Paediatric Asthma Management:
The role of inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs)

Stuart Jones, BPharm, MSc, MBChB

Abstract
Asthma is a chronic disease and optimal management in paediatric patients is imperative in order to optimise functioning and quality of life, while reducing morbidity. Inhaled corticosteroids and leukotriene receptor antagonists have shown measurable benefits in this regard and have been included in all international guidelines at varying stages of asthma management.

Introduction
Asthma is a chronic inflammatory disease affecting the lower airways, which results in reversible airway obstruction, mucosal inflammation and bronchoconstriction. Symptoms include cough, wheeze, breathlessness and tightness of the chest and are evoked by a variety of triggers. It is these triggers that stimulate the hyper-responsive airways to constrict.

Once a diagnosis of asthma has been made in a child, it can be classified according to the following patterns; intermittent or persistent with further divisions of mild, moderate and severe for persistent asthma. This classification aids in the selection of the appropriate therapy depending on the patient’s age and asthma severity. Both ICS and LTRAs are included in the management strategies of asthma with each having benefits and limitations. Treatment of chronic asthma should follow a step-wise approach and when control is achieved, it should be maintained with the lowest effective dosage.\textsuperscript{1,2,3}

Inhaled corticosteroids (ICS)
Chronic asthma is characterised by remodelling of the airways. This develops by hyperplasia of all tissues within the lungs, deposition of collagen, and increases in extracellular matrix causing thickening of the bronchial walls, increased bronchial reactivity and irreversible or poorly reversible obstruction to airflow. This process is most likely a consequence of continuous bronchial inflammation, thus suggesting the rationale for early introduction of anti-inflammatory therapy, preferably with an ICS to prevent irreversible loss of pulmonary function. Corticosteroids increase the transcription of anti-inflammatory genes (producing interleukin (IL) and lipocortin) and decrease the transcription of inflammatory genes (TNFα, IL2, 3, 4, 5, 6) and act either directly on the cell or secondarily by modifying the release of mediators.\textsuperscript{4}

Inhaled corticosteroids (ICS) are safe and well tolerated, and thus the preferred long-term treatment for controlling persistent asthma of all severities in children, especially those older than 5 years. ICS reduce the frequency and severity of symptoms, the use of oral steroids and of hospitalisations. Improved functional status and fewer night-time awakenings due to asthma were observed in children 4–11 years of age with mild to moderate persistent asthma treated with inhaled fluticasone propionate.\textsuperscript{5,6,7,8,9}

Regular use of ICS such as budesonide, during an 18 month period, afforded better asthma control but had more systemic effects than did the ‘as needed’ use of budesonide.\textsuperscript{10} In the CAMP study, discontinuation of ICS treatment was associated with an increase in asthma symptoms and an increased use of bronchodilators.\textsuperscript{6} Compared with other non-steroid asthma medications, ICS have proven superiority in improving lung function, symptom-free days, and inflammatory markers. One study suggested that early intervention with ICS reduces loss in lung function. Whether airway remodelling is reduced or prevented in the long term is still unknown.\textsuperscript{11} According to the PRACTALL report, early treatment from 2 or 3 years of age with ICS does not appear to alter the course of the changes associated with remodelling.\textsuperscript{12}

Due to lack of evidence, ICS treatment in children aged 0–2 years is only indicated for severe persistent asthma. In children 3–5 years, ICS are the agents of first choice.\textsuperscript{12} The starting dose for children over 12 years of age is 200 mcg equivalent of beclomethasone dipropionate (BDP) twice a day, and 100 mcg equivalent of BDP twice a day for children under 12.\textsuperscript{13}

The current recommendations are that ICS be reserved for persistent asthma. This should be considered when a child has uncontrolled asthma, indicated by exacerbations of asthma in the previous 2 years, use of inhaled short acting...
Ciclesonide, a new ICS not registered for use in children less than 12 years, given at 160 mcg once daily showed similar efficacy to budesonide 400 mcg once daily in improving FEV1, morning and evening peak expiratory flow (PEF), asthma symptom score sum, use of rescue medication, percentage of days without asthma symptoms and without need for rescue medication. From clinical trials, it is evident that ciclesonide causes fewer side effects at moderate doses due to lower systemic activity and fewer local oropharyngeal side effects than conventional inhaled steroids.

There is an increasing body of evidence demonstrating that ICSs, at recommended doses, are also safe and effective in infants and younger children with asthma. They are, however, ineffective and not indicated for use in children with episodic wheezing, such as occurs post-RSV (respiratory syncytial virus) infection, which is common in this age group.

**Safety concerns regarding ICS**

The majority of safety concerns related to the usage of ICS include suppression of adrenal function, growth impairment, and interference with normal bone development, especially with long-term use. This in turn could affect patients’ wellbeing, adherence to treatment, and therapeutic outcomes. The adverse effects noted are chiefly caused by systemic absorption, which is dependent on the dose administered as well as the mode of delivery. Inhalation methods deposit a large proportion of the dose in the mouth and oropharynx, from where it is subsequently swallowed and absorbed. Metered dose inhalers (MDIs) typically deliver less than 10% of the dose to the lungs, however, the addition of a spacer device can increase this to 20%. The older ICS may cause temporary slowing of growth velocity, but the limited data available does not show any significant compromise on final adult height. The effect on growth of fluticasone propionate may not be as great as with the older ICS, but there have been case reports of growth suppression in children receiving high doses of fluticasone propionate. Ciclesonide may also cause less growth suppression.

**Inhaler devices**

Inhaler devices are of utmost importance in the management of asthma and it is imperative that the device delivers the drug to the Airways consistently and in the appropriate quantity. There are many devices that are currently available on the market and include pressurised metered dose inhalers (pMDIs) (which can be breath activated or manual), dry-powder inhalation systems (DPIs) and nebulisers. Metered dose inhalers require co-ordination and thus the addition of a spacer is necessary to increase the effectiveness of the medication.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Names</th>
<th>Dosage range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Beclate®</td>
<td>200 800 mcg (usual maintenance range 200 400 mcg)</td>
</tr>
<tr>
<td></td>
<td>Becloforte®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bectide®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovar®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandoz Beclomethasone®</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort®</td>
<td>200 800 mcg (usual maintenance range 200 400 mcg)</td>
</tr>
<tr>
<td></td>
<td>Inflammmide®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Budellam®</td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flixotide®</td>
<td>100 400 mcg (usual maintenance range 200 400 mcg)</td>
</tr>
</tbody>
</table>

There have been numerous studies proving the safety of ICS. However, a UK study published in 2002, reported 33 cases of acute adrenal crisis after abrupt discontinuation of high dose fluticasone. This has been shown not to occur after discontinuation of low to moderate-dose ICS therapy. The risk of growth suppression needs to be taken into account when considering the choice of agent and device. Prescribers should be aware that the risk is increased when ICS therapy is combined with intranasal or transdermal steroid therapy. A study in children aged 1–3 years showed no effect on growth after 12 months of treatment, and the administration of ICS alone has not been associated with any detectable effects on final adult height achieved. In the CAMP study, both growth velocity and bone density were similar between children after 4–6 years of budesonide versus placebo treatment.
required in young children. For children 0–2 years, the NICE guidelines recommend the use of an MDI plus spacer plus a face-mask, while for 3–5 year olds, a MDI plus spacer is recommended. Washing instructions for the spacer must be communicated to the caregiver. DPIs require good inspiratory capacity and are thus suitable for older children. The effectiveness of any device depends on the willingness and ability of a child to use it and to adhere to an effective regimen. Studies have shown that good one-on-one education is the key to correct inhalation techniques. Bearing this in mind, it is still up to the healthcare providers to aid in the selection of the appropriate device. More information regarding device selection is available from the NICE guidelines for inhalation devices.2,7,28,29,30

**Leukotriene Receptor Antagonists (LTRAs)**

As mentioned previously, inflammation plays a pivotal role in the pathogenesis of asthma. Some of the most potent inflammatory mediators are the cysteinyl leukotrienes (CysLTs), which are produced via the action of 5-lipoxygenase on arachidonic acid.31 These leukotrienes stimulate production of airway secretions, microvascular leakage, impair ciliary action, enhance eosinophilic migration into the airways and increase airway responsiveness.32 They are even more potent bronchoconstrictors than histamine, and have been implicated in smooth proliferation and airway remodelling.31 Thus, LTRAs have been developed to prevent these detrimental effects by preventing the binding of CysLT to the CysLT receptors, which are found in abundance on the pulmonary smooth muscle and macrophages and monocytes.31,33

The current asthma guidelines published by the Working Group of the Allergy Society of South Africa specify that LTRAs are indicated for mild persistent asthma as an alternative to ICS (should there be any contraindications to ICS or the patient be unwilling to use them),3,24 and as add on therapy for moderate and severe persistent asthma. British Thoracic guidelines published in 2008 recommend the use of LTRAs only as add on therapy for children aged 5–12 years, while for children aged less than 5 years, they are indicated as either monotherapy or add on therapy. The PRCTALL consensus report advocates montelukast as initial controller therapy for mild asthma in children and promotes its use in viral-induced wheezing in children 0–5 years.24 Some studies have shown that montelukast may be used as short course therapy for viral-induced asthma exacerbations or ‘episodic asthma’.36 Another indication for LTRAs is as an alternative agent for exercise-induced asthma due to its quick onset and prolonged duration of action.15,19,36

Two Cochrane reviews (one comparing LTRAs to ICS as monotherapy and the other as add on to ICS), concluded that the addition of LTRAs to ICS may produce a modest improvement in asthma control. It is unknown whether this benefit is as effective as increasing the dose of ICS, especially as the evidence in children was severely lacking. Thus, the substitution of ICS with LTRAs could not be recommended in children.32,37 However, as previously noted, most other guidelines do recommend these agents as add on therapy.15,34

In children 2–5 years, montelukast significantly improved asthma outcomes compared to placebo. This was not seen in a placebo-controlled trial involving infants 6–24 months of age. The MOSAIC trial compared montelukast 5 mg daily with fluticasone propionate 100 mcg twice daily, with its primary outcome being measured as any day without asthma rescue medication use or health care resource use. The authors of the study concluded that montelukast was not inferior to low-dose ICS. However, certain measures such as FEV1, as needed B2 agonist use and quality of life were significantly better in the fluticasone treatment group.36 It has been noted that some authors argue whether or not this efficacy advantage of ICS over LTRAs will diminish in the practical setting of everyday patient management where adherence and issues regarding education of the patient and follow-up are not as stringent as in randomized clinical trials. The overall findings do however indicate that children 5–17 years of age achieve better outcomes in terms of improved lung function, decreased exacerbations and improved quality of life with ICS compared to LTRA therapy.13,33,39 In a study by Szefler comparing montelukast and budesonide in children 2–8 years with mild asthma or recurrent wheezing, both modalities provided acceptable asthma control. However, overall efficacy measures still favoured the ICS.5,40

LTRAs have a limited side effect profile when compared to placebo in most therapeutic trials. Those side effects more often reported are headache, abdominal pain, dry mouth and thirst, and gastrointestinal disturbances, while the development of skin rashes and flu-like symptoms are far less common. Some concerns do remain, in particular the elevation of hepatic enzymes (which occurs at above therapeutic dosages) and the development of Churg-Strauss syndrome which has been reported in adults, however there is no documented case in children.13,32,39 One study performed by Migoya and colleagues showed safety and tolerability in children aged 6–24 months.41 Another advan-

---

**Table II: Currently available LTRAs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Dosage form</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlukast</td>
<td>Accolate 20®</td>
<td>20 mg film coated tablet</td>
<td>&gt;12 years 20 mg BD</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Singulair®</td>
<td>4 mg chewable tablet</td>
<td>2 5 years 4 mg nocte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mg sprinkles</td>
<td>2 5 years 4 mg nocte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg chewable tablet</td>
<td>6 14 years 5 mg nocte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg film coated tablet</td>
<td>&gt;15 years 10 mg nocte</td>
</tr>
</tbody>
</table>
tage of montelukast in particular is that its bioavailability is not affected by food and it has almost no clinically relevant drug interactions. Montelukast is available as chewable tablets and sprinkles given once daily facilitating administration. In one study, parents reported that montelukast was convenient, less difficult to use and was used as instructed more than the comparative inhaled corticosteroid.  

Conclusion

It is evident that ICS are the mainstay of paediatric asthma management and although they are not registered for use in very young children, their safety has been proven when the appropriate dosages are used. A major concern with ICS is growth restriction, however, it appears that when used according to guidelines, most children achieve normal adult height. Emphasis needs to be placed on the correct use of inhalation devices in order to achieve adequate therapeutic responses. LTRAs have an ever-increasing role in the management of asthma, with their limited side effect profile and ease of administration making them appealing. Their use may be expanded from current guidelines to include their use in episodic asthma.

References:

2. NICE technology appraisal guidance 38. Inhaled devices for routine treatment of chronic asthma in older children aged 5 to 15 years. 2002.
35. Ducharme F, di Salvo F. Anti leukotriene agents compared to inhaled corticosteroids in the management of recurrent and / or chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002314. DOI: 10.1002/14651858.CD002314.pub2.