

THE MAJORITY OF ISSUES regarding drug delivery in early childhood asthma concern inhaled drugs. Current aerosol delivery devices have changed little over the past 10 years. How good are they for use in young children, how can they be used optimally for this age group, and are they likely to survive another 10 years? The following questions address the most important issues relevant to delivery of inhaled drugs to young children.

How can pressurised metered-dose-inhaler-spacers be optimally used in children under five years of age?

Pressurised metered-dose inhalers (pMDIs) have been in common use for over 40 years and pMDIs combined with spacers (pMDI-Ss) have been used for over 20 years to assist in delivery to small children. Yet there have been few studies to determine optimal use of pMDI-Ss. There are a number of variables to consider.

Should a small or large spacer be used?

Small-volume spacers are recommended for use only in very young children.¹ However, the sole study investigating this

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ABSTRACT

What we know

- In preschool children, small-volume spacers perform better than large-volume spacers.
- Detergent is the best antistatic agent for spacers, increasing lung delivery two- to threefold, but it must not be rinsed off.
- A mouthpiece should be used in children aged 2–3 years or older, as lung delivery is two- to threefold higher for oral inhalation than nasal inhalation (ie, by mask).
- Inhaled drug doses do not generally need to be reduced in infants and young children owing to inefficiencies of delivery in younger patients.
- Nebulisers are “dinosaurs” and not needed for most children with asthma.

What we need to know

- What is the best inhalation technique for spacers? How long should children breathe, how many breaths should they take, and at what age should they breath-hold?
- How should children, parents and doctors be instructed to achieve optimal levels of electrostatic charge reduction for spacers?
- How much should inhaled steroid dose be reduced when a spacer is used optimally?
- What dosing instructions should be given for β_2 -agonists delivered by spacer?

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application used a bench-top model to demonstrate poor efficiency of delivery using a large-volume spacer with the smaller tidal volume found in younger children.¹ The poor efficiency was probably due to the slow clearance of aerosol from the spacer, allowing aerosol to be lost due to droplets being drawn onto the spacer wall by gravity or by electrostatic forces. No studies have accurately compared delivery between small- and large-volume spacers in infants and young children.

How important is electrostatic charge?

Removing electrostatic charge by coating plastic spacers with a detergent layer improves lung deposition by 200%–300%.^{2,3} This increase in performance is almost certainly important for inhaled steroids and likely to substantially improve therapy in some children and increase the risk of steroid toxicity in others. For inhaled beta-agonists, for which dosage is much less critical and toxicity is a relatively minor issue, the improvement in delivery by removing static may not be as important clinically.^{4,5} An important question, not yet adequately addressed, is whether patients are able to correctly follow instructions for minimising static.

What is the optimal inhalation technique?

With regard to optimal delivery of aerosols to young children by pMDI-Ss, no study has systematically examined such issues as the optimal time of inhalation, whether the patient should use tidal breathing or the biggest breaths possible, and whether breath-holding is useful.

Should medication be administered during sleep?

Since cooperation is a problem with very young children, administering inhaled drugs during sleep may be worthwhile. Preliminary studies have examined this issue, but no clinically useful data are available, and the practicality of this approach has not been determined.

Should a mask or mouthpiece be used?

Delivery of medication to the lungs is two- to threefold greater when breathing through the mouth than through the nose.⁶

How should the prescribed dose be adjusted for age?

The proportion of the prescribed dose deposited on an inspiratory filter or in the lungs³ increases with age, but the increase appears to be appropriate for the increase in body size, as the serum level of an inhaled drug is similar in children of different size and age inhaling from a given device.⁷ Therefore, the dose of an inhaled agent delivered by a static-reduced pMDI-S probably does not need to be adjusted for age.

Should dry-powder devices be recommended for use in young children?

Dry-powder inhalers (DPIs) are generally not recommended for children under five years of age. Current DPI devices deliver a lower percentage of drug than a pMDI-S used optimally,^{3,8} and DPIs require a mouthwash when used with inhaled steroids. DPIs are also not usually recommended for use in acute asthma, whereas pMDI-Ss can be used.^{9,10}

Are nebulisers “dinosaurs”?

Nebulisers are expensive and slow, and deliver a low percentage of the prescribed dose. The use of nebulisers in the emergency department for treating acute asthma in small children is not essential, as recent studies comparing nebuliser with pMDI-Ss have not found strong evidence that nebulisers provide better therapy.^{9–11} A study has shown that changing from nebuliser to pMDI-S for treating acute asthma is not accompanied by an increase in hospitalisation.¹² A recent Cochrane review found no evidence that nebulisers were superior.¹³

Should high-dose β_2 -adrenergic drugs be made available?

Over recent years, the recommended dose of inhaled β_2 -adrenergic drugs delivered by pMDI-S for acute asthma has increased markedly. The original recommended dose of salbutamol for adults (200 μg) was delivered in two actuations of a 100 μg -per-actuation device, or, in some countries, one actuation of a 200 μg -per-actuation device. Now that more information is available on the percentage of drug dose being delivered to the lungs in children, recommended doses of salbutamol have increased to 500–1000 μg for acute troublesome symptoms.^{9,11} This means that five to 10 actuations of the delivery device are required. To avoid the difficulty of administering so many actuations in an emergency situation, a higher-dose-per-actuation formulation of the most commonly used β_2 -agonist would be helpful for patients and improve therapy for acute asthma attacks. These higher doses are only recommended for acute attacks with troublesome symptoms and should not be used in other situations without careful instruction.

Should drugs be tied to particular devices?

The case against this proposition

There are good reasons to conclude that drug schedules should not be rigidly tied to a particular device. Currently, there is a worldwide move to tie registration of inhaled drugs to particular devices. In some countries, this means that clinical efficacy studies must be completed with the drug and delivery system before they can be licensed for distribution. While this appears to be a sensible move, it has some severe drawbacks. For example, if an improved delivery system becomes available, it cannot be used without full

clinical trials being completed. This is the case even if excellent in-vitro delivery and in-vivo deposition data are available and would allow a reasonable estimate to be made of the reduced dose needed for the new device.

The perception that a clinical trial is the "gold standard" for a new delivery system is one of the greatest misconceptions holding up development of newer and better delivery systems. Current licensing practice completely ignores major changes to and improvements in existing delivery systems. For example, by abolishing electrostatic charge on pMDI-Ss, lung delivery of inhaled drugs is increased two- to threefold,² yet no changes in dosage schedules for β_2 -agonists or inhaled steroid drugs have been made. Demanding rigid evaluation of new, improved devices while ignoring major changes in use of existing devices is illogical. Regulatory authorities should seek more appropriate advice for determining their practices.

The case for this proposition

There are good reasons to conclude that drug schedules should be tied to a particular device. For expensive drugs, such as newly marketed inhaled steroids, the use of the most efficient delivery system will ensure that the lowest dose of the drug needed for effective treatment is prescribed. Use of inefficient devices is likely to result in higher doses of the drug being prescribed than necessary to control asthma, with attendant higher cost. For example, use of a small-volume spacer and face-mask in a child over the age of three will require a prescribed or nominal dose that is two to four times higher than would be needed if a large-volume spacer and mouthpiece were used.

Will current delivery devices still be in use in 10 years' time?

Several companies are now developing devices that will have the potential to provide much better delivery to young children. These devices use sensors to determine inspiratory flow patterns, microchip technology to analyse the signals and energy-efficient, novel methods for generating aerosols.¹⁴ They will be hand-held, small and battery-operated, requiring less coordination to achieve optimal lung deposition of up to 80% of the nominal dose. The push for an inhaled insulin delivery system is helping to drive the development of such devices.¹⁵ Eventually, these devices should be superior in every respect to current delivery systems and will replace them.

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