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Rapid Communication

Manipulating the temperature of pentamidine isethionate solutions in jet nebulisers

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Summary

The effects of changes in the initial solution temperature and local environmental temperature on the temperature of pentamidine isethionate solutions atomized in a jet nebuliser commonly employed for pentamidine therapy have been studied. In all cases the temperature of liquid decreased during atomization, but an initial solution temperature of 30°C or greater, with or without the nebuliser being held at constant temperature maintained the liquid in the nebuliser at a temperature likely to ensure that the drug remained in solution. Hand-holding the nebuliser during use at ambient temperature raised the temperature of the solution in the nebuliser by less than 3°C.

Solutions of pentamidine isethionate are atomized in jet or ultrasonic nebulisers for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia. Previous studies have indicated that the aqueous solubility of pentamidine isethionate is highly temperature dependent (Taylor et al., 1992). The aerosol output from jet nebulisers comprises drug solution and solvent vapour which saturates the outgoing air (Ferron et al., 1976). This loss of vapour increases the concentration of solution remaining in the nebuliser and results in the solution temperature decreasing (Clay et al., 1983). The rapid reduction in solution temperature which occurs during use of jet nebulisers has been reported to result in rapid recrystallization of pentamidine isethionate from solutions, producing blockages within devices and variations in the droplet size of the emitted aerosol (Taylor et al., 1992). Ultrasonic nebulisers increase the temperature of solutions being atomized (Mercer, 1973). A Medix Electronic ultrasonic nebuliser warmed solutions of pentamidine isethionate during use, such that drug solubility was not a problem and the size of emitted aerosol decreased with time (Taylor and Hoare, 1993).

Respirgard II (Marquest, U.S.A.) nebulisers were driven by compressed air from a gas cylinder at a flow rate of 6 l/min to generate aerosols from 6 ml of a 6% w/v solution of pentamidine isethionate in deionised water. Solutions were nebulised to dryness. Pentamidine isethionate was a gift from Norton Health Care, U.K. Nebulisers were adapted to permit insertion of a tempera-

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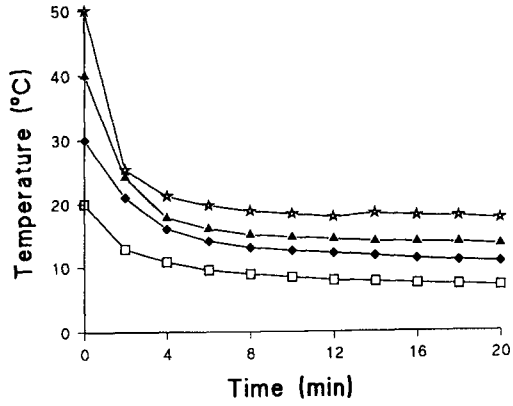

Fig. 1. Temperature of pentamidine isethionate solutions during nebulisation from Respirgard II nebuliser held at 20°C (□), 30°C (♦), 40°C (▲) and 50°C (★). Each point is the mean of three experiments.

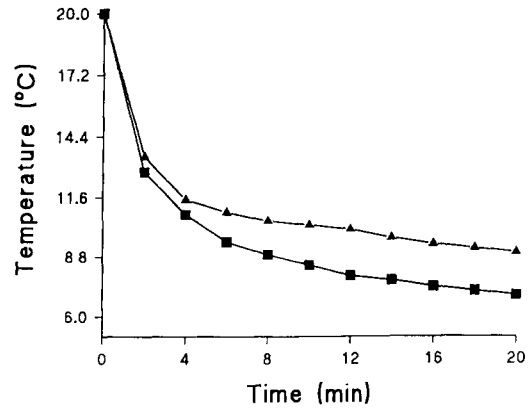

Fig. 3. Temperature of pentamidine isethionate solutions during nebulisation from Respirgard II nebuliser at 20°C with (▲) and without (■) hand-holding. Each point is the mean of three experiments.

ture probe (RS Components Ltd, U.K.) allowing temperature measurements to be made during nebulisation of solutions. The nebuliser was operated with an initial solution temperature and room temperature of 20°C, or with the solution pre-warmed to 30, 40 or 50°C in a water bath prior to loading into the nebuliser and atomization at room temperature. Additionally, solutions were placed in nebulisers which were then held in water baths at 30, 40 or 50°C, the temperature of the solution was allowed to equilibrate before atomization with the nebuliser held in the water bath during use. In some hospitals, patients are instructed to hold their nebulisers during use. Consequently, the experiment at room temperature (20°C) was repeated with the nebuliser held in the hand throughout nebulisation.

Warming the liquid in the nebuliser to between 30 and 50°C and retaining the nebuliser in a water bath increased the solution temperature during nebulisation compared to the solution nebulised at 20°C (Fig. 1). A similar result occurred when solutions were warmed prior to nebulisation at ambient temperature although the overall decrease in solution temperatures was greater (Fig. 2).

Changes in the temperature of a liquid being nebulized may alter its viscosity and surface tension which may also affect the size characteristics of the aerosol produced (Davis, 1978; Newman et al., 1987). Solutions of pentamidine isethionate are nebulised at or near the limit of drug solubility. Below approx. 15°C pentamidine isethionate recrystallizes from a 6% w/v solution (Taylor et al., 1992). When the initial solution temperature was 30°C or greater, the solution within the nebuliser was maintained at a temperature greater than 15°C throughout the period of nebulisation, even when the temperature of the nebuliser was not maintained at a higher temperature. The temperature of the solution atomized at 20°C fell

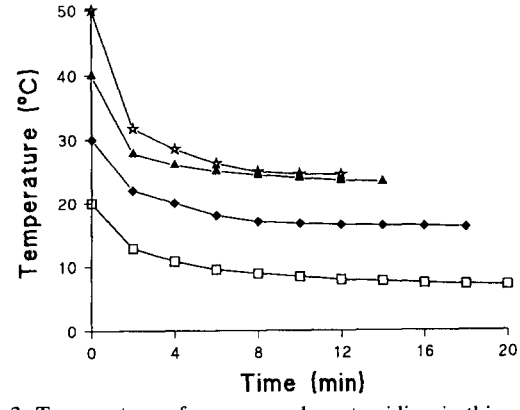

Fig. 2. Temperature of pre-warmed pentamidine isethionate solutions during nebulisation from Respirgard II nebuliser. Initial solution temperatures were 20°C (□), 30°C (♦), 40°C (▲) and 50°C (★). Each point is the mean of three experiments.

below 15°C after 2 min. Below this temperature drug rapidly came out of solution. This recrystallization of drug in jet nebulisers may result in blockages and changes in the size of the aerosol produced (Taylor et al., 1992). Consequently, an ability to control the solubility by a simple procedure such as warming the solution to be nebulised prior to use may prove clinically useful. The increase in concentration of solutions occurring during use of jet nebulisers, due to enhanced loss of water vapour, should also be considered.

Hand-holding increased the temperatures of solutions nebulised at ambient temperature by less than 3°C (Fig. 3) over the atomization period. In the case of pentamidine isethionate solutions this is unlikely to have a great impact on the performance of the nebuliser as precipitation of drug occurred rapidly whether or not the nebuliser was held in the hand.

The results of this study indicate that simple strategies can be employed to maintain the temperature of nebuliser solutions in excess of that resulting in drug recrystallization. This in turn is likely to be beneficial in reducing instances of nebuliser blockage and in ensuring a high output of drug. These results also suggest that clinically the performance of jet nebulisers in inhaled pentamidine therapy may vary dependent upon the local environmental temperature.

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