Drug delivery from jet nebulisers

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Abstract
Maximising the rate of drug delivered in particles small enough to reach the lower respiratory tract from jet nebulisers may allow treatment times to be reduced and thus improve the acceptability of this form of treatment, particularly in very young patients. The role of various technical factors such as driving gas flow (DGF) in determining the rate of drug delivery was studied by constructing a model to simulate the respiratory pattern of individuals with different tidal volumes using a Starling ventilator and filter. Sodium cromoglycate was nebulised under a variety of operating conditions and the dose deposited on the filter was assayed. Tidal volumes of 50 and 400 ml were used at a frequency of 32 breaths per minute.

Increasing the DGF from 4 to 8 l/minute produced a 264% increase in the rate of drug output but only a 32% increase in aerosol concentration. The mass of drug contained within droplets <5 μm increased from 26·8% to 70·8% of the total. The resultant increase in rate of drug delivery to the filter was 34% for a tidal volume of 50 ml and 79% for a tidal volume of 400 ml though the dose contained within droplets <5 μm increased by 4-fold at 50 ml tidal volume and by more than 5-fold at the higher tidal volume. Halving the solution concentration halved the rate of drug delivery. Increasing the tidal volume 8-fold from 50 to 400 ml resulted in an increase in the rate of drug deposition upon the filter of only 2·2 to 3-fold depending upon the DGF so that substantially more drug per ml inhaled was delivered at the lower tidal volume.

These results are explained by considering factors that influence the rate of drug delivery. At low tidal volumes the rate of drug delivery at a given respiratory rate is dependent on the tidal volume and aerosol concentration. At high tidal volumes it is dependent upon aerosol concentration and volume of available aerosol and is essentially independent of tidal volume.

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Jet nebulisers have been used for many years to deliver aerosols to the lower respiratory tract. The doses used for a wide variety of drugs have largely evolved empirically and current recommendations for operating the nebuliser are largely directed towards maximising the quantity of drug leaving the nebuliser chamber. Unfortunately the time required to nebulise a dose may be long and hence regular treatment may therefore be inconvenient and, particularly in young patients, poorly tolerated. If the rate at which drug is delivered to the lower respiratory tract could be increased, treatment times could be reduced leading to improvements in the acceptability and efficacy of this form of treatment.

Radioisotope studies have shown that around 10% of the dose placed in the chamber of a jet nebuliser may reach the lungs of adults,[1-4] though this is greatly influenced by the nebuliser used and the way in which it is operated.[1 5] Current recommendations for the use of jet nebulisers are based on studies which have looked at individual aspects of nebuliser performance such as total output and the way in which these are influenced by altering technical factors such as fill volume or driving gas flow (DGF).

Although these experiments remain the basis for current recommendations, there are a number of problems associated with them. Many of the studies have simply assessed drug output on the basis of the change in weight within the nebuliser,[6-8] which is inaccurate because of the significant evaporation of water during nebulisation.[9 10] More recent studies have addressed this problem by assaying the quantity of drug left in the nebuliser chamber at the end of a period of nebulisation and subtracting this from the initial dose.[11]

More fundamentally, these studies fail to consider the ways in which technical factors such as the DGF interact with each other and with patient factors such as tidal volume in determining the rate at which drug is delivered to the patient. For example these studies have shown that increasing the DGF will increase both the rate of drug output[6 10] and the proportion of drug within the aerosol contained in droplets <5 μm in size.[12-14] These studies do not consider the influence of changes in tidal volume with age upon either the total dose inhaled or the relative dose delivered when corrected for body weight.

As it would not be possible to assess the effects of these changes in children because of ethical considerations, a new approach was devised using an in vitro model to determine how change in tidal volume might interract with the various technical factors influencing the output of jet nebulisers to influence the rate at which drug is inhaled. By combining these results with those obtained with a laser particle sizer, the rate at which drug contained within droplets <5 μm was delivered under each set of conditions was calculated.

Methods

A model was constructed in order to simulate the respiratory pattern of individuals with different tidal volumes. For this a Starling ventilator (C F Palmer) was connected via a Y connector in such a way as to allow air to be drawn in and exhaled out through a filter (Whatman Glass Micro fibre, exposed diameter 3·3 cm; fig 1). The filter paper can be considered to be the 'nose/mouth' of the model. The dose of drug deposited upon the filter represents the total amount of drug inhaled.

A 'face' was constructed from firm rubber so that the facemask of the nebuliser could be firmly applied. To minimise deposition of drug due to aerosol flowing directly into the mask and impacting on the filter, the filter was held in place at the base of a cylindrical funnel, designed for this purpose. A cylinder with a relatively large diameter (4·2 cm) was chosen to ensure that effective mixing would occur within the funnel and facemask. The funnel also allowed calibration of the tidal volume across the filter. It was not possible to place a pneumotachograph within the funnel at the level of the filter and hence it was placed at the level of the face. The effective tidal volume at the filter being obtained by subtracting the volume of the funnel (35 ml) from the measurement obtained at the face.

The Starling ventilator had a limited number of settings and a rate of 32 breaths per minute was chosen for these experiments. No attempt was made to consider the effects of change in respiratory rate and a single setting was chosen to minimise the variables when comparing results. Inspiration occupied approximately 40% of the respiratory cycle. Tidal volumes of 50 and 400 ml were chosen as typical of an infant of approximately 9 months of age and an adult subject. An infant or adult mask was used in these experiments, as appropriate.

The experiments were performed using a single Cirrhus nebuliser (Intersurgical) chosen at random. This is the make most widely used in our unit and it is typical of the commonly

used jet nebulisers. Preliminary experiments had demonstrated variations in output of up to 20% when testing nebulisers of the same make while the mass median diameter and percentage of droplets less than 5 µm in size at a given DGF also varied considerably. Similar results have been described previously.[7] [14] The driving gas was supplied by a cylinder of air and the flow was measured using a flow meter appropriately calibrated for compressed air (BOC Medishield).

Sodium cromoglycate solution (20 mg in 2 ml) was used in these experiments because an ultraviolet spectrophotometric assay (Hewlett Packard Diode Array spectrophotometer) was available and allowed accurate quantification of drug quantities on the filter and in the nebuliser chamber at the end of each experiment. To obtain the quantity of drug left within the nebuliser chamber and that deposited on the filter, both were first washed with known volumes of distilled water and the absorbance at 326 nm was obtained for the resultant solution. This was then used to calculate the total quantity of drug using the formula:

$$\text{Drug dose (mg)} = \frac{\text{Absorbance at 326 nm} \times \text{volume (ml)} \times 10}{E}$$

The system had previously been calibrated using known concentrations of sodium cromoglycate, the constant E (absorbance for a 1% solution using a 1 cm path length) was 159·43. Previous experience with this method has demonstrated excellent reproducibility, this being estimated to be within 0·01 mg.

In most experiments 4 ml of 1% sodium cromoglycate solution were placed within the nebuliser chamber which allowed continuous nebulisation throughout a five minute period. This time was chosen as this is probably the longest period one might reasonably expect a small child or infant to sit still. Experiments were performed using DGFs of 4, 6, and 8 l/minute with a tidal volume of 50 ml, DGFs of 4 and 8 l/minute at a tidal volume of 400 ml, and a single study at 8 l/minute with the Starling pump turned off. In addition, the effects of moving the mask 1 and 2 cm away from the model face on the delivered dose was examined using a DGF of 8 l/minute and a tidal volume of 50 ml. As a more concentrated solution of sodium cromoglycate was not available the effects of altering solution concentration were studied by diluting 2 ml of solution with 2 ml of normal saline when using a DGF of 8 l/minute and a tidal volume of 50 ml. Each experiment was performed four times. The nebuliser was weighed before and after each experiment. The results are presented as the mean and range of the four experiments performed under each set of conditions.

Particle size measurements were performed with a Malvern 2600 laser particle sizer using the Fraunhofer diffraction model. For aqueous aerosols this method permits accurate sizing of droplets as they are generated and avoids the problems of drying associated with methods such as cascade impactors which tends to over estimate the quantity of aerosol in the 'respirable range'.[15]
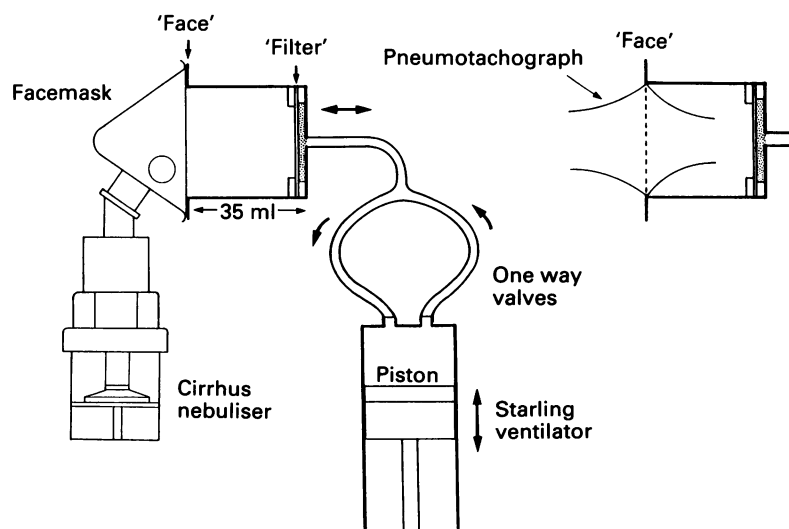
Figure 1   Model used to simulate the respiratory pattern of individuals and so study the factors influencing the rate of drug delivery from jet nebulisers at different tidal volumes. The dose 'inhaled' by the Starling ventilator was deposited upon the filter.

Results

The mean (range) quantity of sodium cromo-glycate leaving the nebuliser during a five minute period of continuous nebulisation increased from 4·61 mg (4·25–5·11) when using a DGF of 4 l/minute to 12·13 mg (11·38–12·96) at the higher DGF.

The effect on total dose deposited on the filter or 'inhaled' of altering the DGF at different tidal volumes is shown in fig 2. With the Starling ventilators switched off (tidal volume= 0), very little drug, 0·029 mg (0·026–0·033) was deposited upon the filter when a 1% solution was nebulised for five minutes using a DGF of 8 l/minute. At 50 ml tidal volume, increasing the DGF from 4 to 8 l/minute produced a 34% increase in the quantity of drug deposited upon the filter in a five minute period. The dose deposited increased from 0·91 mg (0·87–0·96) when using a 4 l/minute DGF to 1·02 mg (0·98–1·07) at 6 l/minute and 1·21 mg (1·18–1·28) at the 8 l/minute. The same change in DGF produced a larger increase in quantity of drug depositing upon the filter of 79% when the tidal volume was set at 400 ml. The dose deposited upon the filter increased from 2·09 mg (0·1·98–1·22) to 3·74 mg (3·57–3·94). The dose deposited on the filter when nebulising 4 ml of a 0·5% solution of sodium cromoglycate for five minutes was 0·57 mg (0·53–0·59) when using a DGF of 8 l/minute and a tidal volume of 50 ml. The effects of increasing the DGF on particle size are shown in the table. As the DGF increased the mass median diameter fell and the percentage of particle mass within the aerosol contained in droplets less than 5 μm in size increased. These results apply only to the individual nebuliser used in these experiments.

Figure 3 shows the appreciable effect of moving the facemask away from the face. At only 1 cm from the face while still directing the aerosol stream towards the filter the dose delivered was only 0·49 mg (0·46–0·51) using a tidal volume of 50 ml and a DGF of 8 l/minute. At a distance of 2 cm the reduction was even greater with only 0·18 mg (0·17–0·2) reaching the filter.

As sodium cromoglycate is a solution, it is possible to combine the results of total drug inhaled with those obtained using the particle sizer to infer the quantity of drug deposited upon the filter contained in droplets <5 μm

Aerosol mass median diameter and mass of droplets <5 μm in size expressed as percentage of the total droplet mass measured when using DGFs of 4, 6, and 8 l/minute. Results were obtained using a Malvern 2600 laser particle sizer

DGF (l/min)	Mass median diameter (μm)	% Of droplet mass <5 μm
4	7·0	26·8
6	4·9	50·1
8	3·6	70·8
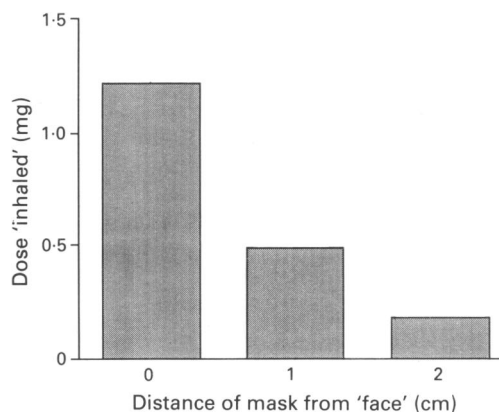
Figure 3   The dose deposited upon the filter in a five minute period of nebulisation with increasing distance between the nebuliser facemask and the 'face' of the model when using a DGF of 8 l/minute and a tidal volume of 50 ml.
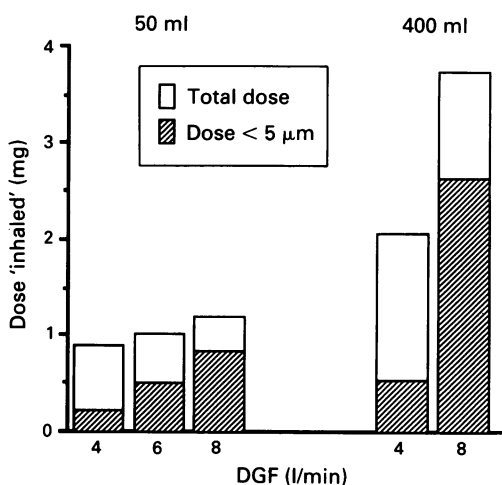
Figure 4   Total dose and dose contained within droplets <5 μm in size delivered to the filter at tidal volumes of 50 and 400 ml when using different DGFs.

during each experiment. The results obtained are shown in fig 4.

From these results a model was constructed in order to consider the factors influencing the rate of drug delivery at different tidal volumes at an arbitrary respiratory rate (fig 5 and 6) while consideration of the interaction of the various technical resulted in a flow diagram illustrated in fig 7.

Discussion

In this study we have used a novel experimental approach in an attempt to elucidate the complex interaction of technical and patient factors which influence the rate of drug delivery to the
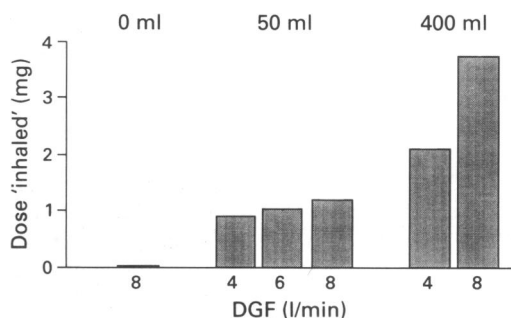

Figure 2   Mean dose of drug deposited upon the filter at tidal volumes of 0, 50, and 400 ml when 1% sodium cromoglycate was nebulised for five minutes using DGFs of 4, 6, and 8 l/minute.
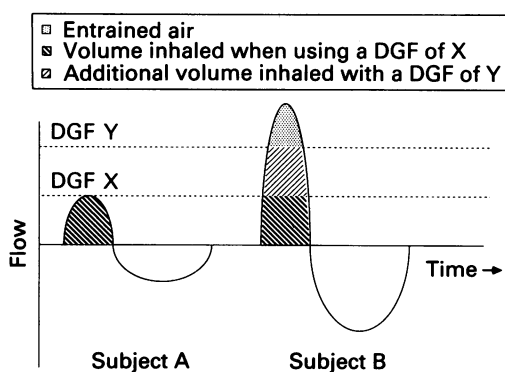
Figure 5 Diagram illustrating factors affecting the rate of drug delivered to individuals at a given respiratory rate. At low tidal volumes (A), the dose is dependent upon the tidal volume and aerosol concentration. At high tidal volumes (B), air entrainment occurs and hence the dose is dependent upon the aerosol concentration and the available volume of aerosol. It is largely independent of tidal volume.
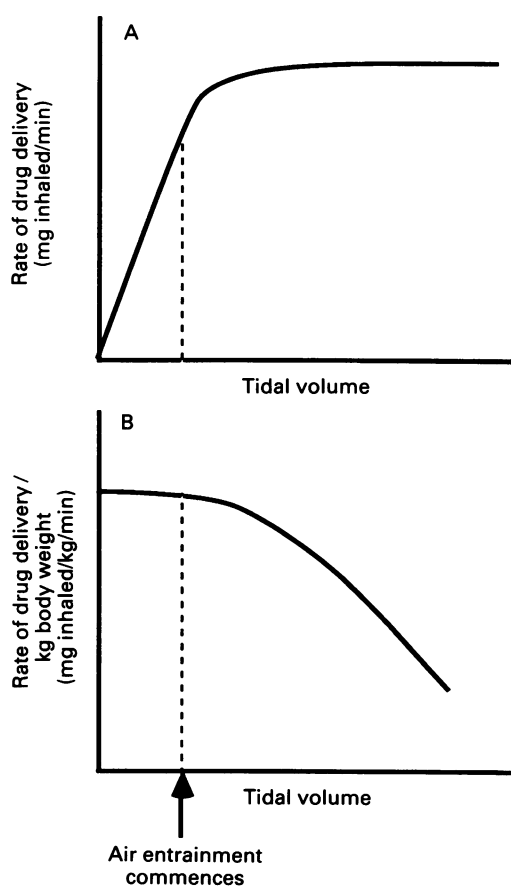

Figure 6 Diagramatic representation illustrating the effect of increasing tidal volume upon (A) the rate at which drug is inhaled from a jet nebuliser and (B) the rate at which drug is inhaled corrected for body weight.

lungs of infants and adults when using jet nebulisers. The model we constructed allows us to simulate the respiratory pattern of individuals and determine the total dose of drug that might be inhaled from a jet nebuliser in a given period of time. As the tidal volume and respiratory rate are reproducible the effect upon the total dose inhaled of altering technical factors, such as DGF or solution concentration, can be assessed accurately. Conversely the effect of changes in tidal volume upon the total dose inhaled can be assessed under a given set of nebuliser operating conditions. By considering these results in conjunction with measurements of particle size we can infer the quantity of drug contained in droplets smaller than 5 μm in size inhaled in a given time and hence obtain a guide to the rate at which the drug is likely to be delivered to the lower respiratory tract from a nebuliser when using a particular set of operating conditions. The actual dose reaching the lungs of an individual will of course be further influenced by other factors such as the degree of airway obstruction beyond the scope of this study.

These experiments have produced some surprising and, at first sight, contradictory results. A 264% increase in the drug output produced by doubling the DGF resulted in only a 34% increase in drug delivery at a tidal volume of 50 ml and a larger 79% increase at a tidal volume of 400 ml. An 8-fold increase in tidal volume from 50 to 400 ml resulted in an increase in the rate of drug reaching the filter of only 2·2–3-fold depending upon the DGF used. In order to explain these results we must consider the factors that influence the rate of drug delivery at high and low tidal volumes (fig 5) and the way in which technical factors such as DGF influence these determinants of drug delivery (fig 7). From fig 5 it is apparent that the total dose inhaled per breath at low tidal volumes is the product of the aerosol concentration and tidal volume. At the higher tidal volume the peak inspiratory flow exceeds the DGF and hence air entrainment occurs. Consequently the dose inhaled is dependent upon the aerosol concentration and volume of aerosol available which in turn is determined by the DGF. The dose inhaled per breath becomes largely independent of the subject's tidal volume as can be seen diagramatically in fig 6. The total dose inhaled increases linearly as tidal volume increases until air entrainment occurs. Further increases in tidal volume result in little additional drug being inhaled while the volume of air entrained rapidly increases effectively diluting the concentration of drug within the aerosol. As there is a fairly constant linear relationship between weight and tidal volume from infancy through to adulthood of 7–10 ml/kg,[16] correcting these results for tidal volume or body weight means that the infant would receive a considerably larger total dose than the adult shown diagramatically in fig 7. Infants have a higher minute volume per kilogram body weight than an adult,[16] hence the dose per kg inhaled per minute is likely to be even higher in infants. A study carried out at the same time as this work indicated that air entrainment commences at the tidal volumes seen in early childhood.[17]

AEROSOL CONCENTRATION

The concentration of aerosol generated by a jet nebuliser is a major determinant of the rate at which drug is inhaled at all tidal volumes. Though drug output increased by a factor of 2·64 when the DGF was doubled, the concentration of aerosol only increased by a third since the volume of aerosol generated had doubled. At a high DGF further increases may result in a fall in aerosol concentration as the rise in output tends to plateau.
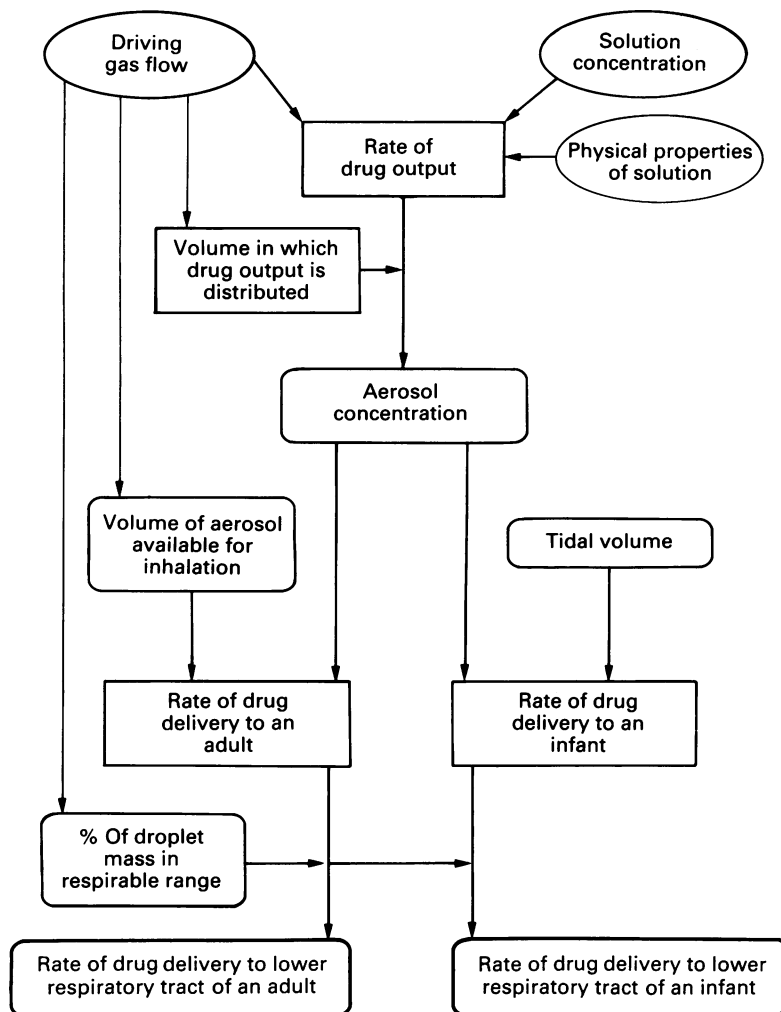
Figure 7   Diagram illustrating the complex interaction of technical factors that influence drug delivery to patient through factors such as aerosol concentration and particle size. The design of a nebuliser affects the particle size distribution and rate of output, therefore further changes have to be considered if changing make of nebuliser.

VOLUME OF AEROSOL AVAILABLE

The volume of aerosol available during the inspiratory phase of each breath was determined by the DGF. Doubling the DGF at the lower tidal volume increased the volume of aerosol lost directly into the atmosphere and therefore did not effect the rate of drug delivery. At the higher tidal volume, increasing the DGF increased the volume of aerosol available hence reducing the volume of entrained air required and directly contributed to the increase in drug delivery. It should be noted that at high tidal volumes the DGF will alter the rate of drug delivery but it will not have a major influence on the total quantity of drug inhaled when nebulising a given volume of solution to dryness as the dead volume is largely independent of DGF.[6] If one third of the respiratory cycle is inspiratory then one third of the total dose discharged from the nebuliser will be inhaled irrespective of DGF.

The use of facemasks will have relatively little effect on the dose inhaled, although a reservoir to contain the aerosols generated during the expiratory phase will increase drug delivery in subjects with high tidal volumes by increasing the volume of aerosol available and so reduce air entrainment.

INTERACTION OF TOTAL INHALED DOSE AND PARTICLE SIZE

Jet nebulisers are designed to deliver drug to the lower respiratory tract. The dose reaching this site will be dependent upon both the total dose inhaled and the fraction of that dose contained in droplets small enough to penetrate into the lower respiratory tract (fig 6). It is believed that droplets 1–5 μm in size are most likely to pass through the upper airway and be deposited in the lung peripheries.[18] Increasing the DGF from 4 to 8 l/minute has altered the rate of drug output, the volume in which this is distributed, the aerosol concentration, the volume of aerosol available during the inspiratory phase, and the size distribution of the droplets. The net effect is that the dose deposited upon the filter contained within droplets less than 5 μm in size, that is the respirable range, increased 4-fold at the lower tidal volume and more than 5-fold at the higher tidal volume (fig 7). These results could not have been predicted from considering a single effect such as change in the rate of drug output.

CLOSELY FITTING FACEMASKS

We often observe nurses and mothers attempting to hold a facemask in front of a struggling toddler. Figure 3 illustrates the dramatic effects of holding the facemask even a very small distance in from the face. The amount of drug inhaled was greatly reduced. At only 2 cm drug delivery was only 15% of that when a closely fitting mask was used. If this were repeated using a low DGF, the quantity of drug inhaled in droplets less than 5 μm in size is likely to be minimal and this may partly explain the poor response to nebulised treatment often seen when treating infants.

When using a 0·5% solution drug delivery in a five minute period was slightly less than half that when using a 1% solution. For solutions, the concentration of drug within each droplet generated by a jet nebuliser reflects the concentration of the solution from which it is generated. Hence, halving the concentration of the sodium cromoglycate solution effectively halved the concentration of drug within each droplet generated. Providing the change in solution concentration does not significantly alter the rate at which droplets leave the nebuliser by altering factors such as viscocity and surface tension, the quantity of drug and hence aerosol concentration generated by the nebuliser will be halved. The eventual total output when 2 ml of saline were added to 2 ml of drug solution was greater. However, diluting the 1% solution significantly reduced the rate of drug delivery and the time required for nebulisation to dryness increased substantially. Designing nebulisers to operate with smaller solution volumes and to have a low dead volume would be advantageous. Physical properties such as surface tension and viscosity will influence the rate of drug and will be dependent upon the drug used.

It is likely that drugs such as β_2 sympathomimetics are used in supermaximal doses when delivered by jet nebulisers.[1][19] This probably explains their efficacy despite the great variations in operating conditions used to nebulise them.[20-22] For other drugs such as antibiotics it is possible that therapeutic effects can be enhanced by increasing the dose delivered. By considering factors which influence the rate of drug delivery it may be possible to minimise treatment periods and so improve compliance and hence efficacy.

In these experiments we have considered the effects of altering DGF and solution concentration upon the rate of drug delivery at low and high tidal volumes. This approach could be used to assess the effects of altering many other parameters such as solution viscosity and nebuliser design and so improve the effectiveness of this form of treatment.

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