

# OPTIMAL AEROSOL DELIVERY

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## ABSTRACT

Pressurised metered-dose inhalers (pMDIs), nebulisers and dry-powder inhalers (DPIs) aim to deliver aerosols to the lungs. With optimal technique, lung deposition ranges from below 10% to approximately 15%. pMDIs are the most frequently used device. Excellent hand-breath co-ordination is required for effective use of pMDIs.

Optimal technique requires slow inspiratory flow of 30 l/min and a breath hold of 10 seconds. Deposition in crying infants is minimal. 'Blow-by therapy' of nebuliser or pMDI aerosol delivered close to the sleeping child's mouth and nose is ineffective. Spacers and valved holding chambers provide an additional volume in which medication is dispersed, before it is breathed into the lungs.

DPIs overcome the difficulties of poor hand-breath co-ordination. Patients who are unable to generate sufficient inspiratory flow and depth of breathing to trigger DPIs should not use these devices. Patients must not exhale into the device prior to inspiration.

Equivalent clinical results can be achieved from any delivery device, providing the patient can use it correctly. Selection of the appropriate device for each patient requires consideration of multiple factors. Inhaler technique should be demonstrated by the patient at each visit, assessed by the health-care provider, and where necessary, training to optimise aerosol delivery should be repeated.

## INTRODUCTION

Achieving asthma control requires improvement in overall asthma care. The act of simply prescribing the correct medication is not an adequate intervention to ensure the health of the majority of asthmatic patients. Most poorly controlled asthma is attributable to factors such as incomplete adherence, incorrect device selection and poor patient inhaler technique. Between 28% and 68% of patients do not use pressurised metered-dose inhalers (pMDIs) or dry-powder inhalers (DPIs) well enough to benefit from their medication and 39-67% of nurses, doctors and respiratory therapists are unable to adequately describe or perform critical steps for using inhalers.<sup>1</sup>

Medical professionals need to be supported and encouraged to recognise asthma, recognise uncontrolled asthma and treat uncontrolled asthma appropriately. Patients need to be sup-

ported and encouraged to access asthma education, adhere to prescribed medication and improve the technique of administration of inhaled medications. Furthermore, doctors need to be trained in how to help their patients in these areas.

## AEROSOL DELIVERY

Aerosols are suspensions of liquid or solid particles within a gas, such as the plume of spray produced by any one of a number of different devices, viz. nebulisers, pMDIs and DPIs.

The size of the particles in an aerosol strongly influences its deposition within the lungs. Aerosols are almost always a mix of different particle sizes. The mass median diameter (MMD) reflects the median size of particles (one half of the mass of spray is contained in droplets of smaller diameter than the MMD and the other half is contained in droplets of larger diameter). The amount of drug that can be delivered (the respirable mass) is affected not only by the MMD but also the measure of how widely dispersed the particles are over a range of sizes, the geometric standard deviation. Factors affecting lung deposition include inertial impaction of larger particles at high velocity and settling time. Particles >10 µm are filtered by the nose or deposited in the oropharynx. Particles of 5-10 µm usually reach no further than the first six generations of the respiratory tree. Particles less than 0.5 µm may be expired as they do not settle effectively. Thus particles of 0.5-5 µm are best for peripheral lung deposition.<sup>2</sup>

Even with optimal technique, lung deposition ranges from below 10% to approximately 15% with most devices.<sup>3</sup> Other places where the drug can be deposited include the oropharynx, the device itself and exhaled air (Fig. 1).<sup>4</sup>

Although different devices deliver approximately the same proportion of their dose, the dose emitted by the device varies widely, and single devices may exist in different strengths. The most gross of these differences exists between nebulisers and other delivery devices, where the dose typically is up to 10 times higher in a (standard concentration) nebuliser than in an MDI or DPI. This (apart from the auditory and visual displays of nebulisers) is responsible for the perception that nebu-

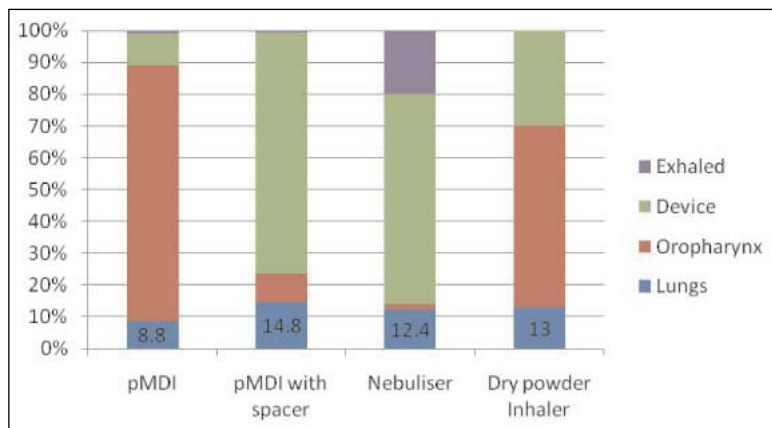


Fig. 1. Drug deposition to different sites with common delivery devices.<sup>4</sup>

lisers are more effective at delivery of medication than MDIs or DPIs. However MDIs can achieve equivalent or even better clinical effect than nebulisers simply if the number of puffs is increased to deliver the same dose. A recent Cochrane review<sup>5</sup> shows equivalent risk of admission for adults whether treated with nebuliser or MDI but a 35% reduction in risk of admission for children when treated with MDIs. In children, the length of stay in emergency departments is significantly shorter with a mean difference of almost 30 minutes when an MDI and spacer are used. In general, equivalent clinical results can be achieved from any delivery device, providing the patient can use the device correctly.<sup>6</sup>

## BREATHING

Breathing patterns influence the efficacy of deposition in the lungs. High inspiratory flow increases inertial impaction. Higher flow results in disruption of laminar flow and deposition of drug in the large airways rather than small airways. Lower flow (about 30 litres per minute) results in better peripheral lung deposition. Patients using nebulisers and pMDIs should not exceed an inspiratory flow rate of 30 l/min. Some devices (e.g. aero-chamber with mouthpiece) have a built in inspiratory flow monitor which sounds when flow exceeds this threshold. DPIs, however, require an inspiratory flow of at least 30 l/min (up to 90 l/min) to actuate the device. This can lead to substantial confusion if patients are using two or more different devices!

Inspiring to full lung capacity and holding the breath enables particles that have reached the peripheral airways to be deposited by gravitational settling or by diffusion. A breath-hold time of 10 seconds is considered optimal to allow this to take place.

Crying infants have a breathing pattern characterised by short, violent inspiratory flow and no breath holding. Deposition in crying infants is minimal,<sup>7</sup> with most of the drug being deposited in the mouth and subsequently swallowed.<sup>8</sup> Inhalation during sleep may be a solution for such infants, but is likely to be associated with sudden waking and subsequent distress. 'Blow-by therapy' of nebuliser or pMDI aerosol being delivered close to the sleeping child's mouth and nose is ineffective and has negligible effect.<sup>9</sup>

## NEBULISERS

Pneumatic jet nebulisers use jets of compressed air or oxygen to create a venturi effect and suspend a liquid as an aerosol. Other technologies include ultrasonic nebulisers and mesh nebulisers which produce a high fine-particle fraction.<sup>4</sup> When jet nebulisers are used, a flow rate of <6 l/min results in large particles which visibly settle towards the floor and have poor lung deposition. A flow rate of 6-8 l/min is required to generate fine particles. The flow from many air compressors is unfortunately too low for optimal aerosolisation, and home-nebulisation is seldom recommended as it is often inefficient and runs the risk of both microbial and allergenic contamination of nebuliser tubing and may give patients a false sense of security, resulting in delayed presentation for emergency treatment during an acute exacerbation.

The volume of solution that remains in the cup and cannot be nebulised is referred to as the dead volume, and typically ranges between 0.5 and 1 ml. Once a nebuliser starts 'sputtering', further delivery is minimal. A fill volume of 4-5 ml is therefore recommended for all medication (including nebulised adrenaline for croup; 2 ml adrenaline: 2 ml saline) unless the nebuliser is specifically designed for lower volumes.

Nebulisers can be used with mouthpieces or face-

masks. Mouthpieces should be used whenever possible as using a mask increases loss of medication to the environment before reaching the patient, and results in deposition on the face, in the nose and in the eyes. Whether a mouthpiece or mask is used, patients must be instructed to breathe slowly and deeply through the mouth, not the nose. T-pieces with corrugated tubing or re-breather bags may be used to prevent aerosol waste during expiration. Deposition is lower in children because of differences in breathing pattern and low tidal volumes. The proportion of the administered dose that is delivered to the lungs is much lower for children and thus the delivered dose per kilogram of inhaled medication is similar for children and adults even when a child uses the same administered dose as an adult. Recommendations to reduce the dose of MDIs and nebulisers for children have not been proven and reduction of dose for children (from adult doses) is probably not necessary.<sup>11</sup>

## PRESSURISED METERED-DOSE INHALERS

pMDIs deliver a precisely measured (metered) dose of medication in an aerosol to be inhaled by the patient. It is the most frequently used mode of delivery of inhaled medications. Deposition is lower in children as a result of differences in breathing pattern and poor technique.<sup>2</sup> Canisters contain both propellant and active ingredient, which may be in solution or suspension. Chlorofluorocarbon (CFC) propellants have been phased out and replaced with hydrofluoroalkane (HFA), resulting not only in lower risk to the environment but also improved aerosol characteristics such as lower particle size, avoidance of low temperature plumes (resulting in the 'cold Freon effect') and a reduced tailing-off effect for doses when the canister is nearly empty. Medication in suspension may settle out if the medication has not been used for some time. Failure to shake such suspensions will result in inaccurate (inadequate) dosing. Shaking mixes ingredients in the canister but not those already present in the holding chamber; therefore the recommendation is to 'prime' a pMDI prior to first use, or after a prolonged period of non-use. Priming comprises shaking the pMDI on each occasion and releasing 1 or more (up to 4 depending on the pMDI) doses into the air, before shaking and delivering a subsequent correctly metered dose to the patient. However, frequent unnecessary priming wastes medication.

Excellent hand-breath co-ordination is required for effective use of pMDIs. Actuation 1 second before inhalation reduces inhaled mass by 90%.<sup>12</sup> Late actuation results in the lung being filled with medication-free air and aerosol merely reaching the anatomic dead space and subsequently being exhaled. When using a pMDI, the patient should first breathe out completely. Thereafter, inspiration should commence at a slow rate followed as soon as possible by actuation of the device. Continued smooth, slow and long inhalation should be followed with a 10-second breath hold, and expiration through the nose. This technique is impossible for young children or those with significant reduction in lung function and/or acute respiratory compromise. Breath actuated pMDIs avoid some of these problems, but require an inspiratory flow of approximately 30 l/min to trigger the device.

It is possible to use a pMDI after the number of doses that are labelled as being present in the canister have been taken; however, there is a progressive tailing-down of the delivered dose until the canister is completely empty. Floating the canister in water to assess the presence of residual medication is no longer recommended as it may lead to substantial inaccuracies and

water entering the nozzle, leading to subsequent dose reduction. Dose counting is necessary to ensure accurate monitoring of whether a full dose of drug is still being delivered by a pMDI. Wherever possible, inhalers with built-in dose counters are preferable.

## **SPACERS AND VALVED HOLDING CHAMBERS**

The term 'spacer' is usually used to refer to any chamber device added between a pMDI and the mouth, but spacers should more clearly be divided into non-valved spacers and valved holding chambers. A non-valved spacer is a tube or additional chamber with no one-way valves placed between the device and the patient's mouth, whereas a valved holding chamber contains additional one-way valves to contain the aerosol until inspiration has occurred and to prevent exhaled air displacing the aerosol from within the holding chamber.

Both devices provide an additional volume in which the medication is dispersed, before it is breathed into the lungs. Because particles are breathed in after dispersing within the chamber, spacers protect against the cold Freon effect, aerosol velocity is reduced and particle size is reduced as larger particles adhere to the sides of the chamber. These factors prevent most of the deposition on the oropharynx. Spacers should optimally be at least 200 ml in size in children and 500 ml in adults. Because these spacers may not be convenient to carry with the patient, it is sometimes suggested that patients use the spacer for their controller medication, but are taught how to use a pMDI without a spacer for their reliever treatment. When manufactured<sup>13</sup> and used correctly, home-made low-cost bottle spacers can be as effective as commercial spacers in treating acute lower airway obstruction.<sup>14</sup> Using a plastic or polystyrene cup as a spacer is ineffective.<sup>11</sup>

Non-valved spacers provide only partial protection for poor hand-breath co-ordination. When using a non-valved spacer it is important to breathe in smoothly and slowly, with preferably one breath inspiring the total contents of the spacer, and to avoid breathing back into the spacer and displacing the aerosol from the chamber. If possible, it may be ideal to commence inspiration shortly before actuating the inhaler in a similar technique to using the pMDI on its own. A second breath may be taken from the spacer to inspire any residual medication. With good technique, the use of a non-valved spacer may increase lung deposition by over 50% and substantially reduce oropharyngeal deposition and systemic absorption of medication.

Valved holding chambers can be considered an extension of the pMDI, converting it into a partially breath-activated device, and offer good protection against poor hand-breath co-ordination. The easiest technique is simply to breathe deeply and slowly in and out of the mouthpiece 5-10 times, but the most effective technique is to inhale aerosol spray as a deep single breath very soon after the actuation of the MDI and to breath hold, similar to the technique when using a non-valved spacer.<sup>4</sup>

In infants (usually under the age of 4) who cannot breathe through their mouths alone, spacers must be used with a mask, and a valved holding chamber is preferable to a simple non-valved spacer. In this case the mask provides an additional dead space and flow must go through the nose leading to additional filtering and nasal deposition. In addition, poor facemask fit may result in leakage of air around the mask and ineffective deposition.<sup>15</sup> When used with a valved holding chamber, poor facemask seal may result in inability to generate negative pressure to open the valve, resulting

in no medication delivery at all. Facemasks thus need to fit comfortably (to avoid distress) but securely (to avoid air leakage) and this balance is often difficult to achieve. Patients using a facemask with their holding chamber should convert to using a mouthpiece as soon as this is possible.

Additional errors in spacer use include firing multiple puffs of medication into the chamber before inhalation, which may result in an even lower dose than a single actuation. There are multiple reasons why two simultaneous actuations deliver less medication than only one. Medications in suspension will have a small decrement in dose when not shaken and the dose is more likely to rain out in the dosing chamber with multiple simultaneous actuations. In addition the second ineffective actuation, containing mostly propellant and little active ingredient, may displace the first effective actuation in the holding chamber. With both suspensions and solutions delivery of two simultaneous doses may make the droplets in the aerosol stick together and to the sides of the spacer, reducing the delivered dose.

## **DRY POWDER INHALERS**

DPIs overcome most of the difficulties of poor hand-breath co-ordination. DPIs do not contain propellant, and the devices are breath-actuated. The patient's respiratory effort (both the inspiratory flow and the volume) determines the delivery of medication from the device. Depending on the device this may require an inspiratory flow rate of between 30 l/min and 90 l/min. As air flow commences, a negative pressure sucks the medication from its container, blister or capsule. This airflow also disperses the powder and prevents aggregation of particles, resulting in delivery of finer particles. Patients who are unable to generate the inspiratory flow and depth of breathing to trigger DPIs should not use these devices. This includes children under the age of 6 years of age, some elderly patients and patients with severe airway limitation either acutely with asthma or acutely/chronically with chronic obstructive pulmonary disease (COPD).

Some DPIs must be held in the correct position during priming (piercing of the doses container, blister or capsule) and inhalation to prevent powder from falling out of the device. Failing to prime the device leads to no medication being administered. Shaking a DPI can lead to inadequate dosing by removing the dose from the inspiratory path. DPIs are also subject to interference as a result of exposure to increased humidity. Patients must always be advised not to breathe into the device prior to inspiration to avoid displacing the powder from the chamber, as well as to avoid humidifying and moisturising the powder.

## **CORRECT DEVICE SELECTION**

All delivery systems may be effective in achieving clinical effects if they are used correctly by the patient.<sup>6</sup> Selection of the appropriate device for each patient requires consideration of multiple factors:<sup>4</sup>

- In which device is the medication available?
- Which device is the patient likely to be able to use correctly, given their age, lung function and general ability?
- For patients on multiple medications: can all the patient medication be prescribed in a similar device?
- Which device is most convenient, portable and acceptable to the patient?
- Cost of the device
- Durability of the device.

## PATIENT TRAINING AND EDUCATION

Language and cultural barriers are significant obstacles to adhering to asthma care in South Africa.<sup>16</sup> It has been calculated that non-adherence probably accounts for approximately 60% of hospitalisations.<sup>17</sup> Intensive asthma education enables better asthma control and reduces emergency department visits, unscheduled doctor visits and hospitalisation.<sup>18</sup> The effect of asthma education is more marked in moderate-severe asthmatics than mild-moderate asthmatics, and education at scheduled follow-up visits is more effective than education given during emergency room visits.<sup>19</sup> Written plans are better than oral instructions and culture-specific programmes are better than generic programmes.<sup>20</sup>

It is not possible to achieve adherence unless the patient is using the correct medication with the correct device and optimal technique. A written action plan modified for each patient documents the patient's regular medication and how to use it. It teaches how to increase short-acting  $\beta_2$ -agonists when necessary and at which level of symptoms to use an emergency dose of oral corticosteroids and seek further medical advice.

Patients should be requested to bring their own medication, devices and spacers with them to every visit to demonstrate the continued functionality of their device and spacer, to allow them to demonstrate to their health-care provider that they can discriminate between their controller and reliever, and to assess residual doses. Inhaler technique should be demonstrated by the patient at each visit, assessed by the health-care provider, and where necessary, training on how to optimise aerosol delivery should be repeated. The National Asthma Education Programme provides patient educational materials, including action plans and information on inhaler devices and how to use them effectively, that can be downloaded from [www.asthma.co.za](http://www.asthma.co.za).

### Declaration of conflict of interest

The author has been sponsored by MSD to attend international congresses overseas, and has been a speaker at events organised by Schering Plough. The author is on an advisory board for Cipla.

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