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Pentamidine isethionate delivery from jet nebulisers

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Summary

This study has investigated the properties of aerosols of pentamidine isethionate produced by two jet nebulisers commonly used in clinical practice. The size characteristics of the emitted aerosols varied throughout the time that drug solutions were nebulised, particularly at low gas flow rates. The aqueous solubility of pentamidine isethionate was found to be highly temperature dependent. As the temperature of solutions within the nebulisers decreased by up to 13°C, recrystallization of drug occurred. Approx. 50% of drug available in the nebuliser was available for delivery from the nebulisers, the remainder being associated with the devices.

Introduction

Inhaled pentamidine isethionate is used for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia (PCP), particularly in patients having the acquired immunodeficiency syndrome (AIDS). Currently, the therapeutic dose is 300 or 600 mg daily for up to 21 days (Monk and Benfield, 1990). The prophylactic dose is usually 150 mg pentamidine isethionate fortnightly or 300 mg every 4 weeks (Monk and Benfield, 1990; Squire et al., 1990). Drug is dissolved in up to 6 ml of Water For Injections, loaded into a nebuliser and inhaled by the patient as the solution is nebulised to dryness.

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PCP occurs primarily in the alveoli, being associated with the type I alveolar epithelial cells (Long et al., 1986). To penetrate to the alveolar regions of the respiratory tract, a particle should have a size less than 5 μm and preferably less than 2 μm (Stahlhofen et al., 1980). To achieve this in the delivery of pentamidine, jet nebuliser systems with additional valves, filters or baffles have been developed to produce droplets of appropriate size (Smalldone et al., 1988). The most frequently employed nebulisers for treatment of PCP have been the Respirgard II, producing median droplet sizes of 0.7–1.7 μm (Monk and Benfield, 1990) and the System 22, producing median droplet sizes of 1.3–3.4 μm (Monk and Benfield, 1990). However, effective therapy and prophylaxis against PCP has been achieved with nebulisers producing droplets with median size of approx. 5 μm (Girard et al., 1988).

For jet nebulisers, the most important factors determining the droplet size of the final aerosol

produced are the design of the nebuliser (Clay et al., 1983b) and the rate of gas flow through the device (Clay et al., 1983a). Properties of the liquid being nebulised, such as surface tension and viscosity (Davis, 1978) may also affect the final aerosol characteristics.

In this study we have characterised the aerosols produced from solutions of pentamidine isethionate by two models of jet nebuliser over the time taken to atomise solutions to dryness.

Materials and Methods

3 or 5 ml of solutions containing 300 mg pentamidine isethionate in deionised water were placed in either Respirgard II (Marquest, U.S.A.) or System 22 (Medicaid, U.K.) nebulisers. The nebulisers were driven by compressed air from a gas cylinder at various flow rates.

Aerosol size analysis was performed with a Malvern 2600c laser diffraction analyser (Malvern, U.K.). Sizing was continued until no aerosol was detectable with the instrument. Following atomization, any drug remaining in the nebuliser was redissolved and the solution assayed for pentamidine isethionate by UV analysis at 262 nm.

Some nebulisers were adapted to allow a temperature probe (RS Components Ltd, U.K.) to be inserted into the nebuliser chamber. Constant temperature determinations were carried out during nebulisation of some solutions.

The temperature-solubility profile of pentamidine isethionate in water was determined by placing a saturated solution in a compact piston filter device. This was placed in a shaking water bath at a specific temperature. Samples were taken at regular intervals and assayed for pentamidine isethionate at 262 nm. Sampling was continued until consistent UV absorbance measurements were observed. The Beer-Lambert law was used to calculate solubility.

Results and Discussion

When nebulisation commenced the Respirgard II produced aerosols having mass median diameter (MMD) less than 4 μm at all flow rates, and MMDs less than 2 μm at high flow rates (Fig. 1). The effect of increased gas flow rates producing decreased droplet size of aerosols from jet nebulisers has been reported previously (Clay et al., 1983a; Newman et al., 1987). However, the droplet size tended to increase towards the end of nebulisation, exceeding a size of 5 μm. Further, pronounced temporary increases in droplet size occurred during use, and at low flow rates blockage of the nebuliser, reversible by agitation occurred, resulting in little or no drug output. Similar results were observed for the System 22 nebuliser (Fig. 2), although at high flow rates aerosol characteristics remained constant. The recommended flow rates for these nebulisers are 5–7 l/min for the Respirgard II and 6–8 l/min for the System 22. All aerosols were polydispersed. Size distribution varied less markedly than MMD with flow rate or time. Current clinical practice requires nebulisation of solutions to dryness. If blockage within nebulisers occurs, or if droplet size increases to the extent that drug is unavailable to its site of action, effective therapy may be compromised.

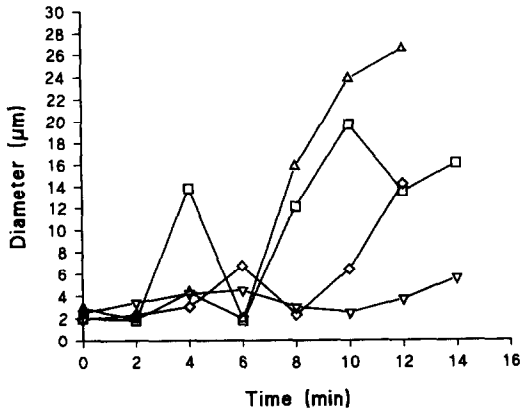

Fig. 1. Median droplet size produced by nebulising pentamidine isethionate (300 mg/5 ml) solutions in Respirgard II nebuliser at 6 l/min (□), 7 l/min (△), 8 l/min (▽) and 10 l/min (◇). Each point is the mean of three experiments.

In addition to producing droplets of smaller median size, increasing the gas flow rate through nebulisers can decrease the overall time required to nebulise a given volume of solution (Clay et al., 1983b; Newman et al., 1987). When the gas flow

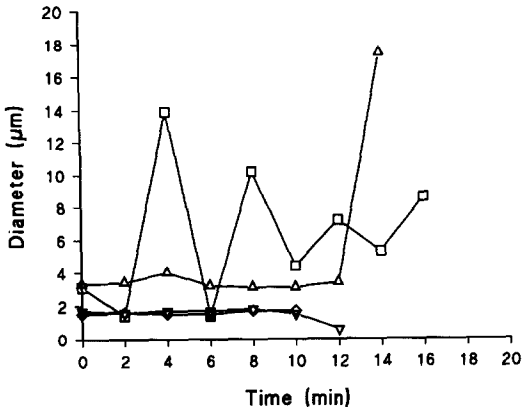

Fig. 2. Median droplet size produced by nebulising pentamidine isethionate (300 mg/5 ml) solutions in System 22 nebuliser at 6 l/min (□), 7 l/min (△), 8 l/min (▽) and 10 l/min (◇). Each point is the mean of three experiments.

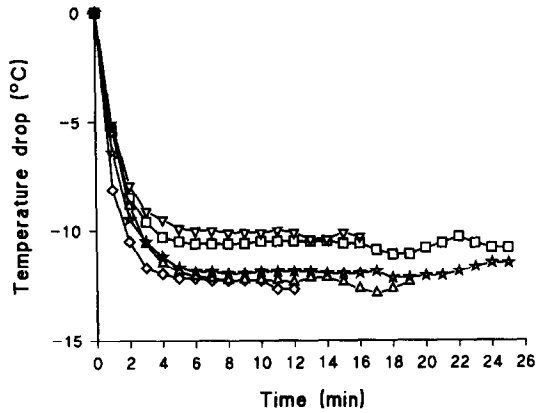

Fig. 4. Temperature decrease occurring in the solution during nebulisation of pentamidine isethionate (300 mg/5 ml) solutions in Respirgard II nebuliser at 5 l/min (*), 6 l/min (□), 7 l/min (△), 8 l/min (▽) and 10 l/min (◇). Each point is the mean of three experiments.

rate was increased from 5 to 10 l/min the time required to nebulise 5 ml of solution was decreased from 22.7 to 12.5 min for the Respirgard II and from 21.2 to 12.0 min for the System 22 (Fig. 3). Very high flow rates may result in increased oro-pharyngeal deposition, consequently flow rates as high as 10 l/min may be therapeutically inappropriate, due to increased occurrence of cough and/or vomiting. Decreasing duration of administration presents advantages in terms of hospital staff time, whilst a short nebulisation time may be more acceptable to patients, since

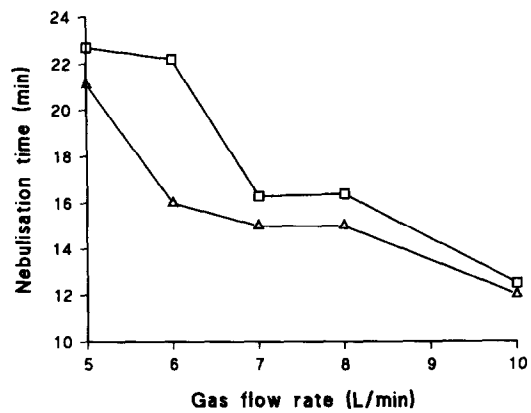

Fig. 3. Time required to nebulise solutions (300 mg/5 ml) of pentamidine isethionate to dryness in Respirgard II (□) and System 22 (△) at various gas flow rates. Each point is the mean of three experiments.

pentamidine isethionate has a characteristic metallic taste and causes bronchospasm and cough when inhaled (O'Doherty et al., 1988; Corkery et al., 1990).

The aerosol output from a jet nebuliser comprises drug solution and solvent vapour which saturates the outgoing air (Ferron et al., 1976). This loss of vapour tends to increase the concentration of the solution in the nebuliser. Loss of vapour may also result in a decrease in the temperature of the solution being atomised (Clay et al., 1983b).

Figs 4 and 5 show the decreases in temperature, below ambient, of pentamidine isethionate solutions occurring at various flow rates in the Respirgard II and System 22, respectively. Within 5 min of commencement of nebulisation, temperature decreases of between 9 and 13°C occurred in the Respirgard II and of approx. 10°C in the System 22. Such dramatic decreases in solution temperature may affect the drug solubility and produce changes in the viscosity and surface tension of the liquid. This may in turn alter the aerosol size characteristics of the emitted aerosol (Davis, 1978).

The aqueous solubility of pentamidine isethionate shows marked temperature dependence (Fig. 6). With both nebulisers the temperature of the

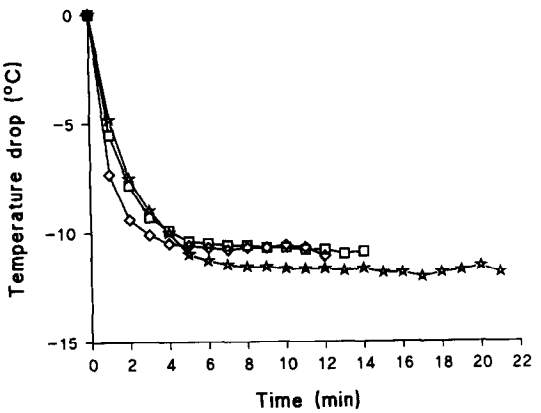

Fig. 5. Temperature decrease occurring in the solution during nebulisation of pentamidine isethionate (300 mg/5 ml) solutions in System 22 nebuliser at 5 l/min (⋆), 6 l/min (□), and 10 l/min (◇). Each point is the mean of three experiments.

solution falls during atomization, from ambient to about 10°C or less.

For treatment of PCP, pentamidine isethionate is used at concentrations of 600 mg in 6 ml or 300 mg in 3, 5 or 6 ml. At 20°C the solubility of drug is approx. 10%. Consequently, solutions of 600 mg/6 ml or 300 mg/3 ml are being nebulised at the limit of drug solubility. As the solution temperature rapidly falls, recrystallization of drug occurs. This was clearly visible with some nebulised solutions and it is likely that this recrystallisation was responsible for the changes in aerosol

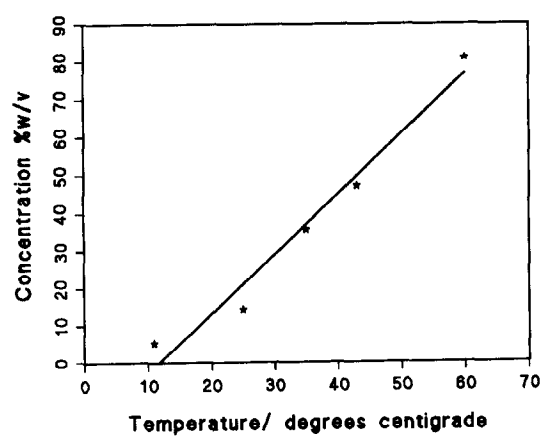

Fig. 6. Temperature solubility plot for pentamidine isethionate in water. Each point is the mean of duplicate experiments.

TABLE 1

Fraction of pentamidine isethionate delivered during nebulisation of a 300 mg / 5 ml solution (each result is the mean of three experiments)

Flow rate (l/min)	Respirgard II (% ± S.E.)	System 22 (% ± S.E.)
5	53.2 (1.8)	52.4 (3.0)
6	46.7 (1.1)	52.7 (3.9)
7	53.0 (1.6)	46.6 (2.7)
8	49.8 (2.9)	59.9 (2.6)
10	49.5 (1.7)	48.5 (2.1)

characteristics with time and occurrence of blockages within the devices.

Drug remaining in the nebuliser was redissolved and assayed for pentamidine isethionate. The output of drug calculated as a percentage of that which was initially available in the nebuliser is given in Tables 1 and 2 for 300 mg/5 ml and 300 mg/3 ml solutions, respectively.

When the more dilute solution was atomised approx. 50% of available drug was delivered from both types of nebuliser. This was increased to up to 63.4% when the more concentrated solution was nebulised at high flow rates.

All nebulisers have a so-called 'dead volume', usually of about 1 ml. This is the volume of atomiser solution which remains in the device following nebulisation (Clay et al., 1983b). This would normally be expected to favour the more efficient delivery of drug from larger volumes of dilute solutions. However, with nebulised pentamidine solutions it seems that the strong temperature dependence of drug solubility combined with the very rapid cooling of drug solutions in

TABLE 2

Fraction of pentamidine isethionate delivered during nebulisation of a 300 mg / 3 ml solution (each result is the mean of three experiments)

Flow rate (l/min)	Respirgard II (% ± S.E.)	System 22 (% ± S.E.)
5	53.5 (2.0)	56.4 (2.9)
7	57.9 (1.8)	61.1 (2.7)
10	48.2 (1.7)	63.4 (2.5)

the nebuliser will result in recrystallisation occurring rapidly from both initially dilute and concentrated solutions. A more concentrated solution, then, permits a more efficient delivery of drug in solution, prior to recrystallisation occurring.

The poor efficiency of pentamidine delivery from jet nebulisers together with blockages in the nebuliser and increases in aerosol size during use may partially explain the small deposited doses of drug found in the alveoli of patients following bronchoalveolar lavage (Conte and Golden, 1988). This may also be a factor in the failure of some patients with PCP to respond to pentamidine therapy and the occurrence of relapse of PCP receiving prophylactic pentamidine therapy, although other factors, such as the blockage of the airways by pneumocysts will also be important.

Ultrasonic nebulisers have been developed that are capable of producing aerosols for alveolar deposition, for instance, the DeVilbiss 646 (Simonds et al., 1990), Ultraneb 99 and Portasonic nebulisers (Dautzenberg et al., 1990)

Ultrasonic nebulisers have been reported to be effective for delivery of pentamidine for the treatment and particularly the prophylaxis of PCP. These studies have included nebulisers producing aerosols of median size approx. 5 μm (Girard et al., 1988), which are generally considered too large to achieve effective alveolar deposition.

Whereas jet nebulisers cause the temperature of liquids being atomised to decrease, ultrasonic nebulisation produces an increased liquid temperature (Mercer, 1973). Thus, ultrasonic nebulisers may be much more efficient in their total drug delivery. The fraction of drug in the appropriate size range may be less, for certain ultrasonic nebulisers, than jet nebulisers, but the total amount delivered may be greater. Studies of the deposition of radiolabelled pentamidine aerosols in subjects infected with the HIV virus have indicated that ultrasonic nebulisers provided up to a 5-fold greater pulmonary deposition than jet nebulisers (Illowite et al., 1990). The greater total drug output from ultrasonic nebulisers and the polydispersed size distributions of the aerosols produced may also have implications for the occurrence and severity of unwanted side effects, i.e., coughing, bronchospasm and metallic taste.

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References

Clay, M., Pavia, D., Newman, S.P. and Clarke, S.W., Factors influencing the size distribution of aerosols from jet nebulisers. *Thorax*, 38 (1983a) 755–759.

Clay, M., Pavia, D., Newman, S.P., Lennard-Jones, T. and Clarke, S.W., Assessment of jet nebulisers for lung aerosol therapy. *Lancet*, ii (1983b) 592–594.

Conte, J.E. and Golden, J.A., Concentrations of aerosolised pentamidine in bronchoalveolar lavage, systemic absorption and excretion. *Antimicrob. Agents Chemother.*, 32 (1988) 1490–1493.

Corkery, K.J., Montgomery, A.B., Montani, R. and Fine, J.M., Airway effects of aerosolized pentamidine isethionate. *Am. Rev. Respir. Dis.*, 141 (1990) A152.

Dautzenberg, B., Meignan, M. Bouchiki, A., Antoun, F., Braga, F., Roy, M. and Becquemin, M.H., Comparison of 5 devices for pentamidine aerosol administration. *Am. Rev. Respir. Dis.*, 141 (1990) A153.

Davis, S.S., Physico-chemical studies on aerosol solutions for drug delivery. I: Water-propylene glycol systems. *Int. J. Pharm.*, 1 (1978) 71–83.

Ferron, G.A., Kerrebijn, K.F. and Weber, J., Properties of aerosols produced with three nebulisers. *Am. Rev. Respir. Dis.*, 114 (1976) 899–908.

Girard, P.-M., Couderc, L.-J., Farinotti, R., Matheron, S., Kernbaum, S., Coulaud, J.-P. and Saimot, A.-G., Ultrasonic nebulised pentamidine for pneumocystis pneumonia. *Lancet*, i (1988) 1165.

Illowite, J.S., Baskin, M.I., Sheetz, M.S. and Abd. A.G., Comparison of delivered dose and regional distribution of aerosolized pentamidine using different delivery systems. *Am. Rev. Respir. Dis.*, 141 (1990) A153.

Long, E.G., Smith, J.S. and Meier, J.L., Attachment of pneumocystis carinii to rat pneumocytes. *Lab. Invest.*, 54 (1986) 609–615.

Mercer, T.T., Production and characterization of aerosols. *Arch. Intern. Med.*, 131 (1973) 39–50.

Monk, J.P. and Benfield, P., Inhaled pentamidine. An overview of its pharmacological properties and a review of its therapeutic use in *Pneumocystis carinii* pneumonia. *Drugs*, 39 (1990) 741–756.

Newman, S.P., Pellow, P.G.D. and Clarke, S.W., In vitro comparison of DeVilbiss jet and ultrasonic nebulizers. *Chest*, 92 (1987) 991–995.

O'Doherty, M.J., Thomas, S., Page, C., Barlow, D., Bradbeer, C., Nunan, T.O. and Bateman, N.T., Differences in the

relative efficiency of nebulizers for pentamidine administration. *Lancet*, ii, (1988) 1283–1286.

Simonds, A.K., Newman, S.P., Johnson, M.A., Talaee, N., Lee, C.A. and Clarke, S.W., Alveolar targeting of aerosol pentamidine: toward a rational delivery system. *Am. Rev. Respir. Dis.*, 141 (1990) 827–829.

Smalldone, G.C., Perry, R.J. and Deutsh, D.G., Characteristics of Nebulizers used in the treatment of AIDS-related pneumocystis carinii pneumonia. *J. Aerosol. Med.*, 1 (1988) 113–126.

Squire, S.B., Lim, S., Simonds, A.K., Newman, S.P. Lee, C.A. and Johnson, M.A., Safety and efficacy of inhaled pentamidine as prophylaxis against pneumocystis carinii pneumonia in HIV disease. *Am. Rev. Respir. Dis.*, 141 (1990) A152.

Stahlhofen, W., Gebhart, J. and Heyder, J., Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. *Am. Ind. Hyg. Assoc. J.*, 41 (1980) 385–398.