Inhalation devices

Recommendations

1. At each contact, health care professionals should work with patients and their families on inhaler technique (level I).
2. When prescribing a pressurized metered-dose inhaler (pMDI) for maintenance or acute asthma, physicians should recommend use of a valved spacer, with mouthpiece when possible, for all children (level II).
3. Although physicians should allow children choice of inhaler device, breath-actuated devices such as dry-powder inhalers offer a simpler option for maintenance treatment in children over 5 years of age (level IV).
4. Children tend to "auto-scale" their inhaled medication dose and the same dose of maintenance medication can be used at all ages for all medications (level IV).
5. Physicians, educators and families should be aware that jet nebulizers are rarely indicated for the treatment of chronic or acute asthma (level I).

This review, which forms the basis for the consensus, covers the clinical issues that are important for the primary care practitioner and asthma educator to understand to optimize the transfer of knowledge and practice to the patient and family. Relevant technical aspects are discussed first, followed by their application to the family. One section deals primarily with applications in the acute care setting.

Literature review

A MEDLINE search from 1996 to present was conducting using the following keywords: "children," "asthma," "inhalation technique," "HFA," "aerosols," "patient education," "asthma education." Appropriate articles were also identified from the authors' own knowledge of the literature as well as reference lists in articles retrieved.

Current evidence review and discussion

Technical aspects

Hydrofluoroalkane (HFA) propellants

HFA-propellant pressurized metered-dose inhalers (pMDIs) have been shown to be effective for the treatment of asthma in adults and children.[1,2] Differences in the metering valve plus actuator mouthpiece of various pMDIs can result in the delivery of varying quantities of medication of different particle sizes. The mass median aerodynamic diameter of the different formulations ranges from about 1 to 4 μm. For example, particle delivery to the lung may be increased 50% of the nominal dose for QVAR, an HFA propellant solution of beclomethasone dipropionate (BDP),[3] but remain at 10%–20% for HFA suspension formulations such as fluticasone and salbutamol.[4,5] If a holding chamber is used with the HFA solution of BDP, lung deposition remains unchanged.[6] However, using a 145-mL valved holding chamber does not change lung deposition, but the oropharyngeal dose is reduced 5-fold.

Other ICSs (flunisolide, triamcinolone) have similar deposition characteristics in adults when used without open tube spacers with either chlorofluorocarbon (CFC) or HFA formulations.[7,8] Not all HFA–BDP preparations are the same. The relative potency for the HFA solution of BDP (Qvar, 3M) in adults appears to be about 2.6:1 compared with CFC-BDP.[1] Using an HFA-BDP preparation delivered via an Easibreathe' (Norton Health Care Ltd., London, UK), one study in children demonstrated a 1:1 potency ratio of CFC and HFA preparations.[2] However, in children the possibility of inadequate technique could favour the use of a holding chamber to deliver an ICS when using an MDI. In addition the deposition of the HFA aerosol solution of BDP is more peripheral because of its low mass median aerodynamic diameter (1.0 μm) compared with CFC–fluticasone (2 μm) or CFC–BDP (3.5 μm).[3]

To date, the only reported study in children was randomized, but open labelled, and compared HFA–BDP delivered via a spring-loaded breath-actuated device and CFC–BDP delivered via a holding chamber.[9] Half the dose was needed in the HFA group to achieve the same efficacy with no differences in growth, adrenal function or bone metabolism markers. In addition, there is little clinical evidence that more peripheral airways should be targeted, and benefit-to-side-effects ratios for peripheral versus central deposition must be determined to substantiate such an approach. In fact, it has been shown that the optimum size of ipratropium or salbutamol in adults is 2.8 μm versus 1.5 or 5 μm,[10] but it is far more difficult to evaluate the benefit-to-side-effect ratio for an ICS. HFA–salbutamol preparations with the same aerodynamic size as CFC preparations have been shown to be equipotent in adults.[11–13]

Holding chamber properties

Spacer size — The size of the holding chamber may lead to different deposition efficiencies for different ages.[14] The valves may have high resistance,[15] the dead space may be too large[16] or the chamber may be too large[15] for infants. These

factors need to be taken into account when choosing a holding chamber. In simulated models representing a 7-month-old infant, a 2-year-old toddler and a 4-year-old child, 4 holding chambers were assessed using CFC–BDP and CFC–salbutamol.[17] Different holding chambers delivered significantly different amounts of fine particles and the dose varied with the medication as well. Depending on the device, variation with age of patient may have been substantial or insignificant. Differences in delivery of HFA products require further study, but it appears that, for HFA–salbutamol, spacer volume is not as critical to delivery.[18]

Electrostatic properties — Different holding chambers have differing electrostatic properties.[19] Electrostatically charged holding chambers cause significant dose variations compared with the metal Nebuchamber and deliver a substantially smaller dose to the patient.[20] Non-electrostatic devices have been recommended for young children as these result in increased deposition[19,21]; as an alternative, plastic holding chambers may be lightly coated with liquid detergent to eliminate the electrostatic forces.[22] Priming the holding chamber with repeated puffs has been shown to be effective[19]; however, this practice is not currently recommended, mainly because of the waste of the medication and thus cost. Deposition of budesonide in the lungs increased from about 25% using plastic spacers to about 35% when the spacer was primed with 20 doses of placebo aerosol, but priming had no effect in non-electrostatic metal spacers where deposition measured 33%.[20] The same effect is seen when plastic spacers are washed and rinsed, and these steps are detailed and recommended on the package inserts for these devices. Oropharyngeal dose may be higher using metal spacers as more of the larger particles in the aerosol are available for inhalation.

Inhalation delay and multiple actuations — In adults, a 20-s delay in inspiration after actuation of an MDI with a large volume plastic holding chamber resulted in a 50% drop in the amount of salbutamol reaching the lungs as measured by serum levels.[23] Although data are not available for children, there is no reason to suspect that the same effect will not occur. In an in vitro study under conditions of constant flow, a delay of 20 s decreased small-particle emission by about two-thirds.[24] There was also a 50% decrease if multiple puffs were used to load the holding chamber.[23] The use of multiple actuations into the spacer before breathing decreased particle emission by a third for 2 puffs and a half for 5 puffs.[24] The tradename, volume and manufacturer for the various spacers and holding chambers are appended as Table 1.

Relative dosing

Different jet nebulizers are associated with different levels of deposition and particle size. However, many studies overwhelmingly demonstrate an approximate 5:1 efficacy ratio for β-adrenergic medications delivered via the jet nebulizer versus the MDI and holding chamber in children of varying ages.[25–27] That is, 500 mg of salbutamol by wet nebulization would be equivalent to 100 mg by MDI with holding chamber or spacer. Studies using more recent designs of nebulizers with inspiratory flow enhancement and a tight-fitting face mask, may result in a 2:1 ratio.[28,29] However, in the practical situation of the child in the emergency department or an infant at home, it is difficult to apply a tight-fitting seal for the duration of the inhalation.

In children between the ages of 3 and 5 years, there is no evidence for the superiority of terbutaline sulfate delivered via an MDI and holding chamber versus a dry-power inhaler (DPI) in the outpatient setting.[30] Similarly, in older children, the benefits and side-effects of the 2 delivery systems in the emergency setting were similar.[31] In adults, deposition of budesonide with a DPI appears to be up to double that using an MDI and holding chamber.[32] Further support for using the DPI was demonstrated in a dose-reduction study in children, which showed that budesonide may be twice as potent in a DPI compared with an MDI with a large-volume plastic spacer.[33] However, other studies

Table 1: Dry-powder inhalers*

Dose storage	Trade name	No. doses per storage unit	Specific resistance	Drug
Single capsule	Aerosolizer (Novartis, Surrey, United Kingdom)*	1	L	Formoterol
	Inhalator (Boehringer Ingelheim, Ingelheim, Germany)*	1	H	Fenoterol
	Spiriva (Boehringer Ingelheim, Ingelheim, Germany)	1	H	Tiotropium bromide
Reservoir	Turbuhaler (Astra Draco, Lund, Sweden)*	200	H	Budesonide
	Clickhaler (ML Laboratories, St. Albans, United Kingdom)†	200	H	Budesonide
	Ultrahaler (Rhône-Poulenc Rorer, Loughborough, United Kingdom)†	200	M	Budesonide
	TwistHaler (Schering Key, Kenilworth, NJ, United States)*	200	M	Mometasone
Multi-unit dose	Blister Diskhaler (Glaxo Wellcome, Ware, United Kingdom)*	4–8	L	Fluticasone
	Blister/tape Diskus (Glaxo Wellcome, Ware, United Kingdom)*	60	M	Fluticasone

*Marketed in Europe, Canada or the United States.
†Under development or regulatory review.
L ≤0.05 cm H_2O/L per s; M = 0.05–0.01 cm H_2O/L per s; H = >0.01 cm H_2O/L per s.

have demonstrated equal bronchodilation with equal doses from these 2 devices.[34,35] Only half the dose of fluticasone has been shown to be delivered by DPI compared with an MDI and holding chamber.[36]

Comparisons between fluticasone and budesonide DPIs demonstrate more consistent delivery of the former over varying inspiratory flows and ages in children.[37] However, the budesonide DPI emitted a much higher dose of fine particles when used by children ages 4 and 8 years; the available dose was twice as high by age 8.[37] In theory, fine particles contribute to the efficacy of the inhaled corticosteroid as they penetrate to the lower airways. Overall, no specific recommendations can be made regarding the use of a DPI or MDI for the treatment of chronic asthma. In the acute care setting, no specific recommendations can be made regarding the use of the DPI, MDI or jet nebulizer. However, a 5:1 ratio for drug dose by conventional jet nebulizer compared with MDI and holding chamber is a good rule in the latter situation.[25–27]

Even within holding chambers, different MDI preparations are affected differently.[38,39] One cannot necessarily predict how a holding chamber will affect a particular medication, and products need to be matched with devices.

Although adding a holding chamber to a DPI has been shown to decrease the proportion of large particles from 52% to 30%, it does not alter the number of small ones.[40] The use of a holding chamber would help reduce side effects arising from oral and gastrointestinal deposition of particles, though these are not very important in children using budesonide. In a review of devices, Bisgaard[16] stated that drug approval processes should clearly specify the device, and discourage the use of other devices, i.e., the device should be an integral part of the prescription.

Overall, these data demonstrate that it is important to have a proper fit of patient and device to obtain optimal benefit compared with risk of adverse effects for the individual patient.

Inhalation techniques — teaching children to use an inhaler

The patient must demonstrate adequate technique when inhaled medication is prescribed. To teach the use of budesonide DPI, children aged 3, 4 and 5 years and their parents were shown a video and given written instructions; others also received training from a nurse.[41] The 3-year-olds performed poorly with or without the nurse's training; however, the 4- and 5-year-olds increased peak flow through the budesonide DPI significantly with nurse-assisted training. The group receiving assistance from the nurse was given an inhaler modified to provide feedback on PEF at home for 2 weeks. On follow-up, a further improvement of about 10 L/minute in PEF was noted in the 4- and 5-year-old children.

Different techniques can be used with an MDI and holding chamber: tidal breathing with sufficient flow to move the valve, 5 breaths, or taking 1 deep breath and holding it for 10 s. These have been demonstrated to be equivalent in school-age children,[42,43] although, surprisingly, there have been no further confirmatory studies. As there may be difficulties with coordination during acute episodes that may not be arise when the young child is well, and breath holding may be difficult during acute episodes, the tidal breathing technique may be the best method to use. Furthermore, many children can only use the tidal method when first taught before the age of 4 or 5. As they already know the technique of tidal breathing, it might be preferable to continue with this method. As well, for simplicity and consistency, it might be best to teach 1 method in general.

Proper technique includes many steps. Some are essential to receive the medication (e.g., removing the protective cap), while others may optimize delivery but have a graded response (e.g., inspiratory flow through the DPI[44]). Others have been consistently quoted as important, but may not be necessary at all. Hansen and Pedersen[45] demonstrated in children that breath holding and tilting the head do not improve response to bronchodilator. In addition, the response was identical whether they inhaled from functional residual capacity or residual volume.

Studies have not been able to demonstrate that giving a patient a preference increases adherence in long-term therapy. In general, the simpler the device, the smaller the chance it will be damaged or lost. Cost is an effective barrier to use of medications. The holding chamber generally represents an additional cost; the cost of the medication is about the same for DPIs and MDIs. In adults, although the MDI was the most widely prescribed device in the United Kingdom, patients preferred DPIs and performed better with them.[46] The most common technique-related problem cited was too-slow an inspiration. In this study, the breath-actuated MDI, an inspiratory flow driven device, was highly preferred as well as easy to use. Another audit of 422 patients of all ages in private practice showed that 63% were using an MDI.[47] However, once again, correct usage was higher with DPIs than MDIs.

Chen and colleagues[48] surveyed 132 children aged 8–13 years and found that children who inhaled medication unaided had a better knowledge of asthma and their technique was superior to those who were helped by their parents. Increased skill was associated with the family's degree of satisfaction with the physician's educational program, reading of related publications, older age and number of asthma attacks in the previous year.[48,49] Kamps and coworkers[50] evaluated patient characteristics in 47 children referred to a tertiary asthma clinic. Good technique was associated with previous repeated instruction sessions that included demonstrating the skill to a health care professional. After 1 session, only 57% demonstrated correct technique, but after 3 sessions this value rose to 98%. Giraud and Roche[51] evaluated 3955 questionnaires from adults regarding inhalation technique and concluded that asthma instability was related to misuse of MDIs, particularly poor coordina-

tion. Comprehensive instructions combined with repeated checks of proper technique in the pharmacy or clinical trial setting dramatically increased good performance, from 39% (general practitioner demonstration only) to 79% and 93%, respectively.[52]

Vodoff and associates[53] found that in children under 4 years of age, the most common errors in using an MDI were not shaking the device before use (48%) and taking 2 consecutive puffs (28%).

Although 1 study[54] clearly demonstrated the superiority of using one type of device versus multiple ones in adults, there have been no similar studies in children. There is a tendency to prescribe β-adrenergic medications using an MDI or an ICS using a DPI. The DPI requires a rapid deep inspiration, whereas the MDI requires a slow one. This can be confusing. In addition, the most common problem associated with the use of a DPI is poor quality of the rapid deep inspiration.[46,49] Provided the drugs are available, we recommend 1 type of device to optimize technique for all children, especially when an ICS is being delivered via a DPI.

A systematic review by Brocklebank and colleagues[55] concluded that the evidence in both children and adults does not reveal any preference for other devices over the MDI and holding chamber for both ICSs (3 pediatric studies) and β-adrenergics (11 pediatric studies). They state that as the MDI is the cheapest device, its use is to be recommended in preference to other types of inhalers. However, a recent review of the literature[56] showed that each type of inhaler system can deliver effective therapy to patients when they use the inhaler properly, suggesting that selection of an inhaler system for patients should be based on several considerations such as availability of the drug prescribed in the preferred device, the patient's age and ability to use the device, the clinical setting and cost.

From a practical point of view, instructions should be kept simple. Using one type of device is important. As mentioned, MDIs with a holding chamber are strongly preferred to MDIs alone in all children. Many children feel they can inhale using the MDI alone, although they have been told to always use the holding chamber. This device is far more cumbersome to transport than a DPI. As well, older children are self-conscious of bulky devices they may need to take to sporting events. Once a child can use the DPI, this is the preferred device.

Age and devices

In children, the budesonide DPI has been shown to be used at inspiratory flows as low as 30 L/minute.[44] However, twice the effect is produced at flows of 60 L/minute. In a study using radiolabelling, 6–16 year old children using a budesonide DPI were found to increase lung deposition with age and height.[57] Children aged 3 or 4 years can effectively use this device,[30] but those under 5 years of age find it difficult to learn consistent technique.[41] Proper education and home training can improve technique in 4 and 5 year olds.[41] One study showed that 43% of 4 year olds, 67% of 5 year olds and 80% of 6 year olds could effectively use the device.[58] Concerns have been raised that although young children may use the DPI successfully when well, they may have problems during acute exacerbations. However, benefit from using the device was demonstrated in children aged 6–17 years, with FEV_1 as low as 25% of predicted value.[31]

Onhoj and associates[59] recently demonstrated that budesonide delivered from an MDI and holding chamber to children aged 2–6 years resulted in the same plasma concentration of budesonide as in adults. They also showed that the total patient dose was independent of age, but that lung dose increases with age, while oropharyngeal dose decreases. Deposition using the MDI and holding chamber in infants may be in the range of 2% of the nominal dose,[60] whereas in adults it is 10%–20%; thus, it appears that children auto-scale dose delivery to the lungs as opposed to delivery at the mouth.[61]

For jet nebulized medications, including cromoglycate and salbutamol in infants, <1% of the wet nebulized dose appears to reach the lungs.[29] Chua and colleagues[62] showed that saline delivered via a nebulizer results in about 3 times the deposition in 6–18 year olds versus infants. If the child uses a mask, lung deposition will decrease as well.[62] Another radiolabelling study[63] showed that children under the age of 4 years had approximately 5% deposition whether a jet nebulizer or an MDI and holding chamber was used, but this increased in children over the age of 4 years to about 10%. One study[64] measured the deposition on a filter placed at the mouth in infants 4–30 months of age using a jet nebulizer and holding chamber and found an increase with age in budesonide deposited at the mouth. Wildhaber and associates[57] demonstrated increasing deposition of salbutamol on a filter at the mouth of infants weighing 6–11 kg. These children are at weights where inspiratory flows would be just starting to match the flow of the air nebulization.[65] The results confirmed the hypothesis that if the driving airflow of the nebulizer exceeds the maximum inspiratory flow of the infant, then medication will be lost to the atmosphere during inhalation. Information about the various dry powder inhalers is provided in Table 2.

The general body of evidence now suggests that there is a good degree of auto-scaling with age for any type of device, but how accurate this is in terms of meaning that 1 dose can be used for all ages is uncertain.

Cognitive state — crying, awake, asleep

Following an anecdote in a study demonstrating the marked decrease in deposition in infants who cried,[60] a well-done controlled trial clearly demonstrated that drug delivery decreased by two-thirds in infants who were distressed compared with infants who were calm during inhalation when using a holding chamber and face mask.[66] It is, therefore, suggested that these devices not be used to deliver ICSs in infants who are crying. However, in 1 study, 38% of

infants repeatedly cried while receiving therapy.[67] Treatment may be tried when the infant is sleeping.[68] Alternatively, behaviour modification approaches may help to habituate the child to the mask. Although wet nebulization is generally not preferred, the mask used with this technique, which is not tight fitting, may be more acceptable to the infant and may be preferred in this setting. On the other hand, in the emergency department, the shorter time needed to use an MDI and holding chamber may make it preferable to the wet nebulizer. A study[69] using jet nebulization to administer radiolabelled aerosol to infants with cystic fibrosis while sedated or awake found no difference in deposition. If difficulties arise because the infant is agitated while awake, a trial while the infant is asleep may be beneficial.

Interface — face mask v. mouthpiece

It has been clearly demonstrated in children that breathing through a mask via the nose decreases lung deposition by up to 67% compared with breathing through a mouthpiece using a jet nebulizer.[62] There are no similar in vivo studies using an MDI with a spacer attached. However, a recent study using a model of the upper airways and face to simulate aerosol delivery in an infant or young child from an MDI and spacer showed the importance of maintaining a good seal between the face and the mask.[70] Face masks with leaks of various sizes were created, and delivery of budesonide MDI aerosol via metal valved holding chamber was measured in the model. The data showed that the lung dose was substantially reduced when the leak occurred near the nose compared with the chin area. Although we cannot be sure that patients using a mask will, in fact, breathe through the nose, it would seem prudent to use a mouthpiece at as young an age as feasible to maximize the chance of increased deposition.

Differences in mask design have been shown to affect the amount of aerosol deposited on the face and in the eyes.[71] In addition, if the dead space of the mask is comparable to the tidal volume of the infant, little aerosol will reach the lung.

Table 2: Spacers and valved holding chambers

pMDI spacer design	Trade name	Volume, mL	Manufacturer
Holding chamber	Aerochamber Plus	145	Trudell Medical, Canada
	AeroChamber MAX	198	Trudell Medical, Canada
	Vortex	194	Pari, Germany
	Nebuchamber	280	AstraZeneca, Sweden
	Babyhaler	350	GlaxoSmithKleine, United Kingdom
	Nebuhaler	700	Astra, Sweden
	Volumatic	750	Glaxo, United States
	Opti-Chamber Advantage	218	Respironics Inc., United States
	PocketChamber	110	Ferraris Respiratory Inc
	FunHaler	225	InfaMed Ltd
	Space Chamber	235	AirFlow Products, New Zealand
	LiteAire Disposable	150	Thayer Medical, United States / Methapharm, Brantford, Canada
Reverse flow	Inspirease	750	Schering Corp., United States
	E-Z Spacer	700	WE Pharmaceuticals, Ramona, CA, United States

Wet nebulizers in acute care

Numerous studies compare MDIs and holding chamber with wet nebulizers in the acute care setting in children over the age of 2 years[1] as well as 4 in infants.[72–75] Three studies in the infants used a 4:1 or 5:1 ratio of medication in the MDI and holding chamber versus jet nebulizer. In fact, 1 study demonstrated a lower admission rate to hospital using the MDI system versus the jet nebulizer.[73] Cates and coworkers[76] performed a systematic review of 21 trials comparing the MDI and holding chamber to jet nebulization in the acute care setting in adults and children. There were no differences between devices in either age group in terms of admission rates, length of stay in the emergency department (except for 1 study in children showing a shorter stay with MDI) or pulmonary function. There were fewer side-effects in children using the MDI, particularly a lower pulse.[77,78] All generally demonstrate the 5:1 ratio of the MDI dose to the wet nebulizer dose, but clearly there will be variation depending on the quality of the devices and the cooperation of the child.

Recently a study demonstrated the equivalence of the budesonide DPI and the MDI with holding chamber for school-aged children as young as 6 years old in the emergency setting with FEV_1 as low as 25% of predicted.[31] These children were all able to generate PEFs through the DPI greater than 30 L/minute.

The barriers to implementation of these devices have often been habit or issues of sterilization. These can be overcome. Cost of medication and time to administer can be greatly reduced. However, 1 adult study has demonstrated that, if time needs to be spent at the bedside observing correct use of the MDI versus leaving the patient with the jet nebulizer alone, then the savings might not be significant.[79] The MDI and holding chamber method is preferred over the wet nebulizer at all ages. After age 6, the budesonide DPI may be used. However, there are no data concerning other DPIs in the acute care setting. As the budesonide DPI can be used in the acute care setting,[31] there is no fear of using it for the complete inhalation therapy treatment in the child 6 years of age and older.

Wet (jet) nebulizers in the chronic setting

There is also debate about the value of wet nebulizers for treatment of chronic asthma.[25–27] The compressor devices and medications are more costly and cumbersome, which may decrease adherence to therapy. As well, particle size from wet nebulizers varies greatly depending on the device and compressor.[80,81] Overall, there is no rationale for considering the use of a wet nebulizer for the vast majority of patients with asthma.

β_2-adrenergic medications do not enhance deposition of ICSs

It has been common practice to inhale a β_2-adrenergic medication "to dilate the airways" before administering the inhaled corticosteroid. No studies have validated this. In addition, in young children, any delay will decrease deposition. It is recommended that the most important medication be used first, not after premedication with a bronchodilator.

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