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Drug delivery from holding chambers with attached facemask

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Abstract

There is much interest in the use of holding chambers with an attached facemask to deliver aerosols from metered dose inhalers to infants. In order to study the influence of various design factors on the dose inhaled at different tidal volumes, a model was constructed in which a Starling ventilator was used to generate an inspiratory/expiratory cycle across a filter. Sodium cromoglycate was administered via a Nebuhaler and mask, Aerochamber and mask, and a coffee cup using tidal volumes of 25, 50, and 150 ml and the dose deposited upon the filter after six breaths was assayed using an ultraviolet spectrophotometric method.

At the lowest tidal volume the high aerosol concentration in the smaller chamber enhanced drug delivery while at the highest tidal volume delivery was greatest from the larger chamber reflecting the larger dose available. Multiple breaths ensured that the dose inhaled per kilogram from each chamber was relatively large and also permitted significant drug delivery despite the introduction of a relatively large dead space between valve and filter. The dose delivered was increased by increasing the dose introduced into the chamber though not proportionately.

These devices appear likely to deliver significant quantities of aerosol to infants, though drug delivery may be enhanced by the use of an appropriate valve.

The development of a simple, effective system for delivering drugs in the form of aerosols to the lungs of infants and young children is likely to be of considerable benefit. The obvious advantage of this form of treatment over systemic administration is that a therapeutic effect can be achieved while minimising systemic side effects. Jet nebulisers have been used to deliver aerosols to infants for many years, though this form of treatment has many disadvantages. It can be very time consuming especially if required several times a day and compressors are bulky and relatively expensive. More importantly it is frequently difficult to persuade an infant to tolerate this form of treatment because jet nebulisers tend to be noisy, treatment periods are generally long, and a closely fitting mask is required for effective drug delivery. Furthermore, effective drug delivery can be greatly influenced by the type of nebuliser and the operating conditions used.[1 2]

The use of metered dose inhaler (MDI) to deliver drugs to the lungs of adults and older children is well established. Spacing devices and holding chambers have been used to overcome problems of coordination and have further advantages in that they allow the aerosol to decelerate and propellants evaporate from the drug particles. Infants and young children are unable to use these conventional devices so that a number of alternative approaches have been suggested. It has been claimed that firing a bronchodilator from a MDI directly into the buccal cavity of infants and young children can have a therapeutic effect.[3] A simple, cheap spacing device, the polystyrene coffee cup, has been in use for several years for delivering bronchodilators to young children,[4] and a larger, similar device has been used in a recent study.[5] Unfortunately these devices have a number of drawbacks in that the MDI is fired directly into the patient's face, which frequently means that then an infant will not tolerate this form of therapy and, unless firmly applied, aerosol is rapidly lost from the chamber.

Although it is more than 10 years since it was proposed that the attachment of a facemask to a holding chamber may provide a suitable delivery system for delivering aerosols to young children,[6] it is only recently that there has been a upsurge in interest in this form of treatment.[7–11] This approach has many potential advantages. The aerosol is not fired directly into the face of the infant and the use of soft facemasks ensures that they do not cause discomfort when applied to the face and hence these devices are more likely to be accepted by very young children. The seal achieved by the facemask also ensures that aerosol is retained within the chamber and as the aerosol settles out relatively slowly this will allow infants to take multiple breaths from the contained aerosol. This may significantly increase drug delivery at low tidal volumes while the usual advantages of holding chambers will also help to maximise the proportion of the inhaled dose that is subsequently deposited in the lungs.

All the systems designed so far have been adapted from systems designed for adults and older children and relatively little attention has been paid to the design factors that will maximise drug delivery to infants. The way in which factors such as aerosol concentration, total dose available, and chamber size interact to influence the total dose delivered at different tidal volumes has not been considered and is difficult to predict.

In an attempt to determine the relative importance of these complex interacting factors, a series of in vitro studies were performed in which the respiratory pattern of subjects with

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different tidal volumes were simulated using a Starling ventilator and the quantity of drug 'inhaled' was collected onto a filter and assayed.

Methods

A model was constructed to simulate the respiratory pattern of individuals with different tidal volumes. A Starling ventilator (CF Palmer) was connected via a Y connector so that air would be drawn in and subsequently exhaled through a filter (Whatman Glass Microfibre, exposed diameter 3·3 cm; fig 1). The filter paper can be considered to be the 'nose/mouth' of the model subject and the dose of drug deposited upon the filter will represent the total dose 'inhaled'. A 'face' was constructed of firm rubber so that the facemask of each device could be firmly applied to ensure a good seal. The filter was held in place at the base of a cylinder designed for the purpose. As it was not possible to measure the tidal volume across the filter, a pneumotachograph (Mercury Instruments) was placed at the level of the face and the effective tidal volume across the filter was obtained by subtracting the volume of the funnel (35 ml).

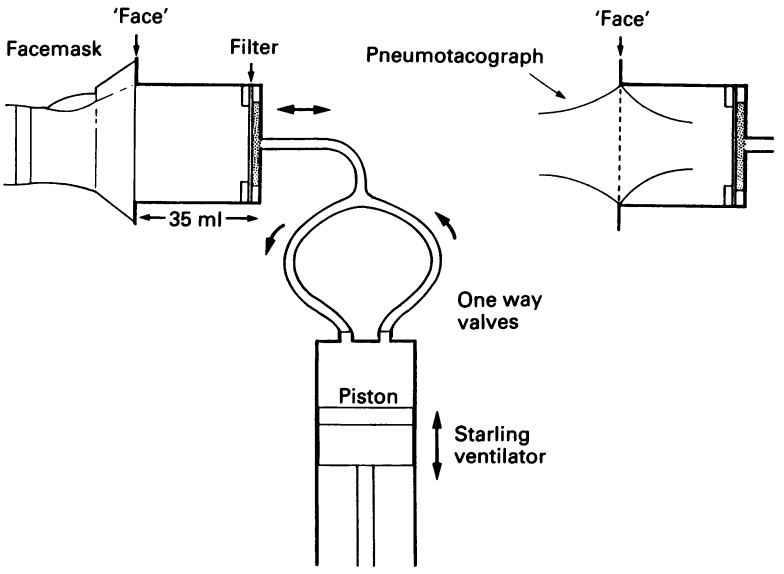

Figure 1 Model used to simulate the respiratory pattern of individuals and so study the factors influencing drug delivery from holding chambers at different tidal volumes. The dose 'inhaled' by the Starling ventilator was desposited upon the filter.

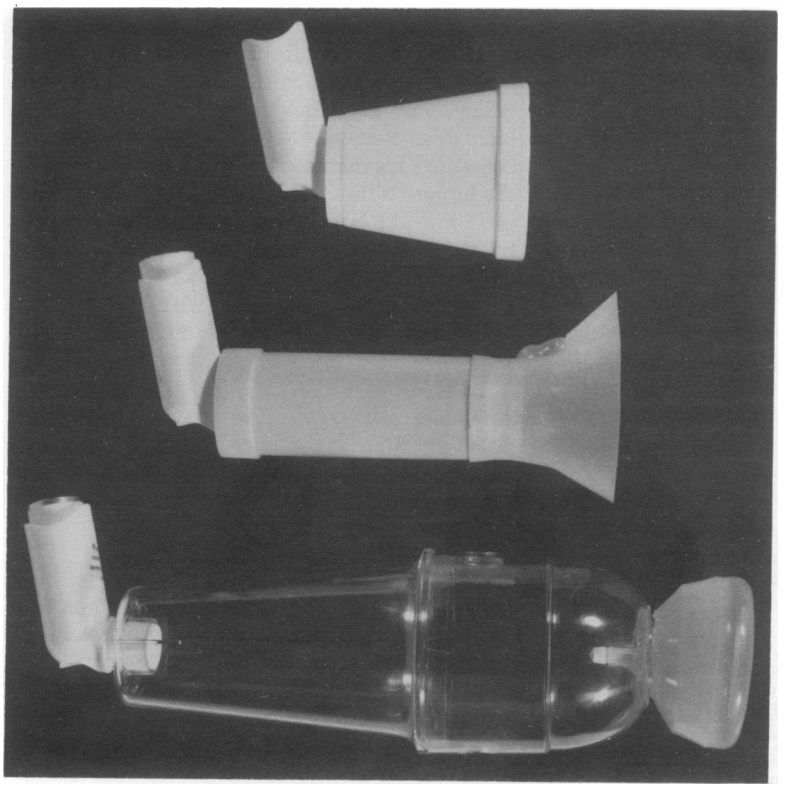

Figure 2 Devices used in these experiments. From left to right: a polystyrene coffee cup, an infant Aerochamber with facemask, and a Nebuhaler with a Laerdal facemask.

Experiments were performed using tidal volumes of 25, 50, and 150 ml to represent the tidal volumes likely to be seen from early infancy through early childhood. The Starling ventilator had a limited number of rate settings and an arbitrary rate of 32 was chosen for all these experiments. Inspiration occupied approximately 40% of the respiratory cycle.

Four devices were used for these experiments (fig 2); a polystyrene coffee cup, an infant Aerochamber with attached facemask (Trudell, Canada), a neonatal version of this device and a Nebuhaler (Astra) to which a size 2 Laerdal resuscitation facemask was attached, having first removed the mouthpiece. The only difference between the 'neonatal' and the 'infant' versions of the Aerochamber was that the former has a lighter valve.

The Nebuhaler was chosen to represent the larger chambers as this is the system currently used in our unit.[8] When using the Nebuhaler, the MDI was actuated with the device in the horizontal position and the valve closed, the device was then tipped so that the MDI was raised by 20°, thus allowing the valve to open by gravity and it remained open for the period of the experiment. This is the method of administration used in our unit. It was adopted because the valve appears to operate inefficiently at low flow rates. At best the valve would only partly open. Unfortunately no large volume chamber with a low resistance valve was available when these experiments were performed.

When using the coffee cup a card was placed between the coffee cup and face while the MDI was actuated to prevent direct deposition on the filter. The card was then removed immediately prior to the first inspiratory 'breath'.

For each experiment the MDI was shaken and then fired just before the start of an inspiratory phase. For these experiments each device was applied for six inspiratory/expiratory cycles, which was considered to be a reasonable period that might be tolerated by infants. To ensure that the quantity of drug deposited on the filter was adequate to obtain an accurate assay result, multiple actuations were used for each experiment. Two minutes was allowed between each actuation to ensure that the aerosol cloud in the chamber had settled out.

At the end of each experiment the quantity of drug on the filter was assayed. Sodium cromoglycate was used in these experiments because an ultraviolet spectrophotometric assay (Hewlett Packard Diode Array spectrophotometer) was available and allowed accurate quantification of drug deposition on the filter.

It was observed that at the end of each set of experiments, drug particles had been deposited within the funnel and this was therefore carefully wiped before being washed. The filter was then washed with Freon 11 to remove surfactants from the surface of drug particles deposited on it. After drying the filter was then washed with a known volume of distilled water. The absorbance at 326 nm was obtained for the resultant solution and this was then used to calculate the total quantity of drug 'inhaled' per actuation using the formula:

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

The system had previously been calibrated using known quantities of sodium cromoglycate, the constant E (absorbance for 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.

DRUG DELIVERY FROM A STANDARD DOSE AT DIFFERENT TIDAL VOLUMES

The initial experiments were designed to study quantity of drug delivered from each system at different tidal volumes. Each experiment involved 10 actuations of a 1 mg dose at two minute intervals. The quantity of drug deposited on the filter after 10 actuations was assessed when the pump was switched off (tidal volume=0) and for the tidal volumes described above.

EFFECTS OF AGITATING THE CHAMBER

In order to assess the effects of chamber movement, the experiment involving a Nebuhaler and a tidal volume of 50 ml was repeated shaking the Nebuhaler once immediately after actuating the MDI.

INCREASING THE DEAD SPACE FROM VALVE TO FILTER

For most experiments the holding chambers were held so that the mask was compressed ensuring that the chamber's valve was as close to the level of the face as possible. To assess the possible effects of a dead space, the mask of the holding chambers was held lightly against the face while a good seal was maintained. By not compressing the mask a dead space was introduced between the valve and face of approximately 50 ml for the Nebuhaler and slightly more for the Aerochamber.

INCREASING THE INITIAL DOSE INTRODUCED INTO THE CHAMBER

Experiments were performed to assess the effects of altering the aerosol concentration within a chamber using multiple actuations of a 1 mg MDI or single actuations of a 5 mg dose MDI. The 1 mg MDI was actuated two or three times before the first inspiratory cycle and this was repeated five or four times respectively. A single actuation of a 5 mg dose MDI was repeated once after two minutes.

Each experiment was repeated four times. The canister was weighed before and after each experiment to ensure that the correct amount of aerosol suspension had been delivered. The results presented represent the mean and range of the four experiments.

Finally, a mathematical model was devised in order to predict the dose that might be delivered by a chamber of different tidal volumes using different numbers of breaths. This model assumes a zero deadspace from valve to patient, a valve opening and closing efficiently, and complete mixing within the chamber once the valve is closed. It also assumes that taking a breath from the chamber does not affect the rate at which the remaining aerosol settles out.

Results

DRUG DELIVERY FROM A STANDARD DOSE AT DIFFERENT TIDAL VOLUMES

The results presented in table 1 represent the mean dose in mg delivered to the filter from 10 actuations of a 1 mg MDI from each device while using different tidal volumes. The range of results obtained from the four experiments performed under each set of conditions appears below. For each device, as the tidal volume increases, the quantity of drug delivered increased. This increase was more pronounced for the larger volume Nebuhaler. At a tidal volume of 150 ml the largest dose of drug was delivered by the Nebuhaler, while at a tidal volume of 25 ml the neonatal Aerochamber with its lighter valve delivered most drug with 5·3% of the initial dose being deposited on the filter.

CHAMBER AGITATION

Shaking the Nebuhaler reduced the dose delivered to the filter from 0·93 mg to 0·25 (0·15–0·36) when the tidal volume was set at 50 ml.

EFFECTS OF INCREASING THE DEAD SPACE

Introducing a dead space of approximately 50 ml between the valve and the face reduced the dose deposited upon the filter when using a 50 ml tidal volume from 0·93 mg to 0·43 (0·39–0·48) mg when using the Nebuhaler. For the Aerochamber increasing the dead space as described reduced the dose delivered to the filter from 1·15 mg to 0·42 (0·37–0·48) mg.

Table 1 Mean (range) dose deposited on the filter after 10 actuations of a 1 mg sodium cromoglycate MDI delivered by each of four devices and different tidal volumes

	Tidal volume (ml)			
	0	*25*	*50*	*150*
Aerochamber (1 mg×10)	0·027 (0·024–0·030)	0·33 (0·29–35)	1·15 (1·08–1·24)	1·41 (1·33–1·46)
Neonatal Aerochamber (1 mg×10)	0·035 (0·028–0·039)	0·53 (0·47–0·58)	—	—
Coffee cup (1 mg×10)	0·031 (0·028–0·033)	0·27 (0·23–0·30)	0·86 (0·76–1·02)	—
Nebuhaler (1 mg×10)	0·008 (0·007–0·008)	0·29 (0·26–0·32)	0·93 (0·91–0·97)	1·55 (1·48–1·61)

EFFECTS OF INCREASING THE INITIAL DOSE INTRODUCED INTO THE CHAMBER

The mean dose deposited upon the filter after two actuations of a 5 mg MDI via the Aerochamber using a 50 ml tidal volume was 0·70 (0·67–0·72) mg while the equivalent dose via the Nebuhaler was 0·74 (0·71–0·77) mg. The dose delivered to the filter from five administrations of 2×1 mg via the Nebuhaler with a tidal volume of 50 ml was 1·02 (0·93–1·10) mg while four administrations of 3×1 mg delivered 0·844 (0·79–0·91) mg to the filter. These results are presented in table 2 in terms of the dose delivered to the filter per administration of the chosen combination and the figure in brackets is that dose delivered to the filter expressed as a percentage of the administered dose.

Table 2 Mean (%) total dose of sodium cromoglycate deposited on the filter from a single administration using initial doses of 1, 2, 3, or 5 mg administered by Nebuhaler or Aerochamber. A tidal volume of 50 ml was used

	1 mg	*2×1 mg*	*3×1 mg*	*5 mg*
Aerochamber (mg)	0·12 (11·5)	—	—	0·35 (7)
Nebuhaler (mg)	0·09 (9·3)	0·20 (10·1)	0·21 (0·7)	0·37 (7·3)

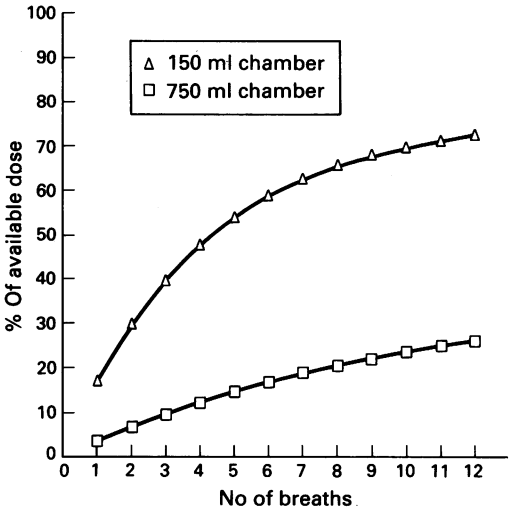

Figure 3 Comparison of the relative delivery efficiency of a 150 ml and 750 ml chamber with a tidal volume of 25 ml and a respiratory frequency of 32 breaths per minute derived from the mathematical model. The 'available' dose represents that contained within the chamber after actuation of the MDI.

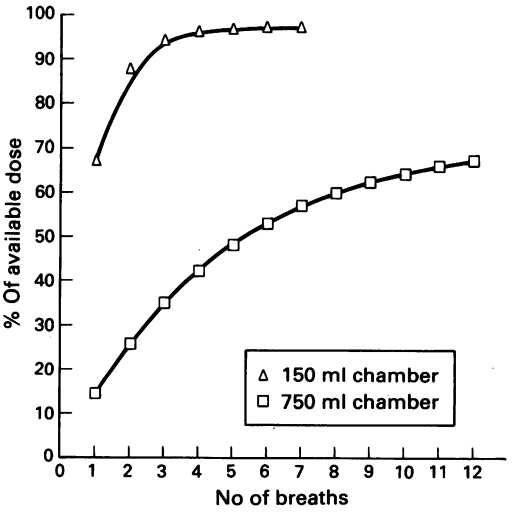

Figure 4 Comparison of the relative delivery efficiency of a 150 ml and 750 ml chamber at a tidal volume of 100 ml and a respiratory frequency of 32 breaths per minute derived from the mathematical model. The 'available' dose represents that contained within the chamber after actuation of the MDI.

MATHEMATICAL MODEL

The fraction of the maximum obtainable dose as a function of breath number and tidal volume was found to be of the form:

$$M/M_{max} = V_t/V . \sum_{i=1}^{i=n} (1-[V_t/V])^{i-1} \exp(-\lambda(i-1)/\gamma)$$

Where: M/M_{max}=dose inhaled as fraction of initial dose available, V_t=tidal volume, γ=breathing frequency, V=chamber volume, i=n=number of breaths, and λ=half life of aerosol held in chamber (see footnote for derivation of the above equation).

Figures 3 and 4 represent typical graphs obtained using this equation; λ was assumed to be 15 seconds based upon previous experimental work. It can be seen that at both tidal volumes drug delivery reaches a plateau earlier for the smaller chamber. In order to calculate the total dose delivered in a given number of breaths, the dose available within the chamber must be known and, as noted above, this is dependent upon both the design of the chamber and the dose delivered into it from the MDI.

Discussion

Holding chambers with an attached facemask potentially offer a major advance in the treatment of respiratory disease in infancy. If they are shown to be effective then their ease of use should ensure that they are widely accepted. It is important therefore that the factors likely to influence the effectiveness of drug delivery are considered so that maximum benefit can be obtained. This model represents a new approach to the problem of assessing the influence of various design features upon drug delivery. The advantages of this model are that the Starling ventilator permits us to use a reproducible tidal volume and respiratory rate so that direct comparisons can be made when changing from one device to another.

The dose deposited upon the filter in this model would represent the total dose inhaled by a subject at these tidal volumes, respiratory rate, and inspiratory flows. The pattern of deposition within the respiratory tract of this inhaled dose will be influenced by a number of patient variables such as airway obstruction and technical factors such as the size of drug particles administered. Particle size will be determined predominately by the MDI formulation, though it will be optimised when using a holding chamber. The single most important variable influencing the dose of drug reaching the lungs that is amenable to manipulation is the total dose that is inhaled from each administration of drug. These experiments allow us to consider some of the factors that might maximise the dose inhaled and hence maximise the dose reaching the lower respiratory tract.

VALVE DESIGN

In adults it has been shown that during acute asthma the expiratory flow of a patient may be too low to close the valve of a Nebuhaler and hence aerosol is blown out of the device during expiration.[12 13] It is claimed that this may contribute to the poor response sometimes seen with these devices in severe acute asthma. A recent study measuring pressure changes within the chambers claimed that the valves of both the Nebuhaler and Volumatic (Allen and Hanbury) will open and close at the low flows generated by infants.[14] Unfortunately this does not necessarily correlate with drug delivery as a partially open valve is likely significantly to impair drug delivery. The importance of a valve that operates effectively at low tidal volumes was emphasised in the experiments comparing the neonatal and infant versions of the Aerochamber at a tidal volume of 25 ml.

DEAD SPACE

Not surprisingly drug delivery fell dramatically by introducing a relatively large dead space. Perhaps more surprising was that despite such a relatively large dead space, drug deposition on the filter was still in the order of 4·2% of each 1 mg dose administered. The likely explanation for the significant drug delivery that occurred despite the relatively large dead space is that during the first breath even if little or no drug reaches the filter, aerosol is drawn into the mask. This aerosol then mixes with expired air and some aerosol is subsequently inhaled from the facemask during the next breath while more drug is being drawn into the mask and so on.

AEROSOL CONCENTRATION AND TOTAL DOSE AVAILABLE

Though the interaction of tidal volume with aerosol concentration, chamber size, and total dose available in determining drug delivery is complex, it can be clarified to some extent by considering the results of these experiments. Increasing the aerosol concentration can be altered in two ways. Either a larger dose can be introduced into the same chamber or the same dose can be introduced into a different sized chamber. Both of these options will also alter the total dose available.

Increasing the dose introduced into a chamber

From table 2 it would appear that increasing the dose introduced into a chamber appears an effective way of increasing drug delivery per treatment, though the delivered dose did not increase directly in proportion to the initial dose used. For the Nebuhaler a 3·8-fold increase in the dose delivered was achieved when using a single actuation from a 5 mg MDI while only a 3-fold increase was obtained when using the Aerochamber. This is probably due to relatively greater drug loss from impaction on the walls of the chamber when using the larger dose. When multiple 1 mg doses were introduced into the Nebuhaler with a tidal volume of 50 ml, two 1 mg actuations did double the dose delivered but further actuations produced very little additional drug delivery. This is probably due to particles of relatively large mass and velocity being introduced into the chamber and causing increased deposition due to turbulence. Another factor which may be contributing is that actuating the MDI in rapid succession may not permit the valve to fully fill with suspension before it is next actuated. This would imply that a single larger dose is more effective in raising the aerosol concentration within a chamber than multiple small doses.

Chamber size

One aspect of design that is much more difficult to predict is the effect of changes in chamber volume, which in turn influences both the available dose of aerosol and the concentration of aerosol within that chamber. In clinical studies it has been shown that for older children[15] and adults[16] large cone shaped chambers are more effective than a MDI used alone while the Aerochamber appears to be as effective as an optimally used MDI.[17] Isotope studies have shown that 37% of the dose introduced into a Nebuhaler may be inhaled by adults,[18] while the comparable figure for the Aerochamber is around 14%.[17] Thus although the total dose of aerosol available within the larger chamber is greater, it is distributed in five times the volume and hence the initial aerosol concentration is less.

The result of the experiments presented in table 1 suggest that at low tidal volumes the high initial aerosol concentration within the Aerochamber is a major factor influencing the dose delivered, but as the tidal volume increases the larger total dose available in the larger chamber becomes more important. These differences are likely to be relatively unimportant clinically as it should be noted that in terms of drug delivery per kilogram body weight an infant is likely to receive considerably more than an adult. An infant weighing approximately 6–7 kg might have a tidal volume of 50 ml[19] yet drug delivery to the filter was in the order of 10%, a 70 kg adult might at best inhale around 37% from a large chamber and considerably less from the smaller one. Clinical studies have shown clinical benefit in this age group when using both large and small chambers.[8 10]

For infants taking multiple breaths from a chamber, predicting the dose inhaled is difficult. If an infant's tidal volume is 50 ml it will extract approximately one third of the available aerosol during the first breath from the 150 ml volume Aerochamber, but only approximately one fifteenth of that available within the 750 ml volume Nebuhaler. Because such a relatively large amount has been extracted during the first breath the aerosol concentration within the Aerochamber available for the next breath will fall to a much greater extent than that within the large chamber. This calculation is further complicated by the fact that the aerosol will settle out progressively with time. Results using the mathematical model support the suggestion that a high aerosol concentration of the smaller chamber will tend to enhance drug delivery at

the lowest tidal volumes but that the higher total dose in the larger chamber enhances drug delivery as the tidal volume increases.

These experiments allow us to assess design factors that might maximise the dose of drug inhaled. There are several factors specific to this form of treatment in infants that may influence the proportion of the inhaled dose that might be deposited within the lungs. Nasal breathing by infants may increase deposition in the upper respiratory tract. If this were shown to be a major problem it could be overcome using a mask similar to the Laerdal mask, which can be gently placed over the upper lip occluding the nasal passages and thus ensuring that the infants breath through their mouth.

Infants will obviously not hold their breath and this will tend to reduce deposition in the peripheral airways by sedimentation. A recent study in older children found a greater improvement in forced expiratory volume in one second at 10 minutes by taking five breaths from a Nebuhaler than by taking two breaths with a five second breath holding after each, though the peak improvements were similar.[20] At low tidal volumes the greater total dose inhaled by taking multiple breaths will probably more than compensate for the reduced time allowed for deposition. The effect of crying cannot be predicted, the greater volume and hence dose inhaled may be off set by increased drug loss in the device and upper airway due to inertial impaction.

In summary the design of a chamber intended for use with infants should have a valve that operates efficiently at very low flow rates if a valve is required. The dead space from valve to patient should be minimised by good mask design. Using multiple doses or, more effectively, a single larger dose can increase the aerosol concentration within the chamber and so increase drug delivery per breath. However, the increase in drug delivery is not necessarily proportional to the increase in dose. Agitation of the chamber will greatly reduce drug delivery.

Both large and small chambers would appear to deliver significant amounts of drug at these low tidal volumes. However, a small chamber would seem to be more appropriate in that they are easier to handle while trying to hold a wriggling infant, they are generally less intimidating for the infant and they deliver at least as much, if not more, drug at these low tidal volumes. Finally in terms of drug delivery per kilogram body weight infants would appear likely to inhale a greater dose than an adult from a standard metered dose. The proportion of the inhaled dose that reaches the lungs remains to be determined.

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Footnote

If the aerosol concentration within the chamber is C_0 and the unhaled tidal volume is V_t then the drug inhaled on the first breath is:

$$M_0 = V_t.C_0$$

Subsequently a volume of clear air equal to V_t will be drawn into the chamber and the concentration will fall to:

$$C_1 = C_0(V - V_t/V).\exp.(-\lambda T)$$

where V is the volume of the chamber and the exponential term represents the time decay of the aerosol cloud; λ=concentration half life, and T=is the time between inhalations.

The dose delivered on the second breath will thus be:

$$M_1 = V_t.C_0(V - V_t/V).\exp(-\lambda T)$$

T is in effect $i-1/\gamma$ where γ is the breathing frequency since T=0 at the first breath. Extending this analysis for third and subsequent breaths the total dose inhaled in n breaths can be obtained by the expression:

$$M = V_t.C_{i=1}^{i=n}\Sigma(1-[V_t/V]).^{i-1}\exp.(-\lambda(i-1)/\gamma)$$

In terms of the maximum dose obtainable from the device becomes:

$$M/M_{max} = V_t/V_{i=1}^{i=n}\Sigma(1-[V_t/V]).^{i-1}\exp(-\lambda(i-1)/\gamma)$$