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Treatment of Childhood Asthma

Options and Rationale for Inhaled Therapy

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Summary

Epidemiological studies suggest the prevalence of asthma is increasing, though some remain sceptical as to the magnitude or indeed the presence of an increase. However, despite improved diagnosis and the availability of the potent drugs now available, there remains considerable respiratory morbidity associated with asthma.

It is clear from a number of studies that failure to deliver drugs to the lungs when using inhaler devices is a factor contributing to this high level of morbidity. Failure of drug delivery may result from the prescribing of inappropriate

devices, failure to use devices appropriately or failure to comply with a treatment regimen.

For most of the currently available forms of asthma therapy there are significant advantages to be gained from administering them in aerosol form. The benefits to be derived from administering these drugs as an aerosol include a rapid onset of action for drugs such as β-agonists and a low incidence of systemic effects from drugs such as β-agonists and corticosteroids.

Over the past 25 years our understanding of the nature of asthma has changed. Though this has been reflected in the emphasis on inhaled corticosteroid therapy in recent guidelines, it has not been reflected in the range of inhaler devices available. Manufacturers continue to place drugs such as corticosteroids in the same devices as short acting β-agonists even though the requirements for these different drug classes are very different. It is likely that this contributes to suboptimal therapeutic responses with inhaled corticosteroids. However, the variability associated with current delivery systems is relatively small compared with the variability introduced by poor compliance. There is no work currently available to indicate how the use of cheap disposable devises which do not incorporate any form of positive feedback influence compliance with inhaled steroids.

Optimising aerosolised drug delivery in childhood involves consideration of the class of drugs, the particular drug within a class but more importantly, the age and abilities of the child. Devices must be selected to suit a particular child's needs and abilities. Devices utilising tidal breathing are generally used such as spacing chambers or, less commonly these days, nebulisers. A screaming or struggling child, or failure to use a closely fitting mask, reduces drug delivery to the lungs enormously. Failure to respond to inhaled therapy in early childhood may be attributable to failure of drug delivery. Drug delivery in early childhood using current devices remains more an art than a science.

1. An Increase in the Prevalence of Asthma?

The evidence indicating an increase in the prevalence of asthma has caused controversy.[1,2] There are fundamental problems with the definition of asthma for the purposes of epidemiological studies. The huge variation of epidemiological methodologies has made direct comparisons within and between countries difficult. Attempting to make firm conclusions about the change in the prevalence of asthma over time is equally problematic. Only since data from paired studies have been published has it appeared that childhood asthma has increased.[3-6]

Serial studies from the UK[3-6] and evidence from other countries[7-9] have suggested that the prevalence of diagnosed asthma and wheezy illness in children may have doubled over the past 20 years. However, even in these paired studies the methodologies were not identical.[5] It is interesting that, although there are no comparable studies in adults in the UK, data from other countries suggest that a similar increase is occurring in adults.[10] The possible reasons for this increase are complex,[10-12] and it has been generally accepted that it is not simply a consequence of the alteration of diagnostic labelling[13] or of improved diagnoses.[4,14]

A cautious analysis of the published epidemiological data, bearing in mind the methodological differences, would suggest the following probable trends:

- There has probably been an increase in the 12-month prevalence of wheeze. The possibility has been suggested that, in the UK, this observed increase has stabilised at about 14%

(range 11.5 to 19.8%) over the past 10 years.[2] However, although recent data suggest that even over the past 5 years the prevalence of wheezing in the UK may still be increasing,[15] this still needs to be confirmed in other areas.

- There appears to be greater willingness of doctors to diagnose asthma. Furthermore, there may also be a greater likelihood of wheezing and asthma being reported by parents in questionnaire surveys because of the greater awareness of asthma.[16] There has been an increase in the number of wheezy children being diagnosed as having asthma. Only 11.0% of wheezy children were diagnosed as having asthma in Newcastle in the late 1970s,[17] but recent studies suggest that between 50 and 60% of symptomatic children are currently being diagnosed as such.[3,18]
- Although the diagnosis rate for asthma has increased, there is still strong evidence for the undertreatment of symptoms, accounting for much morbidity.[18,19] There are certain groups of people with asthma who appear to be at higher risk for undertreatment, such as those from minority ethnic cultures.[20]
- The cumulative prevalence of wheezy illness does not appear to have substantially increased. Thus, it has been considered that over the past 3 decades, the incidence of asthma may not have substantially increased. The increase in the period prevalence of symptoms may simply reflect an increase in the severity of symptoms[2] in a relatively stable population of individuals genetically predisposed to asthma. However, most of the cumulative prevalence questions about wheeze in the prevalence studies are retrospective. Thus, the questions are subject to parental recall bias, so the premise that the cumulative prevalence of wheeze has not increased needs to be questioned.

Even with paired study data there is still great difficulty in making the clear conclusion that the prevalence of wheezy illness and asthma has definitely increased. Exercise challenge[21] and inhalation tests[22,23] have been devised to support subjective questionnaire data with objective measurements of bronchial hyperreactivity (BHR). In both cross-sectional and longitudinal studies, however, tests of BHR are insensitive and insufficiently reproducible to be useful for a direct measurement of asthma in the community. Nevertheless, they may give some idea about the severity of disease in a community.[24-26]

The development of the International Study of Asthma and Allergies in Childhood (ISAAC)[27] has attempted to standardise the questionnaire data collected from worldwide studies of childhood epidemiology. There are now over 161 centres worldwide using the same standardised study format.[28] Thus, it is hoped that this standardisation will enhance the ability to compare data of childhood respiratory symptoms over time and between countries.

2. Difficulties in Making a Firm Diagnosis

There is no simple test which can be used to make a firm diagnosis of asthma, and this poses problems for diagnosing those with atypical symptoms. A number of issues, such as a reluctance to label an individual as having asthma, have contributed to its underdiagnosis in the past.[29,30] Though underdiagnosis remains a problem,[18] it is now accompanied by an increasing trend towards overdiagnosis or apparently overaggressive treatment.[19,31,32]

The new British Guidelines on Asthma Management [British Thoracic Society (BTS) Guidelines] emphasise the need for correct diagnosis and the dangers of escalating treatment in other conditions that produce similar symptoms.[33] It is easy to blame a lack of response to treatment on poor adherence or poor inhaler technique, or be convinced that there has been a response to an intervention. The message that asthma is common and should be treated appropriately should not obscure the fact that in childhood other conditions present with similar symptoms. Diagnosing asthma can be difficult in patients of all ages but it is increasingly clear, particularly in very young children, that all

wheezes are not 'asthma'. Even after excluding conditions such as chronic lung disease of prematurity, cystic fibrosis and recurrent aspiration, it is clear that there are distinct subgroups among infants who wheeze.[34-36] Unfortunately, a lack of clear understanding of the pathology and natural history of the disease entities represented by these subgroups has resulted in various diagnostic labels being used for the same entities.

In the UK and Australia, there has been an enthusiasm to label all infants and young children who recurrently wheeze as having asthma. This is based on a retrospective study performed in Melbourne[37] and the recognition that many children with 'atopic asthma' were not being treated or were being undertreated. Recent cohort studies have confirmed the results of much older studies which showed clearly that most infants who wheeze grow out of this tendency in early childhood and clearly do not have 'atopic asthma'.

The term 'wheezy bronchitis', used to describe infants with apparent viral infections and an associated wheeze, was discredited for many years. More recently, terms such as wheeze-associated virus episode (WAVE) have been advocated by some to categorise those who wheeze during viral infections.[38] In the USA, the term 'acute bronchiolitis' is used to describe this group of patients. In the UK and Australia, however, 'acute bronchiolitis' is reserved for a distinct clinical entity, that usually caused by the respiratory syncytial virus in which the characteristic auscultatory findings are crepitations rather than wheeze/rhonchi.[39]

Differences in labelling account for some of the conflicting results observed in therapeutic trials (of which there are surprisingly few in very young children). Diagnostic transfer, that is, relabelling children previously categorised as having 'wheezy bronchitis' or a 'chest infection' as now having 'asthma', may account for much of the rise in asthma diagnosis in very young children over the past decade. A failure to discriminate between these entities may well account for many of the apparent treatment failures in young children. Further work is required in this area to improve our understanding, labelling and therapy of disease in this age group.

Those children who have cough alone, without wheeze, pose a number of problems, e.g. should they be diagnosed as having asthma? The recognition of 'cough variant' asthma has led to many children with recurrent cough, particularly those with a reported excessive nocturnal cough, receiving bronchodilators and inhaled prophylactic therapy.[40,41] The proportion of children with asthma that have cough alone (in the absence of wheeze or shortness of breath) is unclear, although data from Sheffield suggest that in 8- to 10-year-olds it may be about 14% of those currently labelled as having asthma.[18] To date, 'cough variant' asthma has been essentially defined by the response of this symptom to anti-asthma medication, particularly inhaled steroids.[42] Recent studies have suggested that most children with a reported recurrent cough do not fall within the 'umbrella' of atopic asthma.[43,44]

Follow-up studies suggest that, as with asthma, the prevalence of cough is fairly constant. In those with coughing alone, 2 recent surveys suggest that most children have a reduction in the frequency of their coughing, or stop, and only about 20% progress to demonstrate more typical asthma symptoms.[45,46]

There are, however, problems with the study of cough: (i) the symptom of cough is poorly reproducible on questionnaires;[47] and (ii) cough is unreliably reported when compared with objective measures such as nocturnal recording.[48,49] Cough sensitivity is clearly different between children with asthma and those with recurrent nonspecific cough,[50,51] and these data may lead us to a better understanding of the relationship between asthma and cough. Currently, the exact relationship of chronic cough to asthma remains unclear and, indeed, controversial.[52]

3. Treatment Options and Rationale

3.1 Drug Treatment

3.1.1 Inhaled Steroids

Our understanding of the nature of asthma has fundamentally changed over the past 30 years and this has been reflected in the approach to therapy. Asthma is now recognised to be a disease that is characterised by inflammation within the airways which results in a constellation of symptoms.[53,54] Airways hyperreactivity *per se* is no longer thought to be the basic problem. Consequently, the emphasis on treatment has shifted from the relief of bronchospasm as required to a position where anti-inflammatory therapy is recommended for all patients with asthma except for those with disease at the milder end of the spectrum.[55]

There has been a substantial increase in the use of corticosteroids,[56] even in the US where, traditionally, there has been a marked reluctance to use this class of drugs.[57] The recognition that bronchospasm is a secondary, though very important, phenomenon has relegated bronchodilator therapy to a supportive role in the recent BTS guidelines.[33] This has been accelerated, in part, by concerns regarding the potential harmful effects of using bronchodilators on a regular basis.[58] Additionally, the recognition that inhaled steroids, given at standard doses, rarely result in clinically significant adverse effects, has reinforced this trend.[59]

The BTS Guidelines, based on expert consensus,[33,60] emphasise the role of anti-inflammatory treatment for asthma both in adults and children. These guidelines reinforce the current evidence that the benefits of using inhaled steroids to treat patients with moderate or severe atopic asthma far outweigh their potential harm.[33]

An improved control of asthma, resulting from the delivery of anti-inflammatory drugs to the lungs, can reduce hospital admissions.[61] Furthermore, patients derive considerable benefit in terms of reduced morbidity when appropriate treatment is instituted.[61-63] The annual cost of treating patients with asthma is substantial. In the UK alone in 1994, the cost of paediatric asthma care was estimated to be significantly in excess of £100 million.[16] It is possible that this cost could be reduced by optimising maintenance treatment, thus reducing the very substantial costs associated with hospitalisation.

The early institution of anti-inflammatory therapy may have long term beneficial effects on the natural history of asthma. Studies in adults suggest that the early introduction of effective anti-inflammatory therapy can have long term benefits in terms of disease severity and lung function.[64] In a study of 105 adults, Selroos et al.[65] suggest that the use of inhaled steroids in patients with mild-to-moderate asthma may prevent subsequent chronic airways obstruction. A study of 216 children aged 6 to 13 years has provided some support for this concept in paediatric patients;[61] however, it must be emphasised that this was an uncontrolled study. Thus, the exact role of inhaled steroids in influencing the long term outcome of children with asthma is still unclear.

The adverse effects of inhaled steroids remains an area of intense interest and study. The main areas of concern in children have recently been reviewed, and concern their effects on:

- short and long term growth;[66,67]
- bone turnover and effects on growing bone;[66-68] and
- inhibition of the hypothalamic-pituitary-adrenocortical axis.[66-68]

The main conclusions from these review articles are that the benefits of inhaled steroids outweigh the possible adverse effects and that the emphasis should be on the treatment of the asthma.[33] Poorly controlled asthma will have a deleterious effect on growth *per se*.[69] However, it should be emphasised that it is desirable to use the minimum maintenance dose of inhaled steroids to control the child's symptoms.

3.1.2 Inhaled β-Adrenoceptor Agonists

Short-acting β-adrenoceptor agonists (β-agonists) are primarily intended to provide relief from

symptoms, and patients should use the minimum dosage necessary to control their symptoms on an as-required basis.[33] The major effect of β-agonists is bronchodilation which is mainly caused by the direct relaxation of airway smooth muscle. They have other potential therapeutic features including: possibly influencing mucociliary clearance,[70] reducing vascular permeability,[71] inhibiting the release of histamine from mast cells[72] and exerting effects on cholinergic neurotransmitter function.[73]

For the treatment of acute wheeze and for the prevention of pre-exercise wheeze in school-age children, short acting β-agonists have a clear role.[74,75] β-Agonists are also the primary treatment for acute asthma.[76-78] Long-acting β-agonists are now recommended for use in step 3 of the new BTS Guidelines, i.e. for use with low dose inhaled steroids.[33] Recent work in adult patients has demonstrated that long-acting β-agonists have a narrower therapeutic window compared with salbutamol. Thus, they should be prescribed at the lowest effective dose, twice daily rather than as required. In addition, these data give supportive evidence for the use of these agents in step 3 of the BTS Guidelines.[79] They may also be used successfully for the treatment of nocturnal wheezing[80,81] and for exercise-induced wheezing.[80,82]

Orally administered β-agonists have been widely used, particularly in the treatment of young children, but as in all age groups, the systemic adverse effects resulting from their oral administration are far greater than those resulting from aerosol delivery.[83] It can be argued that at least some of the drug will reach the lungs if administered orally and, for this reason, some clinicians still prefer to use this option in infants. Long-acting β-agonists have been used to control symptoms, particularly nocturnal symptoms, but again it is likely that their usage will decline with the advent of long-acting inhaled β-agonists.[81] It appears that clearance of β-agonists is slightly higher in children than in adults but this is unlikely to be of any clinical significance.[84]

3.1.3 Theophyllines

Theophyllines have both anti-inflammatory and bronchodilator properties[85,86] and hence possess attributes desirable for the maintenance treatment of 'asthma'. However, they must be given enterally or, in acute situations, parenterally, resulting in a relatively low therapeutic index. The need for monitoring and the potential for serious adverse effects has led to a marked reduction in their use in most countries, including the US.[57]

Although most protocols have relegated theophyllines to the third or fourth line of therapy, recent work suggested that they may have beneficial effects at plasma concentrations below those traditionally used to achieve bronchodilation.[86,87] This has prompted some to argue that low dose theophyllines are valuable in some patients whose asthma is poorly controlled by inhaled steroids.[86,87]

In contrast to other forms of treatment, there is an extensive body of literature on the pharmacokinetics of theophyllines in children and these studies have been recently reviewed in a number of publications.[57,85,88] The necessity for monitoring plasma concentrations of theophyllines is one of the great drawbacks of this group of agents and has contributed to the decline in their use in the UK. As mentioned, some authorities now argue that theophyllines may have a role when used at lower dosages than those traditionally used. It is possible, therefore, that monitoring will not be required when they are used at 'anti-inflammatory' rather than bronchodilator dosages. The elimination of theophyllines can be reduced by a variety of pathological conditions, such as cardiac failure, liver disease and hypothyroidism, causing impaired metabolism. It can also be reduced by viral infections leading to persistent pyrexia and a range of drugs including erythromycin, cimetidine and ciprofloxacin. Such concerns have also contributed to the decline in popularity of this form of therapy.

3.1.4 Cromoglycate and Nedocromil

Sodium cromoglycate and nedocromil sodium have been widely advocated as first-line anti-

inflammatory agents for the treatment of asthma in childhood. This has been largely due to their safety profile. In some children, they are undoubtedly effective,[89] but in many they are ineffective and it is unclear how much this can be attributed to noncompliance and how much is a result of the relative lack of anti-inflammatory efficacy of the drugs. A recent study has suggested that it is possible that these drugs may be less effective than steroids in preventing irreversible impaired lung function.[61] Further studies are required to confirm this and to determine whether it is of clinical significance.

3.2 Inhaled Therapy

The benefits of inhaled therapy over orally administered treatment. for drugs with systemic adverse effects, have been clearly demonstrated in many studies using β-agonists.[83,90,91] The onset of action is far more rapid and the maximal therapeutic effect is achieved with far fewer systemic adverse effects. There is little doubt that the systemic adverse effects of steroids are greatly reduced when they are inhaled rather than given systemically. Other drugs, such as sodium cromoglycate, are ineffective when given orally and, therefore, must be inhaled to be effective. Recent advances in anti-leukotrience intervention may improve oral therapy options for asthma, but there still needs to be further clinical studies of these agents.[92]

Aerosolised drug delivery has been used for hundreds of years[93] and many of the factors necessary to maximise drug delivery have been known for many decades. Nevertheless, our knowledge regarding the pattern of deposition of aerosols within the airways and the subsequent fate of the drug is still, in many ways, quite rudimentary. For instance, it is clear that drug deposition will not be uniform along airways, with deposition caused by impaction occurring at or near bifurcations and deposition by sedimentation occurring along dependent portions of the airway.[94] How a drug reaches its site of action through the mucus layer of the airway and epithelial layer has yet to be clearly described. It is known that a host of factors such as disease, exercise and smoking can enhance permeability[94,95] but there have been no such studies performed in children.

Current imaging techniques give, at best, a relatively crude picture of deposition within the airways.[96] In the coming years, newer imaging techniques using powerful computing programs may improve our understanding in this area.[97] The relative tolerability of inhaled therapy for asthma is one of the reasons that more is not known about many of these important areas since there been no urgent need to improve current treatment which, largely, has evolved empirically. However, it has been proposed that, in future decades, an enormous range of nonasthma drugs will be delivered as aerosols and our understanding will, out of necessity, improve before such potent drugs are delivered via this route.

3.3. Confusion and Problems Surrounding the Use of Inhalation Therapy

There are more than 100 portable inhaler–delivery system combinations currently on the market. Clinicians are continually exposed to presentations designed to convince them that a particular delivery system or drug has clear benefits over similar devices or drugs. This barrage of information will mount with the impending arrival of an increasing number of chlorofluorocarbon (CFC)-free, pressurised metered-dose inhalers (pMDIs), particularly as not all manufacturers are following the dose-for-dose 'bioequivalence' approach.

Portable inhalers have undoubtedly contributed to an improved quality of life for many millions of asthma patients since the first pMDI was marketed in 1956. This improvement was particularly noticeable after the advent, more than 25 years ago, of inhaled anti-inflammatory drugs, such as sodium cromoglycate, and corticosteroid preparations.[93] However, despite the enormous annual expenditure on such drugs, there is little evidence that therapy has had a significant effect on mortality. It is argued that since the mortality rate has

changed very little over the decades, despite an apparent increase in the incidence of asthma, the management of asthma has saved lives, particularly over recent years,[98] although the downward trend in asthma mortality in Britain may be due to an increased use of prophylactic treatment.[99] However, there appears to be little doubt that the use of portable inhalers contributed to the epidemic of asthma-related deaths in many countries in the 1960s and probably played a part in a similar episode in New Zealand in the 1980s.[100] The exact role of inhaled β-agonists in these epidemics remains the subject for debate but it seems quite likely that β-agonists delivered via portable inhalers have contributed to an excess of asthma deaths over the last 40 years.[55]

Inhaled therapy clearly has its own particular problems, especially because the respiratory tract, unlike the gastrointestinal tract, is designed to exclude foreign objects. Combinations of factors such as airways geometry, cough and mucociliary clearance are all designed to exclude or remove foreign objects from the airways. Human evolution has failed to design out a weakness in these defences: objects between 1 and 10μm in diameter can penetrate and deposit in the lungs (a red blood cell is approximately 7μm. Smaller objects tend to be exhaled while larger objects tend to deposit in the upper airways. The proportion of objects of a given size within this range deposited in the lower respiratory tract and the pattern of deposition is influenced by a host of interrelated factors. These factors include inspiratory flow, breath holding, differences in upper airways geometry, nasal versus mouth breathing, posture and, very importantly, airways disease.

Aerosol drug delivery systems are designed to exploit this remarkably narrow window of opportunity. Unfortunately, the use of these devices is not intuitive, as evidenced by the enormous efforts required to educate nurses, doctors, pharmacists and patients. Despite these efforts, it is clear that most of these individuals still do not know how to optimally use these devices.[101-103] One of the principal reasons for this is that it is rare for any of these groups to receive any training in the relatively simple basic concepts that underlie aerosol therapy.

These difficulties have a number of effects. Patients are often prescribed inappropriate devices that they cannot use.[102,104] They are not shown how to optimally use these devices and when they are, their technique frequently becomes suboptimal within weeks.[102] One of the reasons for this may well be the device itself. It is a historical accident that drugs such as inhaled steroids were placed in the same devices as β-agonists. This was because the devices were available and marketing divisions perceived an advantage in promoting a common device. Unfortunately, β-agonists are extremely potent and will frequently produce a very good response despite suboptimal inhaler technique. If the response is suboptimal, the patient simply inhales a further dose. The perception of the patient becomes that it does not really matter how the device is used.

Recent developments in inhaler devices, such as multidosing and dose counters, have concentrated on convenience or on cost, particularly with the novel devices for generic drugs that are out of patent. No thought appears to have been given to the different needs of bronchodilator therapy and inhaled prophylactic therapy. The former generally needs to be available in a convenient portable form whilst the reproducibility of lung doses, though desirable, is not necessary. For inhaled steroids used twice daily, very small devices are not necessary whereas reliable and reproducible lung doses are important. Adherence with inhaled prophylactic therapy regimens appears to be even worse than with oral prophylaxis.[105] Devices specifically designed for inhaled therapy should be simple and, as far as possible, intuitive to use, provide feedback on levels of adherence and ensure that lung dose reproducibility is improved.

There has been much debate on the need for equivalence when changing from CFC pMDIs to non-CFC hydrofluoroalkane (HFA) devices. It should be remembered, however, that for any indi-

vidual patient, it is not known what is the required lung dose of a given steroid and, more importantly, what dose that patient is achieving when they use a particular device. The evidence is that, for current devices, the inter- and intra-individual variation in clinical use is extremely high, even when factors such as levels of adherence are excluded. Clinicians generally adopt the pragmatic approach of using the lowest effective dose once control has been established. All of these problems tend to be compounded when treating asthma in infants and young children.

3.4 What Affects Drug Delivery to Infants and Young Children?

The ability of children to comply with complex instructions increases with age. In young children, tidal breathing must be relied upon to achieve effective drug delivery and, hence, delivery systems are limited to nebulisers and holding chambers with face masks. In this age group, the use of face masks will result in nasal breathing and reduced drug delivery. From 2.5 to 3 years of age, children are able to 'pant' when inhaling from holding chambers. Pharmacodynamic studies using β-agonists suggest that this is as effective as taking large breaths[106] but, because supramaximal doses are generally used, it is possible that drug delivery to the lungs may not be equivalent. Between 5 and 6 years of age, most children can effectively use dry powder inhalers (DPIs) and pMDI/holding chambers. Few can effectively use pMDIs alone.

Over recent years, studies have started to clarify the relationship in children between prescribed dose and lung dose. *In vitro* and *in vivo* studies have suggested that for a given nominal dose, the inhaled dose, when corrected for bodyweight, is maximal in infancy for both jet nebulisers and pMDI/holding chambers.[107-113] However, tidal breathing together with nose breathing significantly reduces the lung dose. It appears that the lung dose achieved when treating infants, at least when they are relatively well, is at least comparable with that achieved in adults when corrected for bodyweight. The intra-individual variation is high, as it is in adults,[114] and upper airways deposition is relatively high compared with that described in adults. Static charge of the device may reduce the amount of drug available for inhalation. BTS Guidelines recommend that spacers should be washed, rinsed and dried in air once a week and not wiped dry, as this increases the electrostatic charge.[33]

It is clear that to achieve this level of drug delivery infants must tolerate a closely fitting mask and should not be struggling or crying. Placing a face mask, even a short distance from the face,[109] or treating a screaming child[112,115] results in greatly reduced drug delivery to the lungs.

3.4.1 Holding Chambers with Face Mask

The concept of attaching a face mask to a holding chamber was first described in the late 1970s[116] but it was a decade later until the use of such devices became more widespread. These devices generally comprised chambers designed for adults that were modified by simply attaching a face mask.[109] Subsequently, a number of devices have appeared that are specifically designed for this age group, such as the infant Aerochamber, the Babyhaler and the non-electrostatic (NES) spacer. These are generally smaller and easier to handle and also have a low dead volume and valves that operate at the low flow generated by infants. Chambers of large volume are still widely used as they are available and do deliver the drug to the lungs if tolerated. However, it is important to tilt the chamber to ensure that the valve remains open because they do not operate effectively at low flows.

A range of *in vitro* and *in vivo* studies have been undertaken to compare the effectiveness of these devices. All of these methods have potential problems.[117] It is clear that all of the devices can deliver drug to the lungs of infants and that factors such as noncompliance, screaming or struggling are going to affect drug delivery far more than the choice of device. If all other factors were equal, it would be desirable to use the most efficient device

but the choice of device will inevitably be influenced by cost, availability and most importantly, patient acceptability. These devices have been increasingly used over recent years because of their convenience. As discussed in section 4, there is relatively little evidence that 'asthma' drugs are of great value in many infants with viral-induced wheeze. In most children, the commencement of therapy should be viewed as a therapeutic trial, and this should be explained to the parents.

3.4.2 Dry Powder Inhalers

DPIs have been a very useful addition to the forms of inhalation treatment. Their principal advantage for treating asthma in children is that they do not require the coordination of actuation and inhalation. Their principal drawback is that the energy required to disperse the dry powder particles is generated by the patient's inspiratory effort. Consequently, the disaggregation of particles is relatively inefficient when these devices are used by smaller children as they are unable to impart sufficient energy to generate high flows through the devices. It is clear, however, that beneficial clinical effects can be seen when some very young children use DPIs.[118,119] Although the absolute lung dose will be reduced, it is possible that therapeutic effects are seen because the bodyweight–corrected dose is adequate.

A recent radiolabelled deposition study was carried out in cystic fibrosis patients using the Turbohaler.[120] It showed that, although the absolute lung dose was lower in the younger children, the bodyweight–corrected dose appeared remarkably constant, at approximately 1 to 2 mg/kg, in children ≥5 years of age. It is of interest to determine whether this is a property of DPIs in general. Such a finding may not be a feature of some newer devices whose function is said to be relatively independent of flow.

4. Treating the Wheezy Infant and Preschool Child

There are great changes in physiology, drug metabolism, lung architecture and growth as children develop. Many of these changes occur in the first year of life and their effects on disease manifestation and response to treatment are poorly understood. It is well known that the response to 'asthma' therapy is generally poor in infancy and it has been postulated that infants' failure to respond is attributable to 'immature' β-adrenoceptors or an absence of bronchial smooth muscle. However, from a number of infant lung function studies, it is now clear that the airways of infants are capable of responding to both bronchoconstricting stimuli and to bronchodilating agents.[121]

Since we know that the airways of infants can respond to bronchodilators, it is likely that treatment failure is caused by either a failure to deliver the drug to its site of action or factors such as airways fluid and mucosal oedema playing a relatively greater role in the causation of airways obstruction. As discussed, it appears that drugs can be effectively delivered to the lungs of infants if the technique is optimised. Therefore, it would appear that, in many infants with airways obstruction, a failure to obtain therapeutic effects is largely caused by the use of inappropriate forms of therapy.

There are current recommendations for the stepwise treatment of wheezy children <5 years old[33] and wheezy infants.[122] About 30% of infants experience recurrent wheeze but this can be further subdivided into 10% with chronic wheeze or episodic wheeze with interval symptoms and 20% with episodic wheezing and no interval symptoms. A further 3% of infants will either have been born prematurely, have a chronic respiratory disorder other than asthma or have postbronchiolitic wheezing.[122] As yet, it is unclear how these different subgroups respond to treatment and if treatment affects outcome. However, the general outcome for wheezing in infancy is good; the 3 main associated factors suggesting a poorer prognosis are prematurity,[123] atopy[124] and frequency of attacks.[125]

5. Currently Available Drug Delivery Systems

5.1. Factors to Consider

When considering delivery systems for children, the following factors need to be kept in mind:

- Is the device suitable for the age group in question? Is it likely that an individual patient will be able to use a device and will it reliably deliver the drug to the lungs of patients of that age?
- Is the device acceptable to the patient? An older child is more likely to use a device that they like and, for younger children, acceptance of a device is essential for effective drug delivery.
- Is the device-drug combination likely to minimise systemic effects for a given clinical benefit? Because the systemic availability of different steroids entering the gut varies, the choice of drug can influence the range of possible delivery systems.

As β-agonists have such a wide therapeutic index, the first 2 factors, together with the issue of cost, are of importance. Suboptimal drug delivery on a given occasion that results in incomplete relief is soon corrected by the use of additional doses. For inhaled steroids, the issue of the systemic availability for a given therapeutic effect becomes more important and influences the range of devices available. Traditional pharmacokinetic considerations are relatively unimportant when considering inhaled drugs because of the relatively wide therapeutic index that results from delivering drugs directly to the lungs. The major exception is when considering the potential for inducing the systemic adverse effects of inhaled steroids, particularly when high prescribed doses are being used.

The importance of the steroid/inhaler combination in determining the ratio between efficacy and potential for systemic adverse effects in adults has been discussed in a number of recent publications.[126,127] It is clear that the lung dose accounts for most of the dose reaching the systemic circulation, although the contribution of the swallowed fraction can become significant when pMDIs or DPIs[128] are used to deliver drugs with a relatively low first-past metabolism. Within the available pMDI/DPI/steroid combinations there are significant differences in the lung : systemic dose ratios which can influence the choice of delivery system.[126,127] It is likely that upper airways deposition will be relatively high compared with lung dose when children use DPIs and deposition studies in infants have shown relatively higher upper airways deposition when infants inhale from holding chambers with tidal breathing. Thus, one cannot directly extrapolate conclusions from adult studies and it is possible that for many drug/device combinations, the systemic to therapeutic effect is relatively greater in children as a result of relatively greater swallowed doses.

5.2 Aged-Based Recommendations

5.2.1 Infants and Toddlers (0 to 3 years)

Holding Chambers with Face Masks

These are convenient and appear to be capable of delivering effective quantities of drugs to the lungs of even the smallest infant, if tolerated.

Jet Nebulisers

For a small minority of infants who will not tolerate holding chamber delivery systems, jet nebulisers are an alternative if the infant will tolerate a closely fitting face mask. For steroid therapy, appropriate jet nebulisers should be used.[129]

5.2.2 Preschool Children

pMDIs/Holding Chambers

From an age of approximately 2 to 3 years, preschool children will generally be capable of using a holding chamber with tidal breathing.

5.2.3 Children Aged ≥5 Years

pMDI/Holding Chambers

These remain a suitable option for prophylactic therapy but a more portable system is generally required for bronchodilator therapy. pMDI/holding chambers are valuable in more severe episodes and can effectively replace nebulised therapy in this situation.

Dry Powder Systems

These are widely used for bronchodilator therapy in this age group. They are also used for delivering prophylactic therapy such as sodium cromoglycate and inhaled steroids. The relative merits of different drug/delivery system combinations and how they compare to pMDI/holding chambers have been discussed elsewhere.[126,127]

In acute asthma, there is evidence that using a spacer device for bronchodilator therapy is as efficacious as using a nebuliser on a μg-equivalent or half-μg–equivalent nominal basis.[130,131] The main disadvantages of spacer devices in acute asthma is that they preclude the concomitant use of an oxygen mask and need more patient cooperation and closer supervision.[132] A review of nebuliser therapy in adults and children has recently been published by the nebuliser project group of the BTS and discusses many issues in great detail.[133]

6. Noncompliance with Therapy

This subject covers an enormous area and is central to effective maintenance therapy. A full discussion of this is beyond the scope of this article. It is clear that when objectively measured, the level of adherence with regular medication for asthma is very poor in all age groups. Even in preschool children, for whom parents take responsibility for administering the medication, adherence is poor.[134] Many factors such as the choice of drug, route of delivery, choice of delivery system, physician approach and patient personality will all influence the level of compliance within an individual patient to some extent. The fact that compliance with parent-supervised treatment is poor should not be surprising when we remember that adherence with parent-supervised medication can be very poor in as many as one-third of children with cancer.[135] There have been no studies to determine whether using the same device for bronchodilators and inhaled steroids promotes or impairs compliance with maintenance medication. It is a historical accident that this situation has arisen even though the requirements for the 2 classes of drug are very different and it is possible that designing devices specifically for maintenance therapy would promote adherence, with a consequent reduction in morbidity and cost.

It is generally accepted that, for the treatment of asthma, the most desirable route of delivery for drugs with significant systemic adverse effects is as an inhaled aerosol. By delivering the drug directly to its site of action the dose required can be minimised, hence reducing the potential for systemic adverse effects. From the point of view of the patient, however, the simplicity of oral medication would be preferable if well tolerated effective forms of treatment could be delivered in this way. Not only would this avoid many of the problems associated with currently available aerosol delivery systems, but the simplicity of this route may, on the very limited evidence available, improve compliance.[136] With the advent of effective aerosol delivery systems for even the youngest patients,[109,112,113,137] oral medication is being used much less frequently, even in infants.

7. Conclusions

The prevalence of asthma appears to be increasing, although how significantly remains open to much debate. It is clear that the diagnosis of asthma is improving but, even when children are appropriately labelled as having asthma, there continues to be undertreatment of symptoms.

Inhaled therapy continues to be the main method of delivery for the treatment of asthma; if we are to reduce morbidity from undertreated asthma one of the main focuses of attention must be how the child uses the medication. It is thus of paramount importance that a correct device is chosen for each child. Drug delivery in infants and toddlers remains as much an art form as a science. Any theoretical benefit of a device will disappear if a child starts to struggle or scream. For older children, the choice of a drug/device combination that is liked and easily used will maximise drug delivery and adherence to a treatment regimen. Until effective oral anti-asthma therapy becomes a re-

ality, the rational and appropriate use of inhaled therapy will remain the mainstay for the optimal treatment of asthma.

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