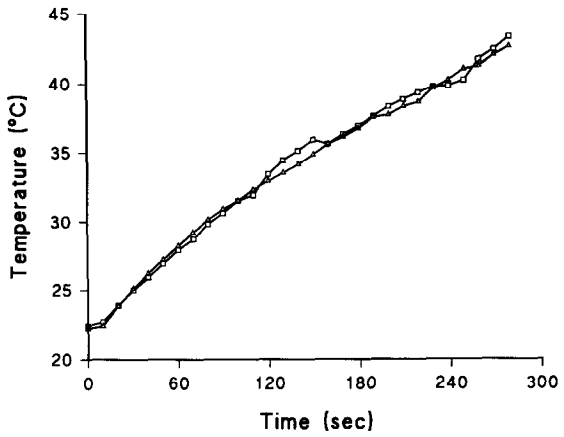

Fig. 5. Temperature increases occurring during nebulization of 300 mg/6 ml pentamidine isethionate solutions at maximum (□) and median (△) settings. Each point is the mean of three experiments.

TABLE 1

Fraction of pentamidine isethionate delivered during nebulization

Fill volume (ml)	Output setting	Fraction delivered (% ± SE)
3	maximum	57.4 (0.5)
3	median	60.6 (1.7)
5	maximum	67.1 (0.4)
5	median	68.5 (0.4)
6	maximum	70.1 (0.6)
6	median	74.1 (0.2)

Each result is the mean of three experiments.

bility of the drug exhibits a marked temperature dependence (Taylor et al., 1992). Pentamidine isethionate is often nebulised at or close to its limit of solubility (300 mg/3 ml or 600 mg/6 ml at 20°C). Solution warming in the Medix nebuliser ensures that drug solubility is unlikely to present problems. This contrasts with jet nebulisers, where temperature decreases up to 13°C may rapidly occur, resulting in rapid recrystallization of pentamidine isethionate, with resultant changes in the aerosol size and blockages in the nebulisers (Taylor et al., 1992). In jet nebulisers, solubility problems are compounded since solution concentration increases during use due to enhanced loss of solvent vapour as it saturates the outgoing air. This does not occur during the operation of ultrasonic nebulisers (Ferron et al., 1976).

Solution remaining in the nebuliser at the end of atomization was assayed for pentamidine isethionate. The output of drug, calculated as a percentage of that initially available in the nebuliser, is given in Table 1.

Between 57 and 74% of the available drug was delivered on atomizing solutions to dryness, depending on the initial fill volume and output setting. These values are higher than the previously reported figure of 49% delivered from a Fisoneb nebuliser when a 300 mg/5 ml solution was atomized at the maximum setting (Smith et al., 1992). Any discrepancy may be explained in that in the present study, the nebuliser was gently agitated towards the end of nebulisation to maximise the output.

All nebulisers have a 'dead volume', usually approx. 1 ml, which is the volume of liquid which remains in the nebuliser at the end of atomization (Clay et al., 1983). Consequently, a more efficient delivery of drug in terms of total quantity delivered was achieved with the larger initial fill volumes.

A more efficient delivery of drug occurred with the lower output setting. This is probably caused by larger amounts of drug being lost to the walls of the nebuliser at the higher setting.

These results may indicate why ultrasonically nebulised pentamidine, although having an aerosol droplet size greater than optimal, has been reported to be therapeutically effective (Girard et al., 1988, 1989), and why measured lung deposition of pentamidine is higher with the Fisoneb than with jet nebulisers for equivalent doses (Ilowite et al., 1990).

Ultrasonic nebulisation produces an efficient delivery of pentamidine in that compared to jet nebulisers a larger proportion of available drug is actually delivered from the device. Also, the size of the aerosols generated decreases with time so that increasingly greater proportions of the aerosols are in the optimal size range. Additionally, the warm aerosol droplets produced ultrasonically are likely to evaporate more rapidly than the cooler droplets produced by jet nebulisers. Thus the size of the droplets in the peripheral airways may be smaller than given by simple in vitro measurements. Smalldone et al. (1988) imposed a breathing cycle on a Fisoneb nebuliser and used a cascade impactor to determine the mass mean aerodynamic diameter (MMAD) of dilute pentamidine aerosols. Such a method affords a greater opportunity for solvent to evaporate from the droplets, and indeed the measured MMAD was 2.5 μm.

Although this study has investigated one model of ultrasonic nebuliser, the results are likely to apply to ultrasonic nebulisers, other than the Medix or Fisoneb, which have been or may be used for pentamidine therapy, since most models produce droplets of similar size and warm the liquid in the nebuliser (Mercer, 1973). For instance, the Ultraneb 99 (De Vilbiss) nebuliser, producing aerosols with a MMD of 4.6 μm, has

been used clinically to deliver pentamidine (Girard et al., 1988, 1989).

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