

Original article

Effectiveness of pharmacotherapy in asthmatic preschool children

The term “effectiveness” relates to the question of whether or not a certain treatment works in practice. Usually, such a treatment was first evaluated under tightly controlled conditions in selected patient populations, and the potential benefits were shown. There is, however, a great difference between the efficacy of a given treatment, indicating its optimal therapeutic action in controlled trials, and its effectiveness when applied to a less well-defined population of patients in daily practice. This is especially relevant for asthma in young children, where many factors are responsible for the difference. Among these are, first of all, the heterogeneity of the wheezing phenotype. Other factors include the compliance with prescribed treatments, as determined by the attitude of doctors and parents towards such treatment, the ease of administration and the perceived effects and side effects. Also, the performance of different inhaler devices may be insufficient for a good, reliable dose deposition in young children in daily life. As a result, the current treatment guidelines for preschool children with recurrent wheeze are probably too optimistic in assuming that inhaled treatment is most effective and feasible at all ages. We propose careful re-evaluation of such recommendations in a first-line setting resembling daily life as closely as possible, and consideration of oral treatments as well. Also, we need methods to separate the different phenotypes within the group of recurrently wheezing preschool children to optimize targeting of asthma treatment to those who have ongoing airway inflammation.

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The efficacy of most drugs and treatment regimens for asthma has been well-documented in adults, but not that well in preschool children. Treatment guidelines for “asthma” in the first years of life are, to an important extent, based on findings in older patients, and on small, well-controlled clinical studies that have shown some degree of efficacy in younger children, often employing insensitive and subjective endpoints. Based on adult medicine and efficacy studies aerosol treatment, especially with MDI/spacer inhalation devices, has been recommended as first choice for treatment of young wheezing children and the use of oral medications is gradually disappearing from recent guidelines for asthma treatment (1–5). It is important to realize that efficacy studies cannot predict the effectiveness of a given treatment in daily life, where the success of a treatment is dependent largely on many factors, besides the potential pharmacological action of a drug. When guidelines for older children and adults are adapted to the very young, several problems arise. These include the heterogeneity of the wheezing syndrome in early life, compliance with treatment regimens especially when drugs are given by inhalation, and the performance of the different inhaler devices in young children.

Validity of guidelines for preschool wheezing

Recurrent wheeze in early childhood is a common and heterogeneous syndrome (6–8). Around one-third of all infants have one or more wheezing episodes in their first years of life, but the majority of recurrently wheezing children will turn out to have no asthma after a few more years (9). Until now, published data suggest that children who wheeze with viral infections only in the first years of life are predisposed, perhaps because of smaller airways, and may not suffer from chronic airway inflammation (10, 11). Another subgroup with recurrent wheeze, independent of infections, may have normal airway calibre but ongoing eosinophilic airway inflammation and develop into persistent atopic asthma. This is supported by results of a study in atopic asthmatics and nonatopic “viral wheezers” where bronchoalveolar lavage revealed increased numbers of eosinophils and mast cells only in the atopic wheezers (12). It is probable that different wheezing subgroups, who are phenotypically similar, will require a different therapeutic approach. Clearly, maintenance treatment with inhaled anti-inflammatory drugs should be given to those with chronic inflammation whereas those with intermittent

symptoms may not have chronic inflammation, and may benefit from intermittent, symptomatic treatment only, and this should be established by long-term prospective studies. There is, however, a remarkable lack of data on targeting of anti-inflammatory treatment to those young children who probably have chronic inflammation. This is due mainly to the fact that it has been difficult to separate the latter group on the basis of clinical signs or symptoms in a valid way, and hence it has been impossible in therapeutic trials to discern early asthmatics and transient wheezers with any degree of certainty. This means that the validity of current asthma drugs remains to be shown for at least half of those who wheeze in early childhood, and that therapeutic trials in preschool children may have been diluted by inclusion of an unknown proportion of nonasthmatic wheezers in whom asthma drugs are not necessarily effective. There is currently no way out of this problem, apart from realizing that the effectiveness of asthma medication may be less in children who lack secondary characteristics of the asthmatic phenotype, such as atopic syndrome and a positive family history of atopic disease.

Towards a better definition of the asthmatic phenotype

Better targeting of asthma pharmacotherapy, especially anti-inflammatory drugs, will become possible when the subgroup of recurrently wheezing children who have chronic airway inflammation and are likely to develop into asthmatics could be more easily identified. This is currently one of the "hottest topics" in paediatric asthma research, and an increasing number of new tests to assess asthmatic airway inflammation is being studied for this purpose. These include inflammatory markers in blood, urine and exhaled air. A useful marker should fulfil several criteria. It should be noninvasive, quick, repeatable, validated against more direct measures of airway inflammation, preferably biopsies, and be (potentially) cheap. Currently, exhaled nitric oxide (eNO) is a marker which seems to fulfil most of these criteria. It can be assessed in exhaled air with excellent reproducibility and is markedly higher in untreated asthmatics than in normal children (13). Extensive guidelines for measuring eNO in adults and children have been published (14, 15). Exhaled NO correlates with induced sputum eosinophil counts in asthmatic children and adults (16, 17). In combination with other markers, it seems possible to use NO as a predictor of steroid effect in asthmatic adults, with relatively high specificity (18). Unfortunately, the recommended methodology for eNO assessment as published in recent guidelines is not applicable to very young children, and there is no standardized technique by which exhaled air can be sampled from young children who cannot perform controlled expirations reliably (15, 19). Nevertheless, the first studies using eNO as an inflammatory marker in infants have appeared, and suggest that in the

first years of life, eNO may also serve as a useful surrogate marker of airway inflammation (20). There are some data suggesting that eNO may separate children with atopic asthmatic wheeze from those with nonatopic wheeze (21). Data validating eNO against direct measures of airway inflammation in young children are needed.

A number of other markers have been studied in young children, including serum immunoglobulin E, eosinophilic cationic protein (ECP), urinary excretion of eosinophilic protein X (EPX) or ECP, and hydrogen peroxide in exhaled air condensate (22–27). Lymphocyte subsets in peripheral blood and cytokine profiles or cytokine receptor molecules may be helpful in identifying a predisposition towards development of atopy, but as most atopics will not develop asthma, their potential relevance for therapeutic decision making will probably be limited. Clough and colleagues found recently that a combination of age of presentation and soluble interleukin-2 receptor level in serum could predict persistent wheeze in a prospective study with an overall accuracy of 67% (28).

Prospective studies are needed to evaluate whether eNO and/or other markers of airway inflammation can be helpful in identifying those children who will benefit from anti-inflammatory treatment for recurrent wheeze and, conversely, to select children in whom inhaled steroids are unnecessary.

Compliance with inhaler treatment

Compliance with treatment regimens is a problem of all ages. For preschool children, parents and physicians are often concerned about the feasibility of giving inhaled drugs for longer periods of time. In a study conducted in general practice, we asked the parents of 553 children who fulfilled criteria for moderately severe asthma and needed maintenance treatment with an anti-inflammatory drug to comply with a regimen of twice-daily inhalations by means of an MDI/spacer device, for a study duration of 5 months (29). At the onset, 104 children were not invited because their GP used his "veto", mainly because of expected bad compliance due to social problems. Another 72 children did not enter the study because their parents expected feasibility problems; 109 children were not included because they were satisfied with their current (mainly oral) treatments. Twenty-seven were reluctant to cooperate with a scientific study; nine refused without giving a reason. During the study, 65 children dropped out for various reasons. The majority of those were 1–2 years and had problems with using the inhaler. This led to the conclusion that, in a general practice setting, and despite special care given by trained nurses, only 167 of the initial number of 553 eligible children could be treated with inhaled medication according to current treatment guidelines, a success rate of only 30%. We evaluated which factors could predict a successful compliance with this treatment regimen, and found that compliance depended

on age (the lower, the worse) and education level of the mother (odds ratio of 5). A positive factor was eczema of the child, and more severe airway symptoms.

Another important finding was that, specifically, maintenance treatment provoked resistance in the parents. In a follow-up contact of the above-mentioned group 8 months after the study was finished, only 21% had continued to use maintenance treatment in any form, despite the same or worse symptomatology. In contrast, most children received inhaled bronchodilators when needed, suggesting that the inhaler device was not the only problem.

Efficacy vs effectiveness of inhaler treatment in young children

Current inhaler devices for use in preschool children have their limitations. Most of the available MDI/spacer combinations have not been tested thoroughly in young children. Deposition studies are few, and often considered unethical in this age group. This leaves us with a lack of knowledge of the behaviour of aerosols and inhaler devices in the treatment of very young children. We have examined dose delivery from MDI-spacer combinations to 1–8-year-old children with recurrent wheeze in a daily life setting, using filters to assess the dose released from of the spacer. We found that cooperation, assessed by video scoring, was the most important determinant of dose delivery in those younger than 5 years (Fig. 1). Both cooperation scores and age were major determinants of dose variation within-children (30). We found a wide scatter of dose variability when using different MDI/spacers in preschool children, which could be explained often not by properties of the devices, but by mistakes in the administration procedure. We feel that the design and performance of the face mask in particular is a neglected

aspect of inhalation devices. Useful data on the behaviour of aerosol administration systems in infants may be obtained from the use of anatomically correct models of the airways of infants and preschool children, where breathing patterns are simulated by a computer-driven pump system, using actual breathing signals recorded from children. Using such a set-up, we demonstrated recently that the breathing pattern and particle size were vital determinants of the dose delivered to the lower airways. Also, the dependency of lung dose on different types of aerosols proved important. The new, ultrafine particle hydrofluoroalkane (HFA) aerosols may well be able to improve targeting of inhaled steroids to the lower airways of young children and studies are needed to establish their possible superiority in terms of therapeutic benefits and safety, specifically in young children.

Oral treatment of asthma: time for a reappraisal

In a clinical trial of sodium cromoglicate, we proposed that parents of preschool children with symptoms suggestive of moderate asthma start inhaler treatment for their children's wheezing. A considerable proportion refused, indicating that they were satisfied with current oral treatments, including anticholinergic, sympathomimetic, antihistamine, antitussive and other drugs (29). This seems to indicate that parents appreciate the ease of administration of oral treatment, and are satisfied with any small benefits such treatment may provide. However, oral asthma treatment (with the exception of oral steroids for exacerbations) is now generally considered obsolete, because its efficacy is generally inferior to that of inhaled treatment. This may well be the case in efficacy studies in older children, where maximum effects, speed of action and safety aspects are much in favour of inhaled treatment, especially with beta-2 agonists and corticosteroids. However, in daily life, effectiveness of inhaled drug treatment suffers from low compliance and discontinuation of maintenance treatment is the rule rather than the exception. This may change the balance in favour of oral drugs with their ease of administration and simplicity compared to inhaled drugs with one or more complicated spacer systems that need specific knowledge, preparation, cleaning and maintenance for an optimal effect. Especially with once-daily dosing, oral drugs are attractive and this is feasible for beta-2 agonists, theophylline and the new leukotriene receptor antagonists. The latter have demonstrated significant protective and bronchodilator effects, and some improvement of eosinophilic airway inflammation, with remarkably few side effects (31). A study in school-age children compared the oral leukotriene receptor antagonist montelukast and inhaled cromoglycate, and found that montelukast reduced symptoms, eosinophilic cationic protein, an eosinophil activation marker, and leukotriene TC₄ in nasal washes (31). The latter effects were not seen with cromoglycate. Also, beta-2

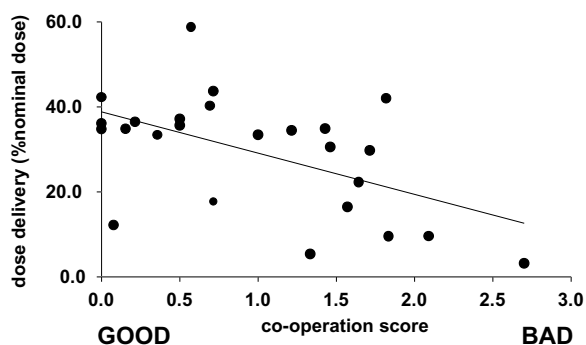


Figure 1. Effect of cooperation on dose delivery of budesonide, delivered via a nebulchamber and facemask to 0–2-year-old children ($n = 22$) in a daily life setting. There was a significant negative effect ($R = -0.5$, $P = 0.009$) of poor cooperation (indicated by a high score on the horizontal axis) on percentage of nominal dose delivered to a filter positioned between spacer and facemask (vertical axis). (H.M. Janssens, personal communication).

agonist use as comedication was lower in children treated with montelukast than in children on cromoglycate. Studies with montelukast as add-on treatment for asthma in large groups of children showed small improvements in symptomatology and lung function, together with reduction in beta agonist use and small benefits in some other relevant parameters of asthma control (32, 33). These studies examined effectiveness rather than efficacy. Until now, the clinical spectrum of activities of leukotriene receptor antagonists is very similar to that of theophylline, which used to be widely prescribed to young asthmatic children. The better safety profile of leukotriene antagonists justifies their careful evaluation in efficacy and effectiveness trials, in direct comparison with inhaled steroids and as add-on treatment. Until now studies in children have been scant, and studies where leukotriene antagonists are given as monotherapy to young children with relatively mild symptomatology of recurrent wheeze are lacking. We believe that oral treatment of proven efficacy needs to be compared to inhaler treatment in effectiveness trials in preschool children, especially those with mild symptomatology. Such studies should reveal whether or not the balance between low efficacy, on one hand, and the advantage of easy administration, proven efficacy and safety on the other hand, would compare favourably with the effectiveness of inhaled treatment (Fig. 2), where the balance between high efficacy and low compliance with inhaler systems limits effectiveness in infants and preschool children with asthmatic or nonasthmatic wheeze in daily life.

Efficacy vs effectiveness in clinical trials

The degree of control and selection in clinical trials determine their relevance for daily life. A study in a small number of highly selected, well-motivated and well-trained children is likely to reveal the optimal efficacy of a given drug. Studies in a general practice setting, where large and heterogeneous groups are studied under conditions similar to daily life, show the limitations of such a treatment and provide insight into the actual benefit in terms of effectiveness. In a recent systematic review, Tasche et al. analysed clinical trials with inhaled sodium cromoglycate in children below 18 years published between 1966 and 1997, and found that the year of publication was the single best predictor of a positive treatment effect (34). This could be attributed to publication bias (under-representation of small studies with negative or equal outcome) and to an age effect, where older studies concerned older patients treated with dry powder inhalers, whereas more recently studies concerned mainly young children treated with MDI or nebulizer. Also, older studies were more likely to test efficacy, whereas newer studies were more likely to test effectiveness and, hence, found less benefit.

Leukotriene antagonists

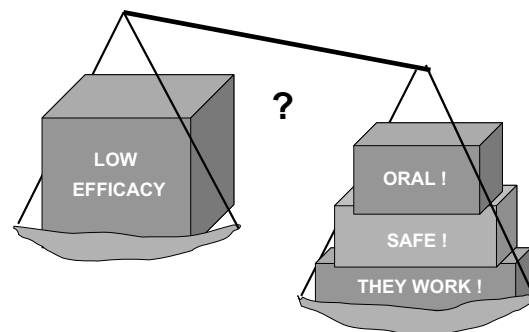


Figure 2. The balance of efficacy and effectiveness may be unexpectedly favourable for oral treatment of children with asthma.

Several small studies of cromoglycate in young children, in whom wheeze was probably not due to asthma, failed to show benefits (35–37). This illustrates that differences in disease mechanisms underlying wheezing in different age groups, and probably also problems with adequate drug administration, lead to a low efficacy of asthma treatment in young children compared to older children. These results do not indicate a lack of efficacy of cromoglycate, but rather the limited benefits of such a treatment, of which numerous short-term studies have documented a clear anti-asthmatic effect, when applied to young wheezing children, especially in a daily life setting.

Another example where efficacy turned out much lower than effectiveness is ketotifen, an oral antiserotonin and antihistamine agent which has numerous interesting anti-asthmatic effects when tested *in vitro*, in animal models or under tightly controlled test conditions in patients, but which fails to show important effectiveness in clinical studies (38–42).

Conclusions

It is important to be aware of the discrepancies that exist between efficacy of a drug when tested in a tightly controlled setting and its effectiveness in a daily life setting. This is especially relevant for asthma drugs when treating young children with recurrent wheeze. We argued that, due to the heterogeneity of the wheezing phenotype in early childhood, limited compliance with long-term inhaler treatment and the intrinsic properties of inhaler devices, low effectiveness is to be expected when treating young wheezy infants and preschool children. Careful re-evaluation of available treatment options, especially with newer oral drugs, seems warranted in order to establish the relative effectiveness of oral vs inhaled asthma medication not only in well-controlled clinical trials, but also in a setting as closely related to circumstances in daily life as possible.

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