Personal practice

Inhalation treatment for asthma

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SUMMARY Inhaled medication has revolutionised the lives of many children with asthma. Despite this we see many children for whom appropriate inhaled medication has been prescribed but whose symptoms continue to be poorly controlled. In our experience this is often due to poor technique or inappropriately prescribed devices and an inadequate understanding of when and how to use the treatment. The prescribing physician must have a clear idea of the optimal inhalation technique. We have reviewed the standard devices available and our use of them in the treatment of childhood asthma.

Inhalation of potentially medicinal substances for chest problems has been advocated for hundreds of years,¹ but it is only in this century that the practice has evolved into an established treatment for asthma. The principle of delivering a drug selectively to the target organ, to be effective rapidly, in small doses, and with consequent minimal side effects has been a pharmacological ideal which ostensibly is easily achieved when applied to the respiratory tract. The respiratory tract, however, has several mechanisms that protect it from the entry and deposition of particles. Aerodynamic filtration, reflexes such as cough and sneeze, and mucociliary clearance all contribute to the rapid elimination of inhaled soluble and particulate materials.

How far particles penetrate into the respiratory tract is to some extent governed by their size. Those larger than 15 μm in diameter are removed by the coarse filter of hairs at the nares while particles more than 10 μm are deposited in the nose and nasopharynx where the total cross sectional diameter of the airway is small and consequently the air flow high. These large particles have enough inertia to cause *impaction* on airway walls when the air stream changes direction. Particles of 0.5 to 5 μm chiefly deposit by *sedimentation* as a result of gravitational forces in areas of low flow. There is a rapid increase in cross sectional area of the airways beyond the 10th bronchial division and consequently a rapid fall in air flow. Particles of less than 0.1 μm are deposited mainly as a result of *Brownian motion*, but particles between 0.5 and 0.1 μm are

least effected by sedimentation or Brownian motion and only about 20% are retained in the lung, the rest being exhaled.²

The site and degree of deposition of particles may be further affected by reflexes such as cough and bronchoconstriction and by disease in the lower respiratory tract.^{3 4} The optimum particle size for the deposition of drugs seems to be about 2 to 10 μm , but while it is generally felt that large doses uniformly distributed through central and peripheral airways is an ideal for all inhaled medications, this is not established by objective evaluation. It is possible that different medications may be optimally placed in different areas, that is bronchodilators centrally in muscled airways and steroids peripherally in smaller airways most affected by mucosal oedema.

The method of production of aerosols and the mode of delivery influence the particle size presented to the airways and thus the amount of drug carried to different parts of the respiratory tract.⁴ In about 1856, an 'atomiser' was designed to deliver medication by inhalation and soon became similar to modern jet nebulisers.¹ There are currently three main systems in use:

- (1) Nebulisers;
- (2) Metered dose inhaler aerosols (with or without spacer devices);
- (3) Dry powder inhalers.

(1) Nebulisers

There are two varieties in clinical use, ultrasonic and jet nebulisers.

Ultrasonic nebulisers (Fig. 1). These generate an aerosol by the high frequency oscillation of a piezo-electric crystal close to the respiratory solution. This causes the fluid to break up into droplets that can be inhaled. The advantage of this type of nebuliser is that it is less noisy than jet nebulisers and will deliver a large quantity of liquid over a prolonged time (as needed in humidification). Disadvantages are that most are very expensive and require more care and maintenance than jet nebulisers. The only relatively cheap model requires the patient to breathe in actively to open a valve: this makes it unsuitable for children who may not generate enough force when unwell.

Jet nebulisers. (Fig. 2). These are most commonly used clinically in this country being cheaper than ultrasonic units. Many models are available but the mechanics are similar in all. A high velocity gas jet is blown through a fine hole, creating a negative pressure by the Venturi effect. This causes fluid to be drawn into the jet stream which is impacted on a baffle, breaking up the fluid into droplets. Large particles fall back into the reservoir while the smaller remain in suspension and may be inhaled. The energy for the jet may be generated from an air compressor or a cylinder of compressed air or oxygen. The many different nebuliser units have slightly different properties while the output of the nebulisers is influenced by the flow rate of the gas through them and the volume of liquid nebulised.⁵ Although this is important in standardisation during clinical trials and bronchial provocation tests, it is unlikely to be as important in clinical practice as long as the general instructions for the device are

Fig. 1 Ultrasonic nebuliser.

Fig. 2 Jet nebuliser.

followed,⁶ but certain standards are recommended. A driving flow of more than 6 litres/minute and filling the chamber to 4 ml seems to be optimum to achieve output of particles less than 5 μm , to release 60 to 80% of the solution from the nebuliser, and to limit the time of nebulisation. Even with optimal use only about 12% of a nebulised solution is deposited in the lungs.⁷ The speed of nebulisation of the medication may influence compliance, five to 10 minutes usually being acceptable. There is no information on whether faster nebulisation by more powerful machines is equally effective, provided an equal dose of drug is given. Several trials have shown an additional benefit of a second dose of bronchodilator some time after a first,⁸ implying that a longer duration of administration may be better. The advantages of a nebuliser are that it needs little cooperation, requiring only tidal breathing. Some of the drugs can be mixed and taken simultaneously (for example salbutamol and sodium cromoglycate). Furthermore, oxygen can be used to drive the nebuliser and this may be important in severe asthma to avoid hypoxia. The disadvantages are that it is bulky, requires power (either from a compressed gas cylinder or from a compressor), and is relatively expensive (£35 for a foot pump com-

pressor to £100 for a compact electric unit), although this is still very economical if its use prevents an admission to hospital. When issued for home use, regular maintenance must be organised. The cheaper foot pump compressor is slower in delivering the medication and needs attention and effort just when a parent is concerned with the child. A potentially serious disadvantage is the possibility that the use of nebulisers with bronchodilators at home may lead to delay in seeking appropriate medical help during severe exacerbations leading to an increase in mortality. A recent increase in asthma deaths in New Zealand has been attributed to this⁹ and may be similar to the epidemic of deaths after the increased use of pressurised aerosols during the 1960s.

(2) Pressurised aerosols (Fig. 3)

These have been used to deliver bronchodilators to the lungs for about 25 years, and more recently other drugs active against asthma and even non-respiratory drugs have been available by this method (for example glyceryl trinitrate, ergotamine).¹⁰ The active drug is suspended in approximately 10 ml of a fluorocarbon propellant at high pressure. When the aerosol is actuated, a metered amount of the fluid is ejected under pressure from a valve mechanism. The propellant safety has been investigated and confirmed in normal usage, although reservations exist when the aerosol is grossly misused.¹¹ When the aerosol is actuated and the mixture of drug and propellant leaves the cannister, there is a rapid phase during which about 20% of the propellant evaporates. Further evaporation occurs at a much slower rate as heat is acquired from the atmosphere. The droplets consist of the drug surrounded by a coating of propellant. Immediately after actuation the particle diameter is about 43 μm . This falls to 14 μm at 10 cm from the cannister, and when the propellant has evaporated completely it is 2.8 to 4.3 μm , although this may take several seconds.

Fig. 3 Metered dose inhaler aerosol.

The deposition of aerosols in the lungs has been investigated using radiolabelled teflon particles. With adults using a standard inhalation technique, 80% of the spray was deposited in the mouth, 10% remained in the actuator, 1% was exhaled again, and 9% remained in the lungs.¹² The importance of particle size on penetration to the small airways has been confirmed using terbutaline sulphate.¹³ The effectiveness of the aerosol is considerably influenced by the technique and coordination during use. Actuation during inspiration, a full slow inhalation, and breath holding for 10 seconds at the end of inspiration all improve lung deposition, and thus increase forced expiratory volume in one second (FEV₁) rise if a bronchodilator is used.

The aerosol has the great advantage of being portable but incorrect technique, with lack of coordination between actuation and inhalation results in decreasing quantities of drug reaching the airways. Spacer devices have been developed to overcome these problems.

Spacer devices. Spacer devices have several theoretical advantages. The aerosol used alone causes much of the drug to be impacted on the posterior pharyngeal wall. The extension spacer allows slowing of the cloud of spray by air resistance and more time for propellant evaporation to occur. This presents smaller particles at a lower velocity with more potential for penetration into the peripheral airways. Studies using labelled Teflon particles have confirmed better deposition in the lungs,¹⁴ but the advantage of distribution to small airways remains unconfirmed. Several devices have been produced commercially, larger ones having the advantage of valves at the mouth end (for example Nebuhaler (Astra), Volumatic (A&H), and Multi-spacer (Medic-Aid) (Fig. 4)), but the smaller ones are much more portable (for example Bricanyl and Pulmicort spacer inhalers (Astra) (Fig. 5)). The decreased need for coordination with valved devices is supported by a study in children showing improved response to terbutaline when using the spacer,¹⁵ but the advantage of a spacer may be minimal when good technique with the aerosol

Fig. 4 Pear or cone valved spacer.

Fig. 5 Tube spacer.

exists. During acute exacerbations, when technique deteriorates and bronchoconstriction precludes a big inspiration and a 10 second breath hold, the advantage may be greater.^{16 8} A simple device that has been used by some paediatricians has been a standard disposable plastic coffee cup with a hole in the bottom for the aerosol. This can be placed over the face of a young child and used as an extension tube, having the advantage of being cheap and readily available.¹⁷ Its value has been confirmed for bronchodilators, but not yet for cromoglycate or steroids. The large, reservoir, valved spacers may also be of value in these small children, if they can get their lips around the mouthpiece and generate enough flow with tidal breathing to move the valve, as no special manoeuvres or coordination are required. A breath actuated aerosol has been developed (Pulmadil auto (Riker)) but in general it remains unacceptable to children because of the noise and vibration accompanying actuation.

(3) Dry powder inhalers (Fig. 6)

These consist of simple devices which either pierce or split a capsule containing the drug. The drug particles are mixed with a coarser carrier substance (generally lactose) and when the capsule is opened, inhalation through the device creates turbulent flow or spins the capsule causing the aggregates of powder to be broken up and inhaled. This system may not be as efficient as the aerosol, which means that some drugs must be administered in larger doses for an equivalent effect (for example cromoglycate, 2 mg by aerosol and 20 mg by dry powder), but with others it may be as effective (for example salbutamol and beclomethasone dipropionate). The advantage is that minimal coordination is required. Despite this, a steady full inspiration through the device is needed to empty the capsule and this may be difficult when a child is unwell.

Fig. 6 Dry powder inhaler.

There are several groups of drugs useful in the treatment of asthma which are available by the inhaled route.

Bronchodilators. Bronchodilators have been administered by inhaler for more than 50 years,¹ and because of their rapid and easily measured effects have been extensively investigated.¹⁰ Initially, non-selective sympathomimetic agonists such as adrenaline and isoprenaline were used in aerosols as was aminophylline, a methylxanthine. Although effective, they were associated with cardiac side effects which were initially blamed for the increase in asthma deaths during the mid-1960s. This put inhalation treatment under a 'cloud' from which it has not fully emerged. Despite evidence that other factors were implicated in the epidemic of deaths, there was a relation between excessive use of inhalers, although it was not necessarily causal. Today, there are several selective β_2 -agonist sympathomimetics available for the treatment of asthma. Studies have shown that administration with intermittent positive pressure breathing has no advantage over nebulisation with tidal breathing. In normal subjects and stable asthmatics, the different inhalation methods of aerosol delivery are equivalent when identical doses of drug are administered.¹⁶ Exercise induced asthma is prevented to a greater extent by inhaled than oral medication.¹⁸ In severe acute asthma, supplementation with systemic sympathomimetics, and sometimes corticosteroids, may be required, although in some cases nebulised medication may be as effective as the same drug administered parenterally. Beta agonists given alone during an acute exacerbation of asthma may cause a fall in oxygen saturation due to vasodilatation,

perfusion/ventilation mismatch, and intrapulmonary shunting, although this is less likely with selective beta₂-agonists and its clinical importance remains unclear.¹⁹ Beta agonists may have a poor effect in children less than 18 months old.

The anticholinergic agent ipratropium bromide is also an effective bronchodilator, with few atropinic side effects in normal dosage. It is particularly useful in the toddlers when the effects of beta agonists may be limited. A few older children show a better response to it than to the sympathomimetics, and in some the two drugs have an additive effect. It is available in an aerosol and as a nebuliser solution, the latter now being made up with physiologic saline and not with water, the use of which may be associated with bronchoconstriction due to hypotonicity. The methylxanthines are also effective bronchodilators. Although they have been administered by inhalation, the oral or intravenous routes are preferred because these drugs irritate the airways.

Sodium cromoglycate. This is an effective prophylactic agent for asthma. Its mode of action is not completely understood but it is a potent mast cell stabiliser. This property may not be its only or even the most important effect, as other potent mast cell stabilisers, absorbed orally, have not been shown to be as effective in asthma.²⁰ Cromoglycate is poorly absorbed and is only effective by inhalation. It is available as nebuliser solution, powder aerosol, and an aerosol and the doses which give equivalent effects are 20 mg by nebuliser or powder to 2 mg by aerosol.

Corticosteroids. Corticosteroids are very effective for the treatment of asthma, but given systemically have many serious side effects. Potent topical corticosteroids, which are rapidly metabolised when absorbed, have revolutionised the lives of many moderate to severe asthmatics. They are as effective as systemic steroids in moderate doses without the severe systemic effects. In children, growth retardation when using long term systemic corticosteroids is a particular problem that does not occur with standard doses of inhaled steroids, and as asthma itself can cause growth retardation, some may actually improve their growth rate when started on this therapy.²¹

Oropharyngeal candidiasis is an occasional complication of treatment. It may be related to impaction of the drug on the posterior pharyngeal wall and responds to conventional treatment. If it continues to be a problem it may improve with the use of a spacer device. Dysphonia, which occasionally occurs in adults, is rare in children.

Several inhaled corticosteroids are marketed in

this country, with little to choose between them. They are available as aerosols in low and high doses and one as a powder inhaler. Once cromoglycate has failed to control symptoms and inhaled steroids are begun, there is no value in continuing the cromoglycate. High dose steroid aerosols may be advantageous in a few patients who respond poorly to conventional doses and require systemic steroids.²² Recently, beclomethasone dipropionate has become available as a nebuliser suspension, but in our experience this mode of administration is not as effective as the others. The reasons for this remain to be delineated.

Clinical usage

The advantages of inhalation treatment are as great for children as for adults, but the problems of compliance are greater, particularly in the younger group. Our practice is as follows:

Under 18 months of age. Inhalation therapy is usually only possible using a nebuliser, although an aerosol and cup spacer may occasionally be of use. In an acute episode of wheezing, beta agonists may not be as effective as they later become, perhaps due to immature beta receptors, but they are worth trying, to evaluate the effect. If they are not helpful, ipratropium bromide may give temporary relief of symptoms. For frequent symptoms, regular nebulised cromoglycate may be effective prophylaxis. Unfortunately the equipment is bulky and expensive, and treatment is time consuming. For many children, oral medication may be more acceptable, and they should be given a treatment trial before resorting to nebulisers.

From 18 months to 4 years. Beta 2 agonists become more effective at this age and some use may be made of the valved spacers, but in general, the nebuliser remains the mainstay of inhaled treatment. As soon as the child is able, a mouthpiece is preferable to a face mask to avoid deposition of drug on the face and eyes. Again, oral medication may be more useful in some patients.

From 4 to 8 years. Children of this age can gain increasing skill in using the powder inhalers as minimal coordination is required. This reduces the time required for treatment and improves portability of equipment, as well as enabling the use of inhaled steroids for those resistant to cromoglycate prophylaxis. In some, the powder is thought to be unpleasant, and cromoglycate may cause transient cough (which may be alleviated by pretreatment with a bronchodilator). The valved spacers in conjunc-

tion with the aerosol may have an advantage in some patients who prefer this technique but the powder systems allow greater parental control of dosage as the capsules used can be counted—unlike the aerosol which has 200 doses, the fates of which are more difficult to trace.

From about 8 years of age. At this age children gain enough coordination to use the aerosol effectively when trained, allowing them the full range of treatment now available. A spacer attachment may help to deliver a bronchodilator in acute exacerbations but seems to have no advantage for maintenance treatment in those able to use the aerosol efficiently. Again, in those who have difficulty in coordinating, the valved devices may be helpful.

The technique for the aerosol that we teach here is:

- (1) Shake the aerosol and remove cap;
- (2) Exhale to a comfortable point below functional residual capacity;
- (3) Place the aerosol between the lips;
- (4) Take a full, steady breath in, to a point near total lung capacity and simultaneously actuate the aerosol;
- (5) Hold the breath in for a count of 10 (or as long as possible).

Beginning of inhalation should precede actuation, and we try to coordinate the actuation early during inspiration, although, surprisingly, this is not as important as the slow, steady inhalation and subsequent breath holding.⁴ Holding the aerosol in front of an open mouth does not seem to be an advantage.

Common faults in technique that we have encountered are:

- (1) Actuation after completion of inhalation;
- (2) Actuation during expiration;
- (3) Actuation with tongue or teeth blocking the aerosol;
- (4) No inhalation (this may occur despite dramatic movement of the head and shoulders);
- (5) Inhalation through the nose after actuation into the mouth;
- (6) 'Snatched' or rapid inhalation;
- (7) Failure to hold breath after inhalation.

These are examples of some of the many errors that must be carefully sought and eliminated. The technique is slightly modified with powder inhalers. The long inhalation needs to be somewhat more powerful (perhaps to create enough turbulent air flow to break up the carrier/drug particles) but coordination is not required and breath holding may not be as important.²⁵ The aim is to empty the capsule of powder in one, or at most two breaths.

When using a valved spacer, they take several

breaths through the device for each actuation, the number depending on the size of the child, with a breath hold at the end of inspiration.

It must be emphasised that in our experience, the main cause of failure of inhalation treatment in children is inadequate technique with the device used or an inappropriate device for that age. A large proportion of children who attend our clinic have previously been prescribed suitable treatment and only require training in when and how to use it. It should be the responsibility of the doctor prescribing an inhalation device to teach its effective use and to check technique at subsequent visits. Although this responsibility may be delegated to another member of staff, a physiotherapist or a practice nurse who has learnt the techniques, the doctor must know the optimal use of the devices prescribed. Aids for teaching technique, placebos and whistle attachments for powder inhalers may help individual patients but there is no substitute for correct tuition. Time spent on this pays dividends in improved control of symptoms.²³ In our department the physiotherapists teach the technique and at the same time train the children in controlled breathing to aid relaxation during exacerbations.

It is also important that the child or parents, or both, know what to do in case of failure of inhalation treatment. In acute exacerbations there may be a relative resistance to beta agonists, difficulty with inhalation technique, and a limitation of inspiratory, as well as expiratory flow,²⁵ so if poor response to the aerosol or powder system is encountered, a nebuliser, with its relatively higher dose, and easier technique should be tried. This may require calling in the family doctor or visiting the casualty department.

There has been an increase in asthma deaths in New Zealand over the past few years and it has been suggested that this is due to an abuse of nebulisers and bronchodilators available over the counter there.⁹ The delay in seeking treatment when using these devices in severe exacerbations may be similar to that thought to have caused the epidemic of deaths associated with the excessive use of aerosols in the 1960s, and so great care must be taken when supplying inhalation devices for home use now. When patients have them at home they should have clear, written instructions on which drugs to use when, and exactly how to make up the solutions for use in the nebuliser. They must also know what to do should that treatment fail to give relief of symptoms and when to seek further help. Therefore our instructions for salbutamol or terbutaline are:

- (a) Careful assessment of the effect of treatment must be made, including, if possible, peak flow recording before and after treatment;

(b) Failure to improve means that further medical help must be sought at once;

(c) Improvement which is transient, with deterioration to the previous state or worse within four hours or less needs similar review;

(d) The nebuliser must not be used more frequently than four hourly;

(e) If the child is very ill or deteriorating rapidly, help must be sought at once, as well as giving the bronchodilator.

It is in these situations that further intervention such as systemic bronchodilator or steroid may be needed to prevent deaths,²⁴ so delay in seeking help must be avoided.

Although we have confined this article to the use of inhalation treatment in asthma, it is used in other conditions, with other drugs. In cystic fibrosis, for example, as well as some use in asthma treatment, the inhaled route has been used for antibiotics and mucolytics.

Future developments include the use of other drugs with potential activity in asthma such as: calcium antagonists, new antihistamines, new xanthines and non-steroidal anti-inflammatory drugs, as well as possible further development of inhalation devices such as breath activated aerosols and multiple dose dry powder inhalers to make them more acceptable to patients.

Nearly 50 years ago, Collison (an English physician) wrote, 'Asthmatics speak of this treatment with enthusiasm compared with the usual forms of therapy . . . The inhalation of adrenaline will stop or avert the attack, and when it is supported by a carefully prescribed course of curative treatment the paroxysms diminish in frequency and the asthmatic habit becomes broken and the tendency to further attacks definitely reduced.'¹ If we change the words 'adrenaline' to 'selective beta 2 agonists', and 'curative' to 'prophylactic', the statement is right up to date. The words 'carefully prescribed' may need underlining as they particularly apply to the training in the use of inhaler devices.

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