

Inhaled corticosteroids and long-acting beta2-agonists for the treatment of chronic asthma in children under the age of 12 years: Systematic review and economic analysis

Personal statement:

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Personal standpoint

I have prepared this submission from my standpoint as a primary care clinician and researcher. I have extensive personal experience of treating children with asthma both in primary and secondary care clinical settings. I am in receipt of Asthma UK Senior Research Fellowship and have a programme of research aimed at understanding and improving the diagnosis and management of asthma in the community. This statement will be mainly directed to asthma management in a primary care setting.

Background

Childhood asthma is a common clinical problem in General Practice and every GP will come across children with asthma and wheezing on a very regular basis. Most childhood asthma is diagnosed and managed in the community, and the cases which reach secondary care are frequently severe, complicated and atypical. Much routine asthma care is now delivered by (hopefully suitable trained!) asthma nurses working to agreed protocols in dedicated clinics in the community. It is aimed to provide structured care by seeing and assessing asthmatic children on at least an annual basis, and proactive asthma care is encouraged in the 'performance related' Quality and Outcomes Framework' payments in the new GP contract. Acute asthma care will often however occur in emergency and out-of-hours settings, and decision making for maintenance treatment will not infrequently occur in this setting rather than in the planned clinic environment.

The BTS (now BTS/SIGN) guidelines for the management of asthma have been present for a number of years and have acted as the basis of GP asthma care for the last decade. They were the first disease specific guidelines that became available to GPs and although GPs have subsequently complained of guideline overload and 'fatigue', the asthma guidelines have generally been well received and have been most influential in determining treatment pathways and influencing prescribing decisions.

Many children wheeze in early childhood and not all go on to manifest true asthma; it is recognized that there are different phenotypes of wheezing illness in children, including transient infantile wheezing and recurrent viral-associated wheezing. There is now evidence that these children with non-asthma wheezing phenotypes have an essentially benign condition and do not need or benefit from inhaled corticosteroid (ICS) treatment, which is the mainstay of true asthma. At presentation it can be very difficult for GPs to tell which pattern of childhood wheezing illness a particular child is showing, although factors such as a personal or family history of atopy or persistent symptoms between viral episodes may point to asthma. The decision on whether or not to commence ICS treatment can be very difficult, and it seems likely that some children have been unnecessarily exposed to the risks associated with ICS treatment. Diagnostic issues are of considerable importance in younger children and are by no means straightforward.

The message that there is an inflammatory basis to true asthma so a need for anti-inflammatory treatment with inhaled corticosteroids has been well assimilated, and GPs and asthma nurses do understand that children with persistent symptoms need treatment with inhaled corticosteroids. The 'flat' and individually variable dose-response relationship between ICS dose and clinical outcome has been less well assimilated and there is a tendency to think that if some is good more must be better, which is not necessarily the case with ICS in children. Indeed, lack of response may indicate steroid unresponsive disease (eg viral associated wheezing, where there is a Cochrane review conforming lack of effect of ICS), and in this situation increasing ICS dose is not always appropriate. Over-use of ICS in children is a real problem.

The BTS/SIGN guidelines for management of children aged 5 to 12yrs. are similar to those for adults (other than reduced dosages) but different guidance applies to those under 5yrs., where lower doses of ICS are used and add-on therapy is with a leucotriene antagonist rather than with a long acting beta agonist; there is however considerable evidence of over-use of high dose ICS, under use of add-on therapy and inappropriate unlicensed use of add-on classes (eg LABA and combination inhaler use in younger children, in whom they are not licensed and in whom there is no evidence base).

The process of care and outcomes of care in childhood asthma have both shown evidence of improvement over the last 10 years (although with considerable local variations), and GPs probably diagnose and treat asthma better and more effectively now than in the past. The model of nurse-run proactive asthma clinics and structured asthma care is very effective and suitable for many children but does not meet the needs of all. Non-compliance with treatment (particularly with ICS treatment) and non-attendance for routine asthma care are common, and asthma outcomes are worse in disadvantaged populations and ethnic sub-groups. Parents harbor considerable concerns about ICS treatment, and sometimes have exaggerated fears about side-effects.

There are now several different inhaled preparations licensed for the treatment of childhood asthma, with different drug classes, different molecules within a class and different delivery systems for the same medication. Fixed dose combination

inhalers have arrived and may be used in older children, and have been heavily marketed in General Practice. The BTS/SIGN asthma guidelines do not specify which of the many therapeutic options is the best for the individual patient. Different preparations have different costs and health resource implications, with metered dose inhalers being generally the cheapest devices. However, poor co-ordination and poor inhaler technique are common in community practice, and poor delivery of active drug may be associated with treatment failure. Compliance is a major problem with regular prophylactic treatment, particularly with ICS, where parents may have excessive fears of steroid-related adverse events. Drug delivery may be problematic in young children.

ICS

ICS are absolutely fundamental to GP asthma management and there is a powerful body of evidence supporting the use of this class of agents in childhood asthma, but evidence of lack of effectiveness in other wheezing phenotypes. Overall use of ICS has improved, but parental fears remain a significant obstacle and many harbor fears of side effects and loss of efficacy over time with long-term ICS use. The safety profile of ICS is very good in lower doses but there are concerns with the use of higher doses particularly over longer periods of time, and there have been reports of serious adrenal suppression and other severe steroid related adverse events with inappropriate high dose ICS treatment. There has in the past been a perception amongst some GPs that ICS are completely safe and it is possible that excessive doses have been used. The guideline recommend that children felt to need >400mcg/day for the under 5s and >800mcg/day for the 5-12s should be seen and assessed by a specialist respiratory pediatrician, yet there is evidence that this frequently does not occur. There are now a number of different steroid molecules available through a number of different delivery systems, some of which are unsuitable for younger children. There is a difference in potency between different molecules and indeed the same molecule may have differing potency with different delivery systems (eg beclomethasone via CFC containing and CFC free MDIs) and this may create confusion and inappropriate dosing. The lower age limit for various preparations is very variable and confusion may occur. Some of the newer steroid molecules such as ciclesonide and mometasone have been claimed to be 'softer', i.e. to have lower systemic bioavailability and so to cause fewer local and systemic side effects, with some data to support these claims; the place of these agents in childhood asthma remains to be established.

LABA

A powerful body of research (mostly industry sponsored) has generally shown better outcomes in older children uncontrolled on standard doses of ICS who have a LABA added to those who have the dose of ICS increased, and this has led to a great increase in the use of this class of drugs, which have been heavily marketed. GPs have certainly found them to be very effective in asthma, and prescribe them widely as stand-alone or as combination inhalers. The LABA safety data from controlled trials has been good but more recently safety

concerns have arisen from post-marketing studies (mainly in the USA). There is general agreement that LABAs should never be used without ICS in asthma, and their license specifies this; however, there is evidence that due to differential non-compliance with ICS treatment they are used alone by some patients in 'real life' settings. There may be some sub-groups (e.g. those with specific genotypes of the B2 adrenoreceptor) who don't do well with LABAs, but at the moment there is a lack of clinical markers to detect such patients. The use of combination inhalers (ICS-LABA) gets around the problem of differential compliance and seems to be effective for many patients. Patients and GPs seem to like the simplicity and easily perceived effectiveness of combination inhalers and this has increased their popularity with both. There has been a tendency for them to be used ever earlier in asthma care, and they are now not infrequently prescribed as the 'first-line' preventer inhaler by some GPs. This may however put some children at risk of adverse outcomes, and it's likely that most children can be controlled on ICS alone.

Cost Issues

GPs are under pressure to limit prescribing costs and the cheapest preventative treatment for asthma is currently beclomethasone via a metered dose inhaler. However the frequent changes in the cost of different inhalers, and the looming CFC transition issue also makes this an area in which cost changes are occurring constantly. There is a body of health economic data stressing that much of the costs of asthma relate to poor control, so cheaper inhalers that are either poorly used or not adhered to may result in higher overall costs if control is poor. Most GPs and nurses would feel that a variety of devices and preparations are needed and involving patients and parents in decision making is a good idea.

Conclusion

This is a complex area with many different factors involved. From the GP standpoint, issues such as patient education, patient, parent and GP preference, adherence and inhaler technique are of crucial importance, and are often not addressed in classical RCTs and standard evidence based medicine approaches. There is a need for more pragmatic evidence from community based studies. Asthmatic children are heterogeneous, there are a number of overlapping phenotypes of childhood wheezing and it is unlikely that a 'one size fits all' approach will suit all patients. Perhaps the best we can do is advise on the order in which different therapeutic approaches should be attempted. As asthma is a chronic condition, safety is important and rare and long-term adverse events need to be considered. The economics of asthma are complex and costs of exacerbations need to be captured.