Delivery of therapeutic aerosols to intubated babies

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Abstract

Delivery of drug aerosols to the lungs of ventilated neonates by metered dose inhaler and spacer (Aerochamber) and ultrasonic nebuliser (Pentasonic) was assessed using sodium cromoglycate.

The mean proportion of a known intratracheal dose of sodium cromoglycate excreted in the urine of four intubated infants was 37·5%. After assuming that 38% of the sodium cromoglycate aerosol reaching the neonatal lung will be excreted in the urine, three puffs (15 mg) delivered by metered dose inhaler and spacer resulted in a pulmonary dose of 258 μg (1·7%, n=7). A dose of 20 mg (4 ml) sodium cromoglycate ultrasonically nebulised over five minutes into the inspiratory limb of a standard ventilator circuit produced a pulmonary dose of 257 μg (1·3%, n=7).

Of two in vitro lung models assessed, a combination of filter and neonatal test lung was superior to a multistage impactor in estimating the in vivo pulmonary sodium cromoglycate dose delivered by metered dose inhaler and spacer (243 μg *v* 1740 μg).

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Therapeutic aerosols are often used in intubated neonates despite a paucity of information on the pulmonary dose or the most efficient delivery system. A number of devices are available for the production of therapeutic aerosols.

Jet nebulisation is widely used and bronchodilators administered by this method have been shown to improve lung function in intubated infants with bronchopulmonary dysplasia.[1] There are, however, problems with jet nebulisation including gas cooling,[2] reduction in humidity,[3] and a requirement for an auxiliary high pressure gas supply. It is also very inefficient, with 0·2% of the drug dose in the nebuliser reservoir reaching the neonatal lung.[4] Ultrasonic nebulisation and metered dose aerosol delivered by spacer are alternative delivery methods which have little effect on ventilator gas humidity or temperature. Neither has been assessed in intubated neonates.

The Pentasonic ultrasonic nebuliser (De-Vilbiss) nebulises drugs using 2·25 MHz pizoelectric crystal. It weights 160 g and is portable. The Aerochamber with 15 mm connection (Trudell Medical) is a modification of an infant spacer device accepting standard metered dose inhalers (MDI) and is designed to be inserted into the inspiratory limb of an adult ventilator circuit. This 11×4·1 cm spacer has an approximate volume of 145 ml and allows aerosol to be generated within the centre of the ventilator gas flow. Both the Pentasonic and Aerochamber can be used in a neonatal ventilator circuit after minimal adaptation.

This study aimed to assess the efficiency of aerosol delivery to intubated infants lungs by using sodium cromoglycate as a marker of drug delivery. Sodium cromoglycate (Intal, Fisons plc) is non-toxic and is excreted unchanged in the bile and urine.[5] We first estimated the fraction of a known intratracheal dose of sodium cromoglycate excreted in the urine of ventilated neonates over 24 hours. By combining this information with 24 hour urinary sodium cromoglycate excretion after an ultrasonic or MDI dose, the total dose deposited in the lung was estimated. Pulmonary sodium cromoglycate deposition by MDI in vivo was then compared with that estimated in vitro by either a test lung with filter or a multistage impactor.

Table 1 Subject details

Subject No	*Gestation (weeks)*	*Weight (g)*	*Diagnosis*	*Sodium cromoglycate delivery method*
1	35	2100	Myopathy	IT+Pentasonic
2	35	4000	Persistent fetal circulation	IT+Pentasonic
3	41	4200	Myopathy	IT+Pentasonic
4	31	1700	RDS	IT+Pentasonic+Aerochamber
5	24	800	RDS	Pentasonic+Aerochamber
6	30	1400	RDS	Aerochamber
7	38	3500	Gastroschisis	Aerochamber
8	26	1000	RDS	Aerochamber
9	25	1100	RDS	Aerochamber
10	27	500	RDS	Aerochamber
11	30	1400	Apnoea	Pentasonic
12	38	4700	RDS (diabetic mother)	Pentasonic
13	36	1400	Congenital abnormalities	IT
14	26	1000	RDS	IT

RDS=respiratory distress syndrome; IT=intratracheal sodium cromoglycate dose.

Methods

IN VIVO ASSESSMENT

Infants studied were receiving intermittent positive pressure ventilation via a pressure limited, time cycled ventilator (Sechrist) for a range of conditions. These included respiratory distress syndrome (n=8), myopathy (n=2), persistent fetal circulation (n=1), surgery (n=1), and multiple congenital abnormalities (n=1) (table 1). All infants were intubated by a shouldered endotracheal tube (Portex) and had blood urea and creatinine concentrations within the normal range.

This study was approved by the ethics committee of the Royal Postgraduate Medical School. Infants were studied after written parental consent.

Intratracheal dose

Isotonic sodium cromoglycate (1400 μg, 0·2 ml)

was instilled through a size 5 French gauge suction catheter wedged in the right main bronchus of intubated neonates. Urine was collected over a 24 hour period and assayed for sodium cromoglycate by radioimmunoassay.[6] If leakage from the collecting bag occurred, the 24 hour collection was discarded. Sodium cromoglycate removed from the lung by suction was measured in the total pool of endotracheal aspirates collected over 24 hours after instillation. The actual intratracheal dose available to the infant was the difference between the intratracheal dose delivered and the amount removed by endotracheal suction. The proportion of the intratracheal dose excreted in the urine over a 24 hour period was then calculated.

The urinary elimination half life of sodium cromoglycate was calculated from a plot of the midtime point for each urine collection (min) against the log excretion rate (μg/min).[7]

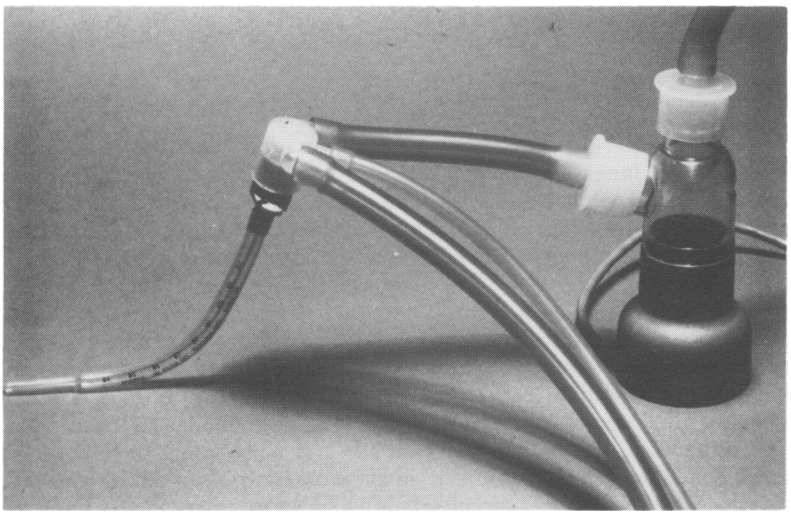

Figure 1 Pentasonic nebuliser inserted into the inspiratory limb of a ventilator circuit.

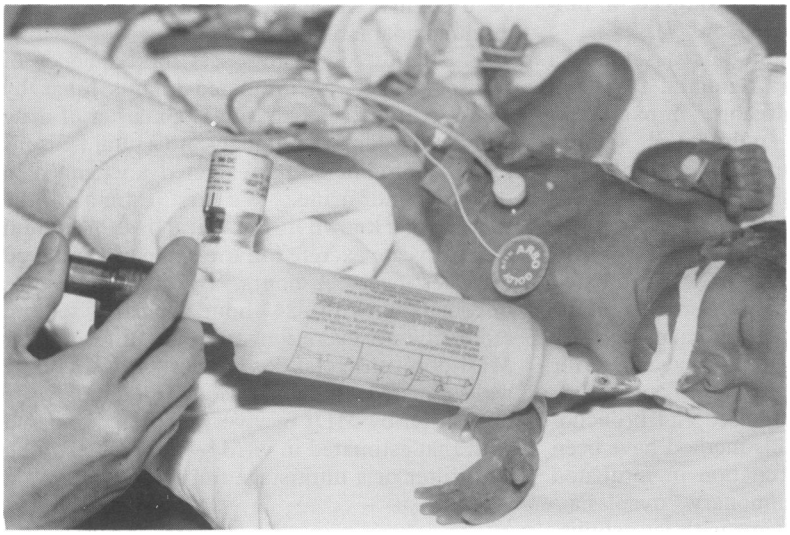

Figure 2 Ventilation through an Aerochamber spacer.

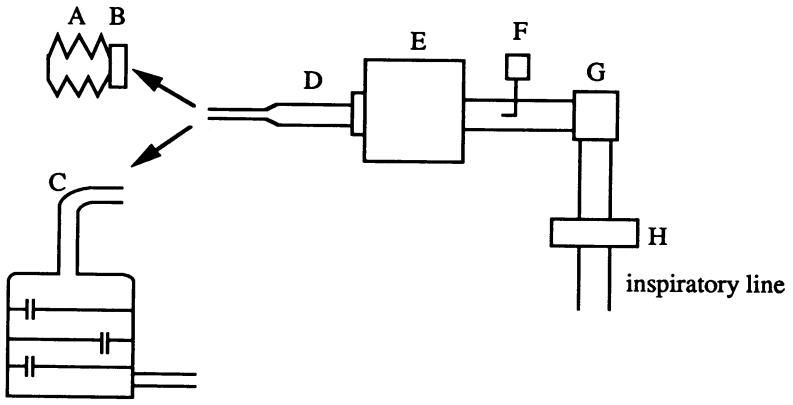

Figure 3 In vitro models of pulmonary sodium cromoglycate deposition by metered dose inhaler and spacer. A=test lung, B=filter, C=multistage impactor, D=3·5 mm endotracheal tube, E=Aerochamber, F=sodium cromoglycate metered dose inhaler, G=thumb occlusion valve, H=pressure release valve.

Assessment of nebuliser and MDI

The Pentasonic ultrasonic nebuliser was inserted directly into the inspiratory limb of the constant flow ventilator circuit, 10 cm from the right angled endotracheal tube connector (fig 1). Before insertion the one way inspiratory valve was removed from the nebuliser chamber. Humidified inspiratory gas entered the nebuliser through the upper part of the nebuliser and exited through a side port. The chamber was loaded with 20 mg sodium cromoglycate dissolved in 4 ml of normal saline and the nebuliser run for five minutes. The 24 hour urinary excretion of sodium cromoglycate was measured by radioimmunoassay on a single pooled sample.

The Aerochamber was inserted directly onto the endotracheal tube after disconnection from the ventilator circuit. Infants were then ventilated by a thumb occluded 'Nottingham puffer' set at a flow of 8 l/min and an appropriate blow off pressure and inserted into the end of the spacer (fig 2).

Each infant received three puffs of 5 mg sodium cromoglycate via MDI. The MDI was actuated at end expiration and each dose was separated by five manual breaths. After removing the spacer, infants were reconnected to the ventilator circuit and 24 hour pooled urinary sodium cromoglycate excretion measured by radioimmunoassay.

IN VITRO MODEL

Aerochamber assessment

The neonatal lung was modelled by a test lung (Draeger) inserted onto a 3·5 mm shouldered endotracheal tube. MDI aerosol passing through the endotracheal tube was collected by a 0·25 μm filter (Aerosol Medical) inserted between the tube tip and test lung (fig 3). The dose of sodium cromoglycate and method of administration were similar to that used in vivo. Inspiratory pressure was set at 20 cm H_2O giving a tidal volume to the test lung of 15 ml. After three MDI doses (15 mg), sodium cromoglycate was eluted from the filter with 20 ml water and measured by radioimmunoassay.

Particle size

The mass median aerodynamic diameter (MMAD) of particles generated by the ultrasonic nebuliser was measured by laser diffraction. Ultrasonic aerosol was generated within a con-

tinuous 8 l/min airflow which passed through 10 cm of ventilator tubing and 3·5 mm Portex endotracheal tube. Particle size was measured by a laser particle sizer (2600 Malvern Instruments) 2 cm from the endotracheal tube tip.

The MMAD of particles generated by MDI was measured by multistage impactor. Aerosol generated by MDI was carried through the Aerochamber and endotracheal tube by a gas flow of 8 l/min. This was then sucked into a multistage impactor operating at 60 l/min and separated into three size fractions (fig 3). Sodium cromoglycate deposited in each fraction after 20 doses (100 mg) was assayed by a spectrophotometer that had been previously calibrated using sodium cromoglycate solutions of known concentrations. The total dose deposited within the multistage impactor and MMAD of the aerosol was calculated from the amount eluted from each size fraction. At the end of the impactor experiment, sodium cromoglycate deposited in the endotracheal tube and Aerochamber was also eluted and assayed.

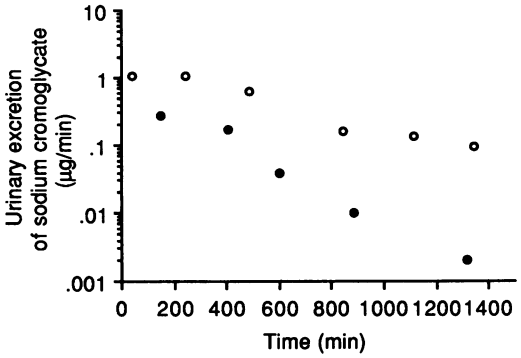

Figure 4 Urinary excretion of sodium cromoglycate from subjects 13 and 14.

Table 2 In vivo urinary excretion and estimated pulmonary deposition after sodium cromoglycate delivered by Aerochamber and metered dose inhaler

Subject No	*24 Hour urinary excretion of sodium cromoglycate* (μg)*	*Estimated pulmonary dose sodium cromoglycate† (μg)*
4	69	181
5	68	179
6	109	287
7	118	310
8	104	273
9	143	376
10	75	197
Mean (SEM)	98 (11)	258 (28)

*After 3×5 mg doses of sodium cromoglycate.
†Assuming urinary excretion 38% of pulmonary dose.

Results

IN VIVO

Four infants (subjects 1–4, table 1) had tracheal aspirates saved after a 1400 μg intratracheal dose enabling an estimation of the actual intratracheal dose available for systemic absorption. Mean urinary excretion as a percentage of the estimated intratracheal dose was 37·5% (range 22·3–59·7%). In two infants (subjects 13 and 14, table 1) several timed urine samples after the intratracheal dose were available, although their endotracheal aspirates were not saved. Their urinary excretion half lives were 100 and 310 minutes (fig 4).

Seven infants received a dose of sodium cromoglycate via the MDI and seven via the ultrasonic nebuliser. Mean (SEM) 24 hour urinary sodium cromoglycate excretion after a 15 mg dose via Aerochamber and MDI was 98 (11) μg (table 2). Mean 24 hour urinary sodium cromoglycate excretion after five minutes of ultrasonic nebulisation with a nebuliser fill of 20 mg was 98 (18) μg (table 3). Endotracheal suction was not performed until at least four hours after aerosolised sodium cromoglycate. However, endotracheal aspirates were not saved for radioimmunoassay.

Assuming that 38% of an inhaled dose of sodium cromoglycate is excreted in the urine, the Aerochamber and MDI delivered 258 (28) μg to the lung (1·7% of the 15 mg aerosolised dose). The Pentasonic delivered 257 (47) μg (1·3% of the initial 20 mg nebuliser fill).

IN VITRO

Mean deposition of sodium cromoglycate onto a filter situated between the endotracheal tube and test lung after 3×5 mg puffs delivered by MDI with Aerochamber was 243 μg (n=3). Total deposition within the multistage impactor after 20 puffs into the Aerochamber was 11·6 mg or 1740 μg per three MDI puffs (table 4). Of the total dose aerosolised by the MDI, 81·4% was deposited within the spacer and 7·8% in the endotracheal tube.

Table 3 In vivo urinary excretion and estimated pulmonary deposition after ultrasonic nebulisation of a sodium cromoglycate solution for 5 minutes

Subject No	*Ventilator gas flow (l/min)*	*Ventilator rate (per min)*	*Inspiratory time (sec)*	*24 Hour urinary excretion sodium cromoglycate* (μg)*	*Estimated pulmonary dose sodium cromoglycate† (μg)*
1	8	30	0·5	104	274
2	8	30	0·5	50	132
3	8	30	0·5	170	447
4	8	30	0·5	138	363
5	12	75	0·4	47	123
11	8	20	0·3	63	158
12	8	30	0·7	115	303
Mean (SEM)				98 (18)	257 (47)

*Nebuliser fill of 20 mg sodium cromoglycate in 4 ml.
†Assuming urinary excretion 38% of pulmonary dose.

Table 4 Comparison of in vitro and in vivo aerosol delivery of sodium cromoglycate

	Initial nebuliser fill or dose generated by MDI (mg)	*Mean pulmonary dose in vitro or in vivo (μg) (% of initial dose)*	*MMAD (μm)*
Aerochamber+MDI in vitro; multistage impactor*	15	1740 (11·6)	9·0
Aerochamber+MDI in vitro; filter+test lung (n=3)	15	243 (1·62)	
Aerochamber+MDI in vivo (n=7)	15	258† (1·72)	
Pentasonic in vivo (n=7)	20	257† (1·28)	3·4‡

*Calculated from 100 mg initial dose.
†Estimated assuming urinary excretion 38% of pulmonary dose.
‡Measured in vitro using Malvern laser particle sizer.

The MMAD of particles generated by MDI, after passing through the Aerochamber and endotracheal tube, was 9·0 μm. MMAD of ultrasonically nebulised sodium cromoglycate after passing through an endotracheal tube was 2·8 μm (table 4).

Discussion

The Pentasonic nebuliser and Aerochamber with MDI delivered a detectable dose of sodium cromoglycate to ventilated neonates. A significant proportion of the sodium cromoglycate aerosol generated by both delivery systems was in droplets small enough to penetrate the distal airways. The pulmonary dose of sodium cromoglycate aerosolised by MDI, estimated from the urinary excretion of a known intratracheal dose, was similar to that deposited on a filter model using a neonatal test lung. However, the dose deposited in a multistage impactor significantly overestimated the in vivo dose.

Estimation of the pulmonary dose in vivo depends on the proportion excreted in the urine. Most published data is from adult subjects. Sodium cromoglycate is not metabolised in the lung or liver and is excreted unchanged in the bile and urine.[5] Some 70–90% of a 1 mg dose of sodium cromoglycate instilled into the adult lung by fibreoptic bronchoscope will be absorbed into the circulation and of this, 33–46% is excreted in the urine.[8 9] The plasma half life of either a bronchoscopically instilled or inhaled dose is 64–165 minutes after an initial rapid half life of 1·9 minutes, with lung absorption being the rate limiting step.[8] The pulmonary dose calculated from urinary excretion is similar to that obtained using plasma data.[10] The wide variability in the fraction of intratracheal sodium cromoglycate excreted in the urine of ventilated neonates in this study is not surprising. Pulmonary atelectasis, mucus, and epithelial damage may have significantly altered sodium cromoglycate bioavailability between infants. When combined with the clinical problems of collecting endotracheal aspirates and urine samples, the fractional urinary excretion must be regarded as only a rough approximation. However, if the urinary excretion half life is less than seven hours, a collection period of 24 hours should have contained most of the dose excreted in the urine.

Combined in vitro and in vivo assessment of aerosolised drug delivery in ventilated neonates has previously been reported. Watterberg *et al*, using a multistage impinger model, detected 19% of the sodium cromoglycate dose placed in the reservoir of a jet nebuliser emerging from an endotracheal tube. However, when the same nebuliser and loading dose (20 mg) were used in vivo, less than 0·1% (20 μg) was excreted in the urine of intubated infants.[4] A similar overestimate of the in vivo pulmonary dose was obtained by the multistage impactor in our study and may result from incomplete modelling of aerosol behaviour. In a conventional pressure limited, time cycled ventilator, inspiration is a result of the build up of pressure within the circuit from obstructing gas exit while fresh gas in-flow continues. The requirement for a continuous gas flow during the rest of the cycle, means that a significant proportion of a constantly nebulised drug will be unavailable to the infant. If all the flow through the circuit is directed into a multistage impactor, drug wasted in the expiratory phase in vivo will be collected. There is a similar reason for the overestimation by multistage impactor of the dose delivered by Aerochamber with MDI. Here, the source of error is that the multistage impactor cannot model inspiratory and expiratory flow as aerosol needs to be continuously drawn through the impactor system. The combination of filter and neonatal test lung does model inspiration and expiration and the agreement between the in vivo pulmonary dose (258 μg) and sodium cromoglycate deposited on the filter (243 μg) after a 15 mg MDI dose reflects this improved modelling.

The filter model also has the advantage that, where aerosol is generated within the continuous gas flow, wastage of drug during expiration is modelled. Filter/test lung models seem to predict accurately jet nebulised aerosol delivery into neonatal ventilator circuits in vivo. Using aminophylline as a drug marker the Ultravent jet nebuliser delivers 0·22% of the reservoir dose to a test lung.[11] A figure of 0·2% has been reported after jet nebulisation in vivo.[4] Despite the errors in estimating the pulmonary dose of sodium cromoglycate aerosol, urinary excretion of sodium cromoglycate by the infants in this study reflects the absolute minimum amount of drug delivered to the lung. About 0·7% of the MDI dose and 0·5% of the ultrasonically nebulised dose was excreted in the urine over 24 hours. Although we did not measure it, the deposition of aerosol into the lungs by ultrasonic nebuliser is likely to be dependent on the pattern of mechanical ventilation, as it is for a jet nebuliser inserted into a ventilator circuit.[12]

The Pentasonic has not previously been assessed in vivo although the Aerochamber has been used to deliver bronchodilators to intubated adults receiving volume cycled ventilation. An Aerochamber and MDI inserted into the inspiratory limb of a ventilator circuit will deliver 5·7% of the original dose to the adult lung.[13] In adult ventilator circuits, there is no continuous flow and most of the aerosolised drug is delivered to the patient's endotracheal tube. By placing the Aerochamber directly onto the neonate's endotracheal tube the problem of continuous flow is overcome and delivery

partially mimics that of the volume cycled ventilator. It may also be possible to enhance ultrasonic drug deposition by placing the nebuliser directly onto the endotracheal tube and ventilating through the chamber.

The therapeutic effectiveness of an aerosol depends not only on the quantity of drug reaching the lung but also on particle size, best described by the MMAD. MMAD is the diameter above and below which 50% of the mass of the particles is found. Particles less than 5 μm are more likely to deposit in the distal airways whereas larger particles impact on the larger diameter airways.[14] Although the optimum aerosol size for neonates is unknown, theoretical models suggest a similar patterm of deposition to adults.[15] In the past, ultrasonic nebulisers have been bulky and have produced a highly variable output containing significant numbers of large droplets.[16] In this study the combination of both the Pentasonic and Aerochamber with an endotracheal tube produced high quality aerosol. The size distribution of aerosol generated by the Pentasonic was similar to that produced by jet nebulisation.[11] The MMAD of particles generated within the Aerochamber was larger (9 μm), as measured by the imperfect multidose impactor model, but a significant proportion of the aerosol was below 5 μm.

The Pentasonic and the Aerochamber were clinically easy to use. The Aerochamber fitted directly onto the standard Portex endotracheal tube connector without adaption and there were no problems in ventilating infants through the spacer. The Pentasonic could be inserted into the inspiratory line with minimal adaption. There was no change in ventilator pressures during ultrasonic nebulisation and no drop in gas temperature, as measured by a thermister sited in the endotracheal tube connector. It was important to remove the one way valve from the Pentasonic to allow any build up of pressure in the circuit to be vented through the emergency inspiratory blow off valve. The 145 ml Aerochamber temporarily increased the ventilator dead space, and for this reason, we preferred to insert the device briefly, and not to try to maintain mechanical ventilation with the spacer in place. However, spacers are important when using a MDI in ventilator circuits. Particles are ejected from the MDI canister with high velocity and mass.[17 18] As the propellants evaporate particles decrease in size toward the respirable range (<5 μm).[18] If generated near a surface, the large particles will impact and will be wasted. A spacer gives time and distance for particle shrinkage as well as acting as a large particle filter.[19] Removing the spacer may shift the impaction of up to 80% of the aerosolised dose from within the device to the endotracheal tube. Although an endotracheal tube may function as a form of spacer,[11] impacted particles may be washed down into the lung during routine nursing care.

Ultrasonic and MDI aerosolisation have merits and drawbacks. MDIs can effectively aerosolise solutions and suspensions but contain surfactants and propellants, a proportion of which will be deposited within the neonatal lung. MDI drug delivery is also limited by the commercial availability of canisters, but has the potential for rapidly delivering higher doses. Ultrasonic nebulisers can nebulise any solution but is far less efficient in nebulising viscous suspensions such as topical steroids.[20]

Therapeutic doses of sodium cromoglycate can be delivered by both systems. In older non-intubated children, 0·26% of a 20 mg dose of sodium cromoglycate generated by MDI and spacer (Medic Aid) will reach the lungs.[21] For a 10 kg infant this represents a pulmonary dose of 5·2 μg/kg. For an adult, assuming 10% pulmonary deposition, a dose of 20 mg delivers 20–40 μg/kg via the lungs. The mean dose delivered to ventilated neonates by the Pentasonic was 107 μg/kg (range 64–213) and by Aerochamber 234 μg/kg (range 88–394).

In conclusion, this study has demonstrated that the Pentasonic ultrasonic nebuliser and the Aerochamber spacer with MDI are both able to deliver aerosolised sodium cromoglycate to ventilated neonates without the disadvantages of jet nebulisation. There was good agreement between the sodium cromoglycate dose predicted from a filter model and the estimated dose delivered in vivo and may therefore be the method of choice in evaluating future delivery systems. The clinical effectiveness of drugs delivered by ultrasonic nebulisation or MDI remains to be determined.

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