What are the relative benefits of the various inhaled corticosteroids for pediatric asthma?

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Inhaled corticosteroids (ICS) play an integral part to the management of asthma in pediatric patients. In 2007, the National Heart Lung and Blood Institute (NHLBI) issued guidelines for the diagnosis and management of asthma in which they assert that initiation of low-dose ICS as a long-term control therapy may significantly reduce overall symptom burden and frequency of asthma exacerbations in pediatric patients.[1] Recommendations are categorized by patient age (0 to 4 years, 5 to 11 years, and >e; years); however, overall, the NHLBI states that ICS are the preferred therapy for initial long-term control in children of all ages. These drugs have been shown to consistently control and prevent asthma symptoms, reverse airflow obstruction, improve quality of life, and decrease the number and severity of asthma exacerbations.[2] Additionally, ICS are deemed to be generally safe, especially when given at low doses, even for extended periods.[1] Of note, while ICS are effective in controlling symptoms, their administration will not alter the underlying disease progression or severity, as demonstrated by worsening of symptoms and airway responsiveness when treatment is withdrawn.

Several ICS are commercially available. In their 2007 guidelines, the NHLBI outlines then-available ICS with estimated comparative daily dosages in children under 11 years of age.[1] This information may be seen in Table 1. These doses were based largely on the results of then-available comparative trials. The NHLBI cautions that the preparations are not absolutely interchangeable on a mcg or per puff basis. Also, different delivery devices may offer greater or lesser amounts of drug to the airways, affecting the dose.

Table 1. Comparative Daily Dosages for Inhaled Corticosteroids in Children Aged 0 to 11 Years.[1]

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Child 0-4	Child 5-11	Child 0-4	Child 5-11	Child 0-4	Child 5-11
Beclomethasone HFA (40 or 80 mcg/puff)	NA	80-160 mcg	NA	>160-320 mcg	NA	>320 mcg
Budesonide DPI (90, 180, or 200 mcg/inhalation)	NA	180-400 mcg	NA	>400-800 mcg	NA	>800 mcg
Budesonide inhaled (suspension for nebulization)	0.25-0.5 mg	0.5 mg	>0.5-1.0 mg	1.0 mg	>1.0 mg	2.0 mg
Ciclesonide[3,4*] (80 or 160 mcg/puff)	NA	NA (80-160 mcg)	NA	NA (>160-320 mcg)	NA	NA (>320 mcg)
Flunisolide (250 mcg/puff)	NA	500-750 mcg	NA	1,000-1,250 mcg	NA	>1,250 mcg

Flunisolide (80 mcg/puff)	NA	160 mcg	NA	320 mcg	NA	≥640 mcg
Fluticasone HFA (44, 110, or 220 mcg/puff) Fluticasone DPI (50, 100, or 250 mcg/inhalation)	176 mcg NA	88-176 mcg 100-200 mcg	NA NA	>176-352 mcg >200-400 mcg	>352 mcg NA	>352 mcg >400 mcg
Mometasone DPI (200 mcg/inhalation)	NA	NA	NA	NA	NA	NA
Triamcinolone acetonide** (75 mcg/puff)	NA	300-600 mcg	NA	>600-900 mcg	NA	≥900 mcg

HFA=hydrofluoroalkane; NA=not approved; DPI=dry powder inhaler
*Not included in NHLBI Guideline recommendations. Doses suggested are for off-label usage.
**No longer available

For children aged 12 years and older, the NHLBI recommends the same comparative daily dosages of ICS as for adult patients.[1] These recommendations may be seen in Table 2.

Table 2. Comparative Daily Dosages for Inhaled Corticosteroids in Adults and Children ≥12 Years.[1]

Drug	Low Daily Dose	Medium Daily Dose	High Daily Dose
Beclomethasone HFA (40 or 80 mcg/puff)	80-240 mcg	>240-480 mcg	>480 mcg
Budesonide DPI (90, 180, or 200 mcg/inhalation)	180-600 mcg	>600-1200 mcg	>1200 mcg
Ciclesonide HFA[3,4*] (80 or 160 mcg/puff)	160-320 mcg	>320-640 mcg	>640 mcg
Flunisolide (250 mcg/puff) Flunisolide HFA (80 mcg/puff)	500-1,000 mcg 320 mcg	>1,000-2,000 mcg >320-640 mcg	>2,000 mcg >640 mcg
Fluticasone HFA (44, 110, or 220 mcg/puff) Fluticasone DPI (50, 100, or 250 mcg/inhalation)	88-264 mcg 100-300 mcg	>264-440 mcg >300-500 mcg	>440 mcg >500 mcg
Mometasone DPI (200 mcg/inhalation)	200 mcg	400 mcg	>400 mcg

Triamcinolone acetonide** (75 mcg/puff)	300-750 mcg	>750-1,500 mcg	>1500 mcg

HFA=hydrofluoroalkane; DPI=dry powder inhaler
*Not included in NHLBI Guideline recommendations
**No longer available

An ICS was approved by the Food and Drug Administration (FDA) in 2006: ciclesonide (Alvesco®).[5] Available as a metered dose inhaler with either 80 mcg/puff or 160 mcg/puff, ciclesonide is approved for maintenance treatment of asthma in adults and pediatric patients aged 12 years and older. While not included in the NHLBI guidelines, comparative dosing of the drug has been suggested and is incorporated in Tables 1 and 2.

Based on the recommendations of the NHLBI, it appears that while the ICS differ in potency and dosage form, they do not differ in efficacy.[1] From a search of the literature, several comparative clinical trials and clinical reviews were identified that discuss potential clinical differences among available ICS. In 2009, Kelly provided an update to his previous publication comparing ICS in which the author reviews pharmacokinetic and pharmacodynamic differences among the ICS and their comparative doses.[3] In this review, the author asserts that ICS potency and efficacy are slightly disparate concepts, with potency defined by the binding affinity at the glucocorticoid receptor and efficacy measured through various clinical endpoints (e.g., improvement in baseline lung function and reduction of asthma exacerbations), represented by the therapeutic index. While the potency determines efficacy of specific doses, differences in efficacy of medications may be overcome by administering comparative or equipotent doses.

In a more recent review, Stoloff and Kelly compared ciclesonide with older ICS in terms of pharmacokinetic and pharmacodynamic characteristics as well as efficacy.[4] While the newer ICS was developed to improve the therapeutic index, the authors assert that the therapeutic index narrows with increasing doses for all ICS. Ciclesonide was found to be similarly efficacious to fluticasone and mometasone in equipotent doses with a potentially improved therapeutic index, but the authors report that further data are needed to assess its systemic effects.

As stated in the NHLBI guidelines, the ICS in general are purported to be safe, particularly at low doses.[1] The Expert Panel concluded that benefits from ICS may plateau at low doses, but increasing the ICS dose in children with more severe asthma may be associated with further benefits and reduction in the risk of exacerbations. There is a concern for an increase in the risk of systemic effects with increasing ICS doses, though. The NHLBI asserts that the clinical significance of these effects is unclear.

Per a review by Murphy, studies of selected ICS have shown mixed results regarding effects of the ICS on growth velocity, one of the major concerns with ICS use in children.[6] When used at approved doses for 1 year, for example, neither mometasone nor flunisolide was found to significantly reduce growth velocity compared to placebo or a non-ICS asthma medication. In contrast, in a study comparing budesonide (dry powder inhaler) to placebo, over a follow-up period of 4 to 6 years, a statistically significant difference in growth of 1.1 cm was

observed. Whether this result is clinically significant is questionable. Regarding suppression of the hypothalamic-pituitary-adrenal (HPA) axis, another major concern with ICS use, no significant issues have been noted with any of the currently available ICS when used at approved doses.

In addition to safety and efficacy, adherence is another issue of concern. Murphy states in his review that several factors may affect adherence to ICS, including behavioral and treatment-related issues.[6] Among the latter, ease of administration and frequency of dosing are cited as possible factors. Thus, it is worth noting that the available ICS differ in frequency of dosing and administration technique. Most ICS require twice daily administration, except budesonide (which may be administered once daily after a maintenance dose is achieved) and mometasone. Budesonide, fluticasone, and mometasone are available as dry powder inhalers which require a minimum peak inspiratory flow rate but do not require a spacer. In contrast, a spacer is recommended for the ICS available as metered dose inhalers, but there is no minimum required peak inspiratory flow rate. There are other notable differences among the dosage forms, including the availability of a dose counter and necessity to prime the delivery device before use, that may affect adherence.

In summary, ICS are recommended as the preferred agents for long-term control of asthma in pediatric patients and are generally viewed as safe. Among the agents, there appear to be differences in potency, but these may be overcome with dose conversion or comparative dosing. Adherence-related issues should be noted, however, as these may factor into the relative benefits of ICS therapy.

References:

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