Research Review
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Oral Steroid Use in Chronic Asthma

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Introduction

Oral corticosteroid prescribing is an accepted part of acute asthma management in New Zealand under well-defined, appropriate circumstances. In fact, it is estimated that some 130,000 of ALL oral corticosteroid scripts written in 2008 by New Zealand GPs were for asthma (source: IMS Health [NZ] Ltd).

However, it is also well known that long-term oral corticosteroid use can have significant side effects. For example, frequent short courses (bursts) of oral corticosteroids (>2.5 courses per year) have been associated with decreased bone mineral density (BMD) in adults with asthma[1]; similarly, multiple oral corticosteroid bursts over a period of years can produce a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in children with asthma.[2]

This publication is intended as an educational resource for New Zealand health professionals to both inform and remind them of the risks and benefits of taking oral corticoid treatment. Information is also provided to assist with better diagnosis resulting in the use of oral corticosteroids only as is necessary, and as part of a well-constructed asthma patient management plan.

Recommendations – Associate Professor Jim Reid

There should be few asthmatics who require systemic corticosteroids for asthma control. They are, however, not uncommonly used as maintenance therapy in developing countries, where the cost of the provision of metered-dose inhalers (MDIs) of inhaled corticosteroid is prohibitive. As everyone is aware systemic corticosteroid usage, even in modest dose, can cause significant side effects, including osteoporosis, skin thinning, diabetes mellitus, cataract, and growth retardation in children. The New Zealand and international guidelines (GINA, BTS/NICE, SIGN) are unanimous in recommending that continuously administered systemic corticosteroids are a "last resort" and should be administered as "add-on" therapy on the advice of a specialist. However, systemic corticosteroids should be used in short courses for acute exacerbations of asthma. Children should be administered 2 mg/kg prednisone, and the same medication should be used in adults in a dose of 40–60 mg for no longer than 10 days. It is generally not necessary to taper the dose.

If disease control is not being achieved with appropriate doses of inhaled cortciosteroid, plus long-acting β-agonist, it is important to check the patient's inhaler technique, and adherence. MDIs are very difficult for some patients to manage, and switching to a breath-activated inhaler may be useful.

It is now generally accepted that long-term systemic corticosteroids should only be used in the lowest possible dose in the severest uncontrolled asthma, and only after referral to a respiratory physician, or in the case of children, a paediatrician.

If long-term systemic corticosteroids are needed, or frequent courses for exacerbations (more than 3–4/year), consideration needs to be given to provision of bone-sparing medication, as well as keeping a close watch to prevent as far as possible other side effects.

Commentary – Dr Lutz Beckert

Before we can comment on the long-term use of oral prednisone and its associated side effects, it is timely to remind ourselves of the disease-modifying and life-saving effect of oral prednisone therapy.

A study that estimated the risks of asthma mortality associated with specific classes of medication and patterns of management found that use of oral preventive (corticosteroid) medication, which included prednisolone, prednisone, betamethasone, or dexamethasone tablets, was significantly more likely in cases of asthma death.[3] On the other hand, the use of oral corticosteroids for an attack of asthma reduced the risk of death by 90%.

This study, which was performed in Melbourne, closely resembles the prescribing practice in New Zealand. It has been accompanied with an editorial by Julian Crane and Richard Beasley. The results of this study come as a chilling wake up call in that 89 asthma deaths occurred in young people with a mean age of 38 years. It also provides the best possible evidence for a written asthma management plan and against the use of home nebulisers. In this context we would like to highlight one aspect of **the bottom line: The use of oral corticosteroids during an asthma attack reduces the risk of death by 90%.**

All guidelines and all evidence, however, argue against the long-term use of oral prednisone.

A Snap Shot

Japanese researchers evaluated the effects of long-term (i.e. 4 years) use of inhaled beclomethasone dipropionate and short courses of oral corticosteroids on bone mass in 35 asthmatic adults.[1] Those who received frequent short courses of oral corticosteroids (i.e. >2.5 courses per year) showed a significantly greater BMD loss than patients who received sporadic courses (≤2.5 courses per year). In contrast, ICS treatment *per se* did not affect BMD.

Reference: Matsumoto Het al. Chest 2001:120;1468-73.

Systemic corticosteroid therapy in asthma

Systemic corticosteroid therapy is recommended for children with moderate to severe acute asthma or in cases that are unresponsive to β_2-agonists.[4] Corticosteroid treatment for less than one month is considered short-term, while treatment continuing for more than 3 months is regarded as long-term, and is associated with numerous undesirable side effects. Risks are related to dose and duration of use.

Side effects from short courses

Oral corticosteroid therapy is sometimes advised for severe asthma attacks in children, but it should only be prescribed when really necessary, as quick-relief medication for its broad anti-inflammatory effects. The recommended initial therapy is 1 mg/kg prednisolone (maximum dose of 50 mg) orally; this may be repeated every 12–24 hours, depending on response.[4]

Short courses of up to 3 to 5 days can be given together with controller medication to gain initial control of asthma and to speed resolution of moderate or severe persistent exacerbation. Courses of 7 days or less are usually sufficient for therapy, but some exacerbations require up to 10 days of treatment. Tapering of the dose is not necessary.[5]

While much evidence links long-term corticosteroid use to decreased bone mineral density (BMD), data are lacking from large, prospective studies regarding the effect of short courses of oral corticosteroids on the BMD of children with asthma. Notably, many treated children are going through adolescence, a time of rapid bone accrual that precedes the attainment of peak bone mass. Factors that compromise peak bone mass during this period might increase the risk of osteoporosis and fracture later in life.[6]

One prospective study has evaluated the effect of multiple short courses of oral corticosteroids and use of inhaled corticosteroids on bone accrual in 877 children aged 5–12 years (531 boys and 346 girls) participating in the Childhood Asthma Management Program (CAMP) trial over a 7-year study period.[2] Multiple short courses of oral corticosteroids in boys, but not girls, were a dose-dependent risk factor for decreased bone mineral accrual and osteopenia. Inhaled corticosteroid use in boys, but not girls, was also associated with decreased bone accrual, but the association was not dose-dependent. Neither oral nor inhaled corticosteroid therapy increased the risk of fracture.

These findings appear to indicate that long-term corticosteroid use does not compromise bone mass enough to cause morbidity (i.e. fractures).[6] However, it is less clear as to whether corticosteroids lead to reduced peak bone mass in adulthood. More data are required from large, longitudinal studies with long follow-up periods, to determine the effect of corticosteroids on peak bone mass, osteoporosis and fractures later in life.

Clinical evidence suggests that short-term corticosteroid therapy will accelerate resolution of moderately severe and severe-acute attacks of asthma without significant suppression of adrenal function.[4,7] However, 20% of children who are administered 4 or more "bursts" (less than 7 days) of short-term, high-dose prednisone (1 to 2 mg/kg/day) per year for acute exacerbations show suboptimal adrenal response.[7]

Just as is the case in children, adult patients may experience side effects of oral corticosteroids, even during a short course. These side effects can include: stomach irritation, fluid retention causing a sense of bloating, hunger, sleeplessness, blurry vision, short temper, increased or decreased energy, and difficulty concentrating. Women may develop irregular menstrual cycles and vaginal yeast infections.

Side effects from longer term treatment

Oral corticosteroids are associated with an increased risk of fractures from negative effects on sex steroids and vitamin D with a negative calcium balance, together with negative effects on the bone cells and the bone matrix.[8] Interestingly, it has been proposed that the increase in fracture risk with oral corticosteroids is linked more to daily than to cumulative dose.[8] A small daily dose may consequently be more detrimental than a large cumulative dose given as intermittent doses.

Due to the associated decrease in BMD, screening for osteoporosis and therapies for bone loss prevention should be considered in all patients who require long-term corticosteroids. Preventative therapy includes calcium, vitamin D and a bisphosphonate, as well as hormone replacement therapy in postmenopausal women. Treatment is most effective when started at the same time as the corticosteroids, as most bone loss occurs within the first few months. This is most important for patients prescribed more than 7.5mg of prednisone (or the equivalent dose of another oral corticosteroid) for 3 months or more.

Long-term use also predisposes to suppression of corticotrophin secretion and atrophy of the adrenal cortex, making it dangerous to suddenly discontinue oral corticosteroids after regular use in moderate to high doses for more than about 3 to 4 weeks. In such cases, supplemental corticosteroids are advised.

Complications of long-term corticosteroid use include aseptic necrosis of bone, stomach ulcers, psychosis, and sleep disturbance. Oral corticosteroids are a known risk factor for the development of glaucoma and subcapsular cataracts, with risk influenced by daily cumulative dose, age, and ethnic origin.[9,10]

Prolonged or high doses of oral corticosteroids are also associated with various side effects affecting the skin, including an increased risk of skin infections such as bacterial infections (e.g. cellulitis) and fungal infections (e.g. tinea, candida).[11] Patients may also experience thinning of the skin, leading to easy bruising (purpura), skin tearing after minor injury, slow healing, and stretch marks (striae). Some patients are also prone to acne, which tends to develop as clusters of small spots on the face, chest and upper back.

US researchers recently noted that a substantial proportion of patients receiving long-term corticosteroid therapy do not receive BMD measurement or preventive therapy for osteoporosis, as recommended in GIOP (glucocorticoid-induced osteoporosis) practice guidelines.[12] They recommend that future research should focus on understanding barriers to GIOP identification and facilitating osteoporosis management.

Clinical studies have proven the efficacy of bisphosphonate therapy in the prevention of blone loss in patients treated with corticosteroids, and etidronate has been associated with a reduction in height loss and vertebral fracture.[13] However, in a five-year study involving patients with asthma who had been taking regular oral and/or inhaled corticosteroids for 1 year and more, etidronate and calcium used alone or combined failed to reduce fracture rates.[14]

Are oral corticosteroids too risky to use?

A severe attack of asthma that fails to improve with other treatments is risky. A short course of oral corticosteroids for severe asthma can prevent admission to an emergency department for treatment of asthma, avoid hospitalisation, and even save a patient's life. While their overuse or prolonged continuous use is associated with unwanted side effects, long-term oral corticosteroid use is inappropriate for most asthmatics because of other readily available effective treatment strategies.

Side effects of oral corticosteroids

Side effects of short-term oral steroids include:

- upset stomach or nausea
- increased appetite
- mood changes
- hyperactivity

Side effects of long-term oral steroids include:

- skin thinning and bruising
- poor wound healing
- increased risk of skin infections
- diabetes mellitus
- acne
- weight gain
- growth retardation in children
- hypertension
- accelerated bone loss
- cataracts
- aseptic necrosis
- psychosis
- sleep disturbance
- glaucoma
- skin striae (stretch marks)
- Cushingoid feature

Local guidelines on oral corticosteroids in the treatment of asthma

Local guidelines on the diagnosis and management of asthma in children aged 1–15 years and those under 5 years have been issued by the Paediatric Society of New Zealand.[15,16] The Society notes that few infants who wheeze have asthma. The guidelines advise that during acute episodes of recurrent or persistent wheeze, supportive treatment should be provided as described under management of acute wheeze. There is insufficient evidence to recommend the use of regular daily oral corticosteroids in infants with recurrent or persistent wheeze. For children aged 1–15 years, the guidelines advise oral administration of prednisolone or prednisone early in the treatment of acute asthma attacks, at a dose of 1–2 mg/kg per day. A maximum dose of 40mg per day is usually sufficient, but up to 60mg may be used. Treatment for up to 3 days is usually sufficient, but can be extended as required to effect recovery. Tapering of short courses (up to 7–14 days) of corticosteroids is not necessary.

New Zealand guidelines suggest that in those newly diagnosed adults with asthma who have moderate to severe symptoms, or a FEV_1 <60% predicted, a short course of oral corticosteroids should be considered to quickly establish control of the asthma, e.g. prednisone 40mg for 4–10 days following an acute exacerbation of asthma reduces the number of relapses requiring additional medical care and decreases β_2-agonist use without any apparent increase in adverse effects.[17] The guidelines advise there is no evidence of benefit in using a dose of more than 100mg of prednisone or prednisolone. Oral prednisone is recommended for all acute severe episodes. For the management of chronic asthma, the stepwise approach to drug therapy for increasing severity of asthma lists oral corticosteroids as the last step, at the lowest dose possible and preferably under specialist review.

These treatment recommendations are supported by international guidelines on the management of asthma issued by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guideline Network (SIGN), as well as those issued by the Global Initiative For Asthma (GINA).[17,18]

Corticosteroid-resistant asthma

Some asthmatics suffer attacks despite regular use of corticosteroid therapy, meaning they fail to respond to either inhaled or oral corticosteroids or they need such high doses that side effects are experienced. The cause of corticosteroid-resistant asthma (CRA) is unknown, but there is an urgent need to increase our understanding of the condition and to find ways to improve symptom control. In the UK, the management of CRA consumes up to 70% of total annual National Health Service (NHS) asthma costs; in the USA, as many as 50% of diagnosed asthmatics have asthma that can be resistant to corticosteroid therapy.[16,17]

Modern technology may enable tailor-made new treatments for asthma, as researchers begin to better understand how corticosteroids alter cell function, and how these may affect patients differently. For example, US-based researchers have found that Th17 cells mediate corticosteroid-resistant airway inflammation and hyperresponsiveness in animal models of asthma.[17] It may therefore be that corticosteroid therapy effectively suppresses the inflammatory process in asthma induced by esosinophil and mast cell activation, but has no such effect in inflammatory processes driven by different cell mechanisms.

When faced with CRA, it is important not to use increasing doses of corticosteroid (whether ICS or oral), in attempts to obtain control in this type of asthma.

It is also worth noting how recent UK research has demonstrated short-course oral prednisolone to be no more effective than placebo in children between the ages of 10 and 60 months presenting to hospital with viral-induced wheeze.[18] Routine administration of corticosteroids as recommended by national guidelines is therefore questionable for the treatment of preschool children with viral-induced wheezing.

Corticosteroid treatment options for asthma

In New Zealand, the most commonly used tablet formulation used in asthma therapy is Prednisone, which is issued in sizes of 1mg, 2.5mg, and 20mg. Dexamethasone is available in tablets of 1 and 4mg, Medrol as 4mg tablets, and Betnesol (0.5mg soluble tablet). Dosage is tailored to the individual patient – from 2–3mg to 40mg per day.

Aspects of long-term corticosteroid use

Dr Beckert highlights four possible aspects of long-term corticosteroid use.

1. Tapering may cause confusion and be an inconvenience to patients and paradoxically some patients stay on prednisone inadvertently for weeks or months.

The reasoning behind corticosteroid tapering was to prevent a rebound of worsening asthma after a presumed suppression of the hypothalamic-pituitary-adrenal axis following corticosteroid therapy. In 1993, a randomised controlled trial suggested that corticosteroid tapering is unnecessary after short-term therapy.[19] In that study, 35 adult patients with acute asthma requiring hospital admission received oral prednisolone 40 mg/day for 10 days followed by a 7-day tapering course of either prednisolone (active taper) or placebo (placebo taper). After 10 days' treatment, mean peak expiratory flow rate was significantly improved from baseline and did not change significantly during the 7 days of tapering or during the following 10 days. **Bottom line: A 10-day course of prednisone 40mg for acute asthma is adequate. The prednisone can then be stopped abruptly, with tapering not being necessary.**

2. The lack of adherence to therapy leading to inappropriate escalation of therapy and possible prescribing of oral steroids.

In the AIRE study, involving almost 3000 patients with all severity groups of asthma, only approximately a quarter of all patients adhered to inhaled corticosteroid therapy.[20] Recent evidence suggests that adherence with inhaled corticosteroid therapy may improve with combination therapy. **Bottom line: Many patients who have ongoing symptoms of poor asthma control don't take their prescribed inhaled corticosteroids.**

3. The effect of obesity on breathlessness and its possible link to asthma.

A recent review examined the clinical and epidemiological evidence linking obesity with the development and severity of asthma and weight reduction with improvements in asthma severity and symptoms.[21] Some possible links between asthma and obesity include:

a) Shortness of breath and wheeze in obese patients can be due to increased BMI on airway calibre, a sensation of breathlessness and lung stiffness, confounded by an increased cost of oxygen for movement, frequently a degree of deconditioning and possibly associated cardiac disease. This is not classical airway hyper-responsiveness (e.g. Thorax 2001;56:4-8).

b) Approximately 15% of adults have a mild degree of airway hyper-responsiveness but no overt asthma symptoms. These patients may become symptomatic as their BMI increases and to some extent they are suffering from 'real asthma', but without more airway inflammation (e.g. Int J Obesity 2008;32:502-509).

c) Epidemiological evidence indicates that large amounts of adipose tissue release inflammatory cytokines, which may cause asthma requiring increased doses of corticosteroids to control symptoms (e.g. Am J Respir Crit Care Med 2008;178:469-475 and JSCI 2009;123:S84).

4. The differential diagnosis of dysfunctional breathing or paradoxical vocal cord movement in patients with asthma.

In a UK-based survey involving 219 adult patients with diagnosed, treated asthma, 63 scored a total Nijmegen score of ≥23, indicative of dysfunctional breathing.[22] This reminds us that not 'everything that wheezes' is asthma. The authors of this study have been criticised for the fact that the Nijmegen questionnaire they used hadn't been validated in an asthma cohort. However, the prevalence of dysfunctional breathing in nearly a quarter of all patients with asthma is still astonishing. **Bottom line: Vocal cord dysfunction and 'dysfunctional breathing' may mimic difficult-to-control asthma and lead to inappropriate oral prednisone prescribing.**

Conclusions – Dr Beckert

Short courses of oral corticosteroids can be life saving in asthma. Our guidelines don't suggest the long-term use of corticosteroids and we have reviewed a few pitfalls regarding how patients may end up on long-term corticosteroids: 1) Patients become confused by complicated tapering protocols, 2) Non-adherence is being interpreted as non-response to inhaled therapy, 3) Obesity may confound asthma symptoms and finally 4) Vocal cord dysfunction or dysfunctional breathing may mimic or co-exist with asthma.

Approximately 5% of patients with asthma may indeed be corticosteroid-resistant and may actually consume up to 50% of the health care cost associated with asthma. See: The cost of asthma. Barnes PJ et al. Eur Respir J 1996;9:636-642. These patients will probably benefit from a second opinion and possibly specialist input.

The GINA 2007 guidelines remind specialists whenever they are faced with an asthmatic corticosteroid-dependent patient to reflect on the following questions:

- Is the diagnosis of asthma confirmed objectively?
- Can we confirm patient adherence with the correct medication?
- Does the patient have a history of current or past smoking i.e. we may be dealing with not fully reversible airways disease (COPD) rather than asthma?
- Are there comorbidities aggravating the asthma symptoms like chronic sinusitis, gastro-oesophageal reflux, obesity/ obstructive sleep apnoea or psychological and psychiatric disorders.

Some patients will require long-term prednisone therapy and special care must be taken to protect them from opportunistic infections and iatrogenic osteoporosis.

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