

Challenges in evaluating controller asthma therapy in children

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Clinical data about the efficacy and safety of controller medications for pediatric patients of all ages are limited, especially when compared with the amount of data available for medications for adults. The considerable data collected so far in adults about these therapeutic agents need to be confirmed in children because pharmacologic profiles will not necessarily be the same for children. Clinical research studies need to include younger populations so that the necessary information can be available for physicians who want to use controller therapy for their pediatric patients. Special challenges confront the pharmaceutical companies and the research investigators who undertake these clinical studies, but such challenges are surmountable. (*J Allergy Clin Immunol* 2000;106:S165-70.)

Key words: Controller medications, growth suppression, inhaled corticosteroids, delivery systems

Asthma is the most common chronic illness in children. At least one half of all children who experience the development of asthma do so before the age of 3 years.¹ Nevertheless, with the exception of theophylline, there are no asthma controller medications, which include inhaled corticosteroids (ICSs), cromolyn, nedocromil, theophylline, and leukotriene modifiers, that have labeled indications for children younger than 2 years. Most controller agents have indications for children who are only as young as 4 to 6 years (Table I). The ICSs, the most effective and widely used category of antiinflammatory controller medication for asthma, have official labeling for children who are 6 years of age and older, the only exception being fluticasone powder, which is indicated for children as young as 4 years of age. In general, clinical data about the efficacy and safety of controller medications for pediatric patients of all ages is sorely limited, especially when compared with the amount of data available for medications in adults. The considerable data collected so far in adults about these therapeutic agents need to be confirmed in children because pharmacologic profiles will not necessarily be the same as those for children.

Controller medications must be studied further in children for many other reasons (Table II). With the increasing prevalence and morbidity of asthma in children, an increasing reliance on treatment with controller medica-

Abbreviations used

BDP:	Beclomethasone dipropionate
BIS:	Budesonide inhalation suspension
DPI:	Dry powder inhaler
FP:	Fluticasone propionate
ICS:	Inhaled corticosteroid
MDI:	Metered-dose inhaler
TAA:	Triamcinolone acetonide

tions has developed. New guidelines for the management of asthma, in both adults and children, have suggested that intervention even earlier than previously recommended be coupled with a lower threshold for the initiation of controller medication therapy and a longer overall treatment period.² Finally, long-term follow-up studies of asthmatic children have provided evidence that early and prolonged antiinflammatory treatment may make a significant difference in the prevention of the accelerated loss of lung function seen with untreated asthma and its associated chronic inflammation.³

SPECIAL PROBLEMS IN STUDIES WITH CHILDREN

The clinical evaluation of controller medications in children presents special challenges, which may partially explain why research information about these agents for this age group is limited (Table III). To begin with, starting a child on controller agent therapy implies that the asthma is considered to be chronic or persistent, yet simply recognizing persistent asthma in very young children can be difficult. In fact, the definition of persistent asthma for very young children can be problematic. The current national asthma guidelines, directed more toward the diagnosis and treatment of adults, are somewhat helpful; but pediatric-specific parameters are greatly needed, and the National Asthma Education and Prevention Program has released a set of practice guidelines that were designed specifically for children with asthma.⁴ Research protocols for the evaluation of controller therapy will be able to use these guidelines to define more clearly the patient population to be studied.

The actual recruitment and enrollment of children in clinical trials that evaluate controller medications can also present several challenges. Parents are often reluctant to allow their child to be part of what they consider to be an experiment or to be involved in a trial in which the child could receive placebo. Naturally, children will be afraid of procedures such as skin testing and blood

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TABLE I. Lower age indications for controller medications

Agent	Indication (y)
Cromolyn ampules	2
Cromolyn MDI	5
Nedocromil MDI	6
Theophylline	Infancy
All ICS MDI aerosols	6
Budesonide powder	6
Fluticasone powder	4
Montelukast	6
Zafirlukast	7

TABLE II. Reasons for studying asthma controller medications in children

The rise of asthma prevalence/morbidity
New treatment guidelines that recommend
Earlier intervention
Lower threshold for treatment
Longer treatment period
Possible long-term difference because of early treatment
Confirmation of adult findings in children
Availability of new therapeutic agents

TABLE III. Challenges in the evaluation of asthma controller medications in children

Definition of chronic asthma
Need for pediatric guidelines
Recruitment/enrollment
Compliance
Ethics of a placebo group
Indirect symptom reporting
Objective assessments
Seasonal variation
Age-related differences
Pharmacokinetics
Inhaler/delivery techniques
Adverse effects
Growth suppression
Osteoporosis
Cataracts
Drug formulation
Taste
Tablet vs capsule; chewable vs liquid
Time-released agents
Delivery systems
MDI with or without spacer
Powder vs MDI aerosol
New vs old propellants
Different DPIs
Different nebulizer systems
Dose response/minimal effective dose/plateau dose

draws and, understandably, will be reluctant to volunteer. The long-term commitment needed for many of the controller medication studies can hinder recruitment. Some parents will not allow their child to participate in trials that study ICSs for fear of their adverse effects. Many other practical obstacles to enrollment exist such as the parent's or child's inability to make follow-up visits, the

problems caused by split-parent families, or an unwillingness to discontinue the child's present therapy. These and other considerations prevent children from being entered into clinical research trials that are important for the development of new pediatric asthma therapies.

Once enrolled in a study, however, other challenges exist with children. Assessment of a clinical response to an intervention has to occur indirectly through the parent or caregiver, and this assessment is not always accurate. Objective tests are preferred over subjective ones, but not all children can perform the tests needed (such as spirometry) to quantify a response to therapy. Seasonal variations in asthma stability commonly occur in children, with asthma worsening in the fall and winter. This can pose special challenges in the design and performance of research protocols for this age group. Age-related differences may occur with the pharmacokinetics and pharmacodynamics of controller medications, and studies must be conducted with this possibility in mind. Certain special adverse effects that are unique to children (such as the possibility of growth suppression) make clinical research evaluations in this age group different from those evaluations performed in adults. Features of drug formulations (such as taste, tablet versus capsule, or chewable versus liquid) can affect the patient's acceptance of the medication that is being tested, a problem that does not happen as often with adult studies. If an inhaled agent is used, the type of delivery system must be such that children are able to use it effectively. Finally, dose-response studies are especially needed in children to determine both the minimal effective dose and the plateau dose of a controller medication, useful information for ensuring that a child is exposed to the lowest effective dose possible. Studies of dose response, however, are not always easy to conduct.

ICS THERAPY

In the evaluation of ICS therapy in children, 4 issues are pertinent: (1) pharmacokinetics, (2) dose response and minimal effective dose, (3) delivery of the drug, and (4) growth.

For asthma, there are now 5 marketed ICS agents (Table IV), with another (mometasone) soon to be released. Information about pharmacokinetics and pharmacodynamics with these agents is minimal. The pharmacokinetic data available for adults are predominantly with budesonide, although some information is available for beclomethasone dipropionate (BDP).⁵ Information available for children is limited and is exclusively with budesonide. More important, essentially no published data exist concerning the pharmacodynamics of ICSs in the pediatric population. Pedersen et al^{6,7} studied the pharmacokinetic properties of budesonide in children by using an intravenous versus inhaled dose (either the Turbuhaler [AstraZeneca Pharmaceuticals, Wilmington, Del.] or the metered-dose inhaler [MDI] with spacer) and measuring serial blood levels of budesonide. Children had a 40% higher clearance of budesonide than did

adults, with a serum half-life of 1.5 hours, in comparison with 2.3 hours in adults. The Turbuhaler powder resulted in approximately 2 times as much systemic bioavailable drug as did the MDI with spacer, which proved that ICSs can be absorbed readily through the pulmonary system. Half-life data for other ICSs in children are not yet known. Age-related differences in pharmacokinetics are probably most important for the prediction of systemic adverse effects of ICSs and less important for determining efficacy. In a recent review of the pharmacokinetics of ICSs, Lipworth⁵ states that the higher clearance and shorter half-life of ICSs in children may help reduce the burden of systemic effects of this drug category, especially with steady-state dosing. For example, in adults, the longer the serum half-life of the ICS, the greater the potential exists for adrenal suppression. Lönnebo et al⁸ measured serial cortisol levels and determined area under the curve in patients who were treated with single versus repeated doses of fluticasone propionate (FP; $t_{1/2}$, 14.4 hours) and budesonide ($t_{1/2}$, 2.3 hours). They found a larger step-up in adrenal suppression with repeated doses of FP compared with budesonide (25% to 55% vs 26% to 34%). Wilson et al⁹ confirmed this with repeated daily dosing of these 2 ICSs. These findings suggest that, in adults, the FP's longer half-life permits drug accumulation to occur with repeated dosing to a greater extent than with budesonide, which has a significantly shorter half-life. It may be that FP, like budesonide, has a shorter half-life in children than in adults, and therefore the issue of drug accumulation is less of a problem in the pediatric population. But until more pharmacokinetic studies are conducted in children, questions such as this, along with many others (Table V), will remain unanswered.

Doses of ICSs in children are often extrapolated from the doses used in adults, and the usual recommended dose reduction for children simply parallels the known reduction in their total airway volume. Recommended doses for children with asthma, however, do not always take into account the differences in drug delivery and drug metabolism between children and adults that may make the recommended lower ICS doses not entirely sensible. These differences include children's reduced ability to coordinate and correctly use an MDI, their lower inspiratory forces, and the enhanced clearance of ICSs from the body. Studies that help define the proper dose of an ICS for children of differing ages, sizes, and asthma severity are sorely lacking.

More studies looking at the effect of ICS dose in children are needed for 2 important reasons. First, information obtained from dose-response trials can help determine the minimal effective dose for a given ICS, important because of renewed concerns about long-term adverse effects of ICSs in children, with growth suppression being highest on the list. Physicians want to use the lowest possible dose of an ICS that will control the asthma of a young patient. Dose-response studies also help provide information about the plateau dose, the dose beyond which most patients obtain no further benefit. The dose-response curve to ICS in adults has been found

TABLE IV. List of available ICSs

Generic	Tradename
BDP	Vanceril, Vanceril DS, Beclovent
Budesonide	Pulmicort Turbuhaler
Flunisolide	AeroBid, AeroBid M
Fluticasone	Flovent 44, 110, 220
Triamcinolone propionate	Azmacort
Mometasone furoate	Asmanex (not yet available)

Vanceril, Vanceril DS: Schering Pharmaceuticals, Kenilworth, N.J.; *Beclovent:* GlaxoWellcome, Research Triangle Park, N.C.; *Pulmicort Turbuhaler:* AstraZeneca, Wilmington, Del.; *AeroBid, AeroBid M:* Forest Pharmaceuticals; *Flovent:* GlaxoWellcome; *Azmacort:* Aventis Pharmaceuticals, Frankfurt, Germany; *Mometasone:* Schering Pharmaceuticals.

TABLE V. Pharmacokinetic studies needed of ICSs in children

Basic pharmacokinetics data (eg, $T_{1/2}$) for all of the ICSs
Single and steady-state dosing
Daily vs twice daily dosing
Spacer vs no spacer
Differences among various age groups
Effect of airway obstruction on pharmacokinetics

to be somewhat flat and shallow with regard to efficacy, but less flat with regard to adverse effects.¹⁰ In adults, increasing an ICS dose beyond the plateau dose usually leads to enhanced systemic adverse effects with little increase in asthma control. It is difficult to say whether this is the case with children because so few dose-response studies in children have been done, and, as with the pharmacokinetic data, these studies have all been done with budesonide. Two studies with nebulized budesonide in several infants and young children were unable to demonstrate a clear dose-response relationship with treatment over a 12-week period.^{11,12} The lowest dose used (0.25 mg/d) was effective compared with placebo. In contrast, Pedersen and Hansen,¹³ using budesonide MDI with spacer given at 3 different doses in a double-blind, cross-over design study in older children, did detect a dose-response effect, but it was observed primarily with budesonide's ability to protect against exercise-induced asthma, not with budesonide's effects on other parameters such as symptoms, use of rescue medications, or peak flow measurements.

Dose-response trials with ICSs are difficult to perform for a variety of reasons (Table VI), but the information they yield is important for guiding the selection of a dose. We conducted what could be an example of an informative dose-response study in adults that should be performed in children.¹⁴ Two hundred eighty-five patients with moderately severe asthma were treated with either placebo or doubling doses of triamcinolone acetonide (TAA; 100 µg/puff; 1, 2, 4, 8 puffs twice daily) for 6 weeks. All patients were ICS dependent; that is, to be enrolled in the study, they needed to demonstrate symptoms of asthma when withdrawn from ICS therapy at baseline. A dose response in efficacy was seen over the 4 doses of TAA, with the lowest dose (200 µg/d) being effective. Adverse events did not occur with any dose

TABLE VI. Requirements for dose-response studies of ICSs

Large sample size
Homogeneous population
Preferably ≥ 3 doses (wide range)
Symptomatic patients
Sensitive and multiple assessment tools
Placebo group preferable

TABLE VII. Types of delivery systems for ICSs

Press and breathe MDI (CFC)
Press and breathe MDI (HFA)
MDI with spacer (different types)
Autohaler
DPIs (different devices)
Nebulizer (different types)
Spiros (a new type of automatic multidose dry-powder inhaler device; still in development and not yet finally approved by the Food and Drug Administration)

CFC, Chlorofluorocarbon; HFA, hydrofluorocarbon.

response. Most patients were treated adequately with doses of TAA between 200 μg (1 puff twice daily) and 800 μg (4 puffs twice daily); a dose beyond 800 $\mu\text{g}/\text{d}$ did not result in further benefit. A drug effect was seen as early as 1 week, although the average time required to reach peak effect was 3 weeks. This study is a good model for a clinical trial with ICSs that provides practical dosing information, such as minimal effective dose, plateau dose, and time of onset and peak effect.

ICSs are delivered by inhalation, and therefore the delivery system and the patients' inhaler techniques are critically important for their pharmacologic and clinical profiles. The different types of delivery systems have increased steadily over the last 10 years (Table VII), resulting in the largest source of variability in attempting to predict the effectiveness and safety of a given ICS agent. Clinical research evaluations of various ICSs in children must contend with all of these different delivery systems as potential variables. The results of a clinical trial that investigated an ICS must be interpreted only in the context of the delivery system used, and changing the delivery system for that ICS can significantly alter the study's results. For example, delivery of an MDI aerosol with spacer, as opposed to no spacer, definitely changes the amount of drug delivered to the lungs versus to the gastrointestinal tract, altering the drug's risk-benefit ratio.⁹ A major flaw with clinical trials and evaluations of ICSs in children to date is that they often have been conducted without a spacer even though spacers are recommended and widely used in children placed on ICS therapy. Future studies are needed to answer the many questions that arise from the introduction of a spacer in children who use aerosolized MDIs (Table VIII). Dry powder inhalers (DPIs) are beginning to be prescribed in the United States. Two such delivery systems (Turbuhaler, Diskhaler [GlaxoWellcome, Research Triangle Park, N.C.]) are available

for ICSs. Budesonide administered with the Turbuhaler DPI has about twice the potency of the same drug administered by MDI with spacer¹⁵; the opposite may be the case with FP and its 2 forms, MDI and DPI.¹⁶ The number of DPI systems for ICS use is likely to expand in the future (eg, Diskus [GlaxoWellcome], Clickhaler [Innovata Biomed, St Albans, England], Spiros [Dura Pharmaceuticals, San Diego, Calif.], and the new Turbuhaler). An important challenge for future studies with ICSs with the use of a DPI device is to determine whether there is a difference in drug delivery between the aerosolized and powder forms in children and how important this difference is. Carefully designed clinical trials must be conducted to answer a variety of other questions (Table IX) about children and the use of DPIs.

Nebulized budesonide inhalation suspension (BIS) is soon to be available in the United States for the treatment of pediatric asthma. Consequently, nebulizer technology and lung delivery has become increasingly important for controller medication therapy. Drug dose and effect from nebulized drugs is closely tied to the nebulized delivery system, and not all nebulizers are the same. Using BIS, Smaldone et al¹⁷ measured the inhaled mass (amount of drug nebulized and expelled from the mouthpiece) of 27 different nebulizer systems under simulated pediatric breathing conditions. Results showed that the inhaled mass of BIS varied widely among nebulizers, from as low as 2% to as high as 18% of the amount of medication initially placed in the nebulizer bowl. Future studies with nebulized corticosteroids in children will require careful attention to the nebulizer system because it can significantly affect the amount of medication delivered to small- and medium-sized airways.

POTENTIAL GROWTH SUPPRESSION WITH ICS

The safety issue of potential growth suppression with ICS use in children has been on the minds of pediatricians and parents since a Joint Pulmonary-Endocrine/Food and Drug Administration Advisory Committee meeting on this topic took place 2 years ago.¹⁸ At this meeting, information was presented that suggested all ICSs have the ability to suppress short- and intermediate-term growth velocity. Since then, clinical trials of ICSs in children, whether with oral or ICSs, are now carefully measuring growth as part of their safety monitoring. The new concern about growth is the result of a number of clinical studies conducted over the last 10 years that have demonstrated mild but statistically significant differences in the height of patients who were treated with ICSs as compared with control patients.¹⁹ The magnitude of the suppression is in the range of 1.0 to 1.4 cm per year. Most of the well-designed studies showing such an effect are those in which BDP was used and in which the dose was not excessive (eg, 400 $\mu\text{g}/\text{d}$ of BDP). ICSs other than BDP, however, can potentially retard growth. Skoner et al²⁰ reported growth suppression of about 0.8 cm per year in children who were treated with standard

doses of TAA (600 µg/d). Similar suppression was seen over 1 year in a study that investigated nebulized budesonide at usual doses.²¹ The long-term significance of these intermediate-term growth studies is unknown. Limited but reassuring information suggests that children with asthma treated with ICSs attain normal final adult height, or at least a height comparable with patients not treated with ICSs.^{22,23} These reports, however, are flawed in a number of ways. They have a small sample size, a retrospective design, or a relatively short overall exposure time to ICSs or the patient was started at a late age on ICSs, making it difficult to come to any definite conclusions about the long-term effects of ICSs on height. This issue of growth suppression with ICSs needs to be studied further. Recent trends with the use of ICSs make this potential problem even more worrisome because ICSs for asthma are being started at an earlier age than ever before and are being used for longer durations at higher doses, often in conjunction with nasal ICSs (also known to be systemically bioavailable). Furthermore, the newer ICSs (such as fluticasone, budesonide, and mometasone) are more potent than their predecessors and have inhaler devices, such as the Pulmicort Turbuhaler, resulting in improved delivery to the lungs, which can help promote systemic absorption.

There are many challenges for future research studies of the effect on growth in children of the various ICSs (Table X). It is imperative that height be measured with the use of a calibrated, quality stadiometer, not an inexpensive weight scale that happens to also serve as a tool for measuring height. It is essential that personnel be trained in performing stadiometry. Variability in height measurements between untrained observers can be significant, sometimes greater than the actual effect of ICSs on height. In an ideal study of growth, researchers would have available growth data of children who were entering the treatment period, before they were treated with ICSs. Researchers could then observe if pre-ICS growth is altered by ICS exposure in the same patient. Because asthma itself may suppress growth, the population of children with asthma that is being studied should be as homogenous as possible, with regards to severity of asthma; having a placebo or a non-ICS treatment group, or both, is essential for comparison. Treatment with ICSs should be for an adequate period of time to allow for any valid conclusions about the effects of ICSs on youth. Many prospective growth studies with ICSs have been for 6 to 12 months; data from longer-term observation periods (2 to 4 years or even longer) are necessary. Efforts should be taken, of course, to minimize children's exposure to oral steroids, because systemic steroids are known to suppress growth. Given the extended nature of these studies, this is not easy. At least, the exposure to systemic steroids should be equivalent between the ICS-treated group and the control group.

Puberty is a time of great fluctuation in height, and with the onset of puberty being so variable, it is important that the children who are monitored for growth effects from ICSs not enter puberty during the study peri-

TABLE VIII. Questions regarding spacers and ICSs

Do they improve lung delivery?
Do they enhance or decrease systemic effects? Is the therapeutic index the same?
Do all the tube spacers perform the same? (eg, valve, durability, electrostatic charge)
Is the static charge on a plastic spacer really important?
When is a child too old for a closed bag spacer system?
Do spacers with masks really work to permit ICS treatment for infants? Which ones are the best?
Should the non-rebreathing valve in the tube spacers be removed for infants?

TABLE IX. Questions regarding DPIs and ICSs

What is the youngest age at which children can effectively use them?
Is there efficacy with suboptimal technique?
How do the different DPI devices differ clinically?
Are there significant advantages over the aerosol MDI?
Is dose to lungs same, higher, or less than MDI?
Do DPIs enhance or decrease systemic effects?
Are DPIs always safe in the setting of acute asthma?

TABLE X. Challenges for future studies of ICSs and growth

Conducting careful stadiometry
Obtaining growth data before study entry
Controlling for asthma severity
Including placebo or non-ICS treatment group
Treating for adequate duration
Minimizing oral steroid use
Assuring prepubertal status
Including multiple doses
Assessing bone age
Using proper statistical analysis

od. Thus, a careful assessment of pubertal status must be made at entry and throughout the study. Determining bone age (with a wrist radiograph, for example), before and after the study, should be part of the protocol to help determine whether any growth suppression effect observed is associated with delay in bone age. This information can help predict whether catch-up growth is likely and also help further the understanding of the mechanism of ICS-induced effects on growth. It would be ideal if these studies could have multiple ICS-dosing arms so that the observation could be made as to whether growth effects are dose dependent, particularly if there is a lower-level dose that does not result in suppression. Finally, proper statistical analysis of height data is imperative to ensure that any observed changes are statistically significant.

CONCLUSIONS

Asthma in children continues to be a serious medical, social, and economic problem. Considerable information exists in adults about the use and importance of controller medications, such as ICSs, in successfully manag-

ing the symptoms and complications of persistent asthma. Future clinical research studies must include younger populations so necessary information can be available for physicians who want to use similar controller therapy in pediatrics. Special challenges confront the pharmaceutical company and the research investigator who undertake these clinical studies, but such challenges are surmountable. We can hope this new decade will bring with it new information and experience about controller therapy in children that will allow us to make a significant impact in reducing asthma's overall morbidity and mortality rates in this age group of patients.

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