Editorial

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Two current hot topics are discussed in detail in the review section of this issue. Professor Neil Thomson highlights the important issues related to inhaled topical steroids and their use in adult asthma. Evidence related to add-on therapy with long acting ß2-agonist bronchodilators, leucotriene antagonists or theophyllines enables the reader to choose between these options and identifies areas for further research.

Professor van Schayck *et al*, present evidence based recommendations for the management of COPD. This paper provides us with options and strategies for diagnosing and treating this prevalent condition. Our intention, in presenting these two papers, is to stimulate a lively discussion, through correspondence to the journal, on these two very topical issues.

The pilot study by Christopher Hand tackles the complexities related to high quality questionnaire development and implementation in order to improve our understanding of our patients beliefs related to inhaler treatment. This type of study is invaluable in our struggle against poor patient as well as health professional compliance.

David Price and colleagues have elegantly summarised the process and outcome of a public meeting to address issues related to people's beliefs on steroids.

It is evident that *Asthma in General Practice* is attracting a high quality of papers. We hope these papers stimulate our readers to think about their practice and would really value some feedback on the clinical practical value of the ideas and issues raised. Constructive criticism of papers published will further enhance the value of our journal. Please address any correspondence to *The Editor* and we will endeavour to publish this on our website soon, with selected correspondence published in the journal.

Finally, please let me remind you that we are currently calling for papers for our XIIth Annual Scientific Meeting on the 4th and 5th June 1999: deadline for abstracts is 31 January 1999. Please contact Strategic Medical Publishing for abstract forms and for more information about the ASM please contact the Secretariat, MMI.■

Mark Levy
Editor

Review

What is the future for inhaled steroids in adult asthma care?

N C Thomson

Inhaled steroids are the most effective, locally administered drugs available for chronic asthma. Patients with mild to severe asthma respond to inhaled steroids; demonstrating improved asthma symptoms and lung function as well as reduced bronchial reactivity and rates of exacerbation from asthma.[1] The revised British Asthma Guidelines[2] emphasise the importance of the early introduction of inhaled steroids as first-line therapy for those with mild disease (step 2) and of gaining rapid control of asthma by inhaled steroid therapy at a dose high enough to control the disease. High-dose inhaled steroids also have an important place in steps 3 to 5. Although inhaled steroids have a central role in the management of adult asthma, a number of important issues remain unresolved about the most effective use of these drugs.[3]

DOSE-RESPONSE AND STEPPING DOWN

Several studies have demonstrated a dose-response relationship as regards efficacy of inhaled steroid administered in doses of up to 800 µg daily.[3,4] The therapeutic value of higher doses is less clearly established which is in part due to the poor design of some previous studies. Another important factor to consider when assessing dose-response studies of inhaled steroids is that the effect on one outcome measure (for example, PEF recording) may occur at a different dose to that for another outcome measure, such as inhibition of exercise-induced asthma. For many asthmatic patients a plateau in the therapeutic response to inhaled steroids occurs at doses below 1000 mcg daily, although some patients will benefit from higher doses. The task of predicting which patients with severe chronic asthma should receive high-dose inhaled steroid therapy is a difficult one. The value of non-invasive tests of airway inflammation such as induced sputum cell counts or exhaled nitric oxide in predicting the dose of inhaled steroid therapy appropriate for an individual patient has not been established. Currently a trial of high-dose inhaled steroids remains the only method of assessing clinical effectiveness.

It may be possible to step down the inhaled steroid dose in a sizeable proportion of patients with chronic stable asthma who are receiving ≥1000 mcg daily. Several short-term studies suggest that many patients can achieve large reductions in inhaled steroid dosage without asthma control deteriorating.[5-7] A major concern is whether the dose of inhaled steroid can be reduced in the long-term with the same effect. Furthermore, greater use of oral corticosteroids to treat exacerbations may override any attempt to minimise steroid-induced side-effects by the reduction of inhaled steroids. The recently published British Asthma Guidelines[2] recommend that, providing the patient's asthma is stable, reductions should take place every one to three months; decreasing the dose of inhaled steroid by approximately 25-50% at each step. The criteria used to define asthma control both before and during steroid reduction are not well established. Further research is required to establish simple criteria to help identify those patients who can safely step down from high doses of inhaled steroids.

STEROID-RESISTANT ASTHMA

A very small percentage of patients with asthma are resistant to the anti-asthma effects of inhaled or oral steroids.[8,9] In these individuals a two week course of 30-40 mg daily of prednisolone fails to increase the FEV_1 or PEF value by >15% despite maintaining an acute bronchodilator response of >15%. The presence of a good acute bronchodilator response helps differentiate patients with steroid-resistant asthma from those with COPD. The mechanism of steroid-resistance is poorly understood but may be due to increased activation of transcription factors by cytokines involved in airway inflammation in asthma. In susceptible individuals these transcription factors may cause consumption of activated steroid receptors within cells and so prevent the anti-inflammatory actions of steroids. Treatment must centre on the use of broncho-dilator therapy with short and long-acting ß$_2$-agonists and theophyllines. It is important to minimise oral steroid therapy in these patients, as they are at risk of developing systemic steroid-induced side-effects despite the resistance to steroid actions within the airways. However, during attacks of acute severe asthma in these patients, most physicians tend to administer short courses of systemic steroids. The value of leukotriene antagonists or immuno-suppressive drugs such as cyclosporin or methotrexate in treating steroid-resistant asthma remains uncertain.

It is possible that there could be a spectrum of steroid-responsiveness within the asthmatic population, which is genetically determined, but this remains to be investigated. Environmental factors such as cigarette smoking may also influence the effectiveness of inhaled steroids. A recent study reported that an improvement in airway function in response to inhaled steroid therapy was reduced in asthmatic smokers compared to asthmatic non-smokers.[10]

SYSTEMIC SIDE-EFFECTS

There is considerable interest in the issue of possible adverse systemic effects from different inhaled steroid therapy in asthma. Interpretation of these studies is complicated by the use of different inhaler devices with widely different patterns of deposition, previous oral steroid treatment and the pharmacological properties of the inhaled steroid (receptor binding affinity, volume of distribution, lipophilicity, and plasma half-life). It is also important to recognise that topical nasal steroids may add to the systemic effects of inhaled steroids.

Although suppression of adrenal function tests can be shown with doses above 800 µg per day of inhaled steroids, there is no evidence to indicate that these changes are of direct clinical relevance to acute adrenal failure. Nevertheless, the Committee on Safety of Medicines has advised that additional systemic steroid cover should be considered during periods of stress or elective surgery for patients who have received prolonged treatment with high doses of inhaled steroids.[11] The suppression of biochemical markers of adrenal function is of interest because it is a very sensitive indicator of systemic absorption of inhaled steroids; more so than biochemical indices of bone metabolism.[12] Inhaled steroids can have effects on markers of bone metabolism, such as serum osteocalcin, but whether they cause osteoporosis is more controversial. Studies have shown reductions in measurements of bone densitometry in chronic asthmatics receiving high doses of inhaled steroids.[13] However, this may be due to the confounding effects of previous oral steroid therapy or other risk factors for osteoporosis. A cross-sectional study found that in women, inhaled steroid therapy reduced bone density in the spine and estimated this effect to be equivalent to a 0.11 standard deviation reduction in bone density per 1000 µg per day inhaled steroid per year.[14] Boulet *et al*[15] found no differences in bone densitometry between patients receiving a mean dose of 1140 µg per day of inhaled beclomethasone or budesonide for over 24 months and a group of mild asthmatics receiving less than 100 µg per day for an average of 15.7 months. Neither group in this study received oral steroids during assessment. Of note for the clinician is guidance on which patients receiving high-dose inhaled steroids, should be referred for bone densitometry. The British Asthma Guidelines[2] do not address this issue, but patients at risk of developing osteoporosis might include those receiving three or more short courses of oral steroids, per year, for acute exacerbations of asthma and those with other risk factors for osteoporosis. In addition to the possible systemic effects with high-dose inhaled steroids on bone mineral density, their use has been associated with a slightly increased risk of the development of posterior subcapsular and nuclear cataracts[16] and glaucoma.[17] Easy skin bruising is a side-effect of inhaled steroids, which increases in prevalence with increasing age, dosage and duration of use.[18]

WHICH ADD-ON THERAPY?

The flat dose-response relationship, as regards efficacy and the potential risk of systemic absorption from high-dose inhaled steroids, makes the addition of alternative treatment an attractive option for the majority of patients receiving low-dose or medium-dose inhaled steroids, whose asthma control is inadequate. There are several therapeutic options open to the clinician at step 3 of the British Asthma Guidelines.

Long-acting ß$_2$-agonists

The long-acting ß$_2$-agonists, salmeterol and eformoterol fumarate, have an important role as additional therapy in chronic asthma and are an alternative to high-dose inhaled steroids at step 3.[19-21] Salmeterol when added to low-dose inhaled steroid improved lung function and symptom control to a greater extent than doubling the dose of inhaled steroid. Eformoterol fumarate has similar beneficial effects on asthma symptoms and lung function when added to budesonide 200 or 800 µg daily when compared to the low or medium dose inhaled steroids alone.[21] Both severe (oral prednisolone therapy) and mild exacerbations (more bronchodilator therapy) were less in the eformoterol fumarate treated groups. There have been no controlled clinical trials comparing the efficacy and side-effect profile of salmeterol and eformoterol fumarate. The choice of drug is likely to be influenced mainly by the delivery device already used by a patient to administer inhaled steroid and short-acting ß$_2$-agonist therapy.

Theophyllines

The current British Asthma Guidelines recommend theophylline as an additional treatment to inhaled ß$_2$-agonists and high-dose inhaled steroids (beclomethasone dipropionate or budesonide 800-2000 mcg daily or fluticasone propionate 400-800 mcg daily) for patients whose asthma is not controlled.[2] A recently reported randomised parallel study compared the addition of oral theophylline to moderate-dose inhaled steroid (budesonide 800 mcg daily) with high-dose inhaled steroid (budesonide 1600 mcg daily) in a group of 62 asthmatic patients.[22] At 12 weeks clinical outcome assessments including FEV_1, FVC, morning peak expiratory flow rate and rescue medication requirements during the day, improved in both

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treatment groups. Treatment with moderate-dose budesonide plus theophylline resulted in slightly greater increases in FEV_1 and FVC. Unfortunately, the study lacked a third treatment arm in which the budesonide dose was maintained at 800 mcg daily. Nevertheless, the findings suggest that the addition of oral theophylline to moderate-dose inhaled steroid is an alternative strategy to increasing the dose of inhaled steroid. A further recently published study has reported similar findings.[23] A multi-centre study of 189 moderate to severe asthmatic patients found inhaled salmeterol (100 mcg daily) to be more effective and better tolerated than oral theophylline.[24] This result would suggest that on the basis of efficacy and tolerability, inhaled long-acting ß2-agonists should be considered before oral theophylline as an additional bronchodilator for patients with poorly controlled asthma despite receiving inhaled steroids.

Anti-leukotrienes

The leukotriene receptor antagonists have been shown to have a mild bronchodilator effect in those patients with airflow obstruction and to attenuate bronchoconstriction induced by exercise, allergens and aspirin.[25] There is also some evidence to indicate that they have anti-inflammatory actions. In clinical trials, the leukotriene receptor antagonists, zafirlukast and montelukast have shown evidence of efficacy in mild to moderate asthma when compared to placebo and have been generally well tolerated.[26,27] In the UK, the leukotriene receptor antagonist montelukast is licensed for the treatment of asthma as an add-on therapy in adults and children (≥ six years) with chronic mild to moderate asthma who are inadequately controlled with inhaled steroids. It is also prescribed as a prophylactic agent against exercise-induced asthma. Zafirlukast is licensed 'for the treatment for asthma'. There are to date no fully published studies comparing the effectiveness of these drugs with other add-on therapies.

COST-EFFECTIVENESS

There is very limited data on the cost-effectiveness of inhaled steroids in asthma. Campbell *et al*[28] found no difference in clinical effectiveness of 400 µg budesonide per day compared to 800 µg per day although the higher dosage cost an extra £15.54 per person over six weeks. The introduction of inhaled fluticasone propionate to a general practice in the UK was reported to have improved indicators of good asthma control and to reduce costs for short-acting bronchodilator prescriptions.[29] Thus, although the average asthma medication costs increased in those patients receiving fluticasone propionate the reduction in other health costs resulted in a modest increase in costs for fluticasone propionate of £2 per patient over one year. The study design of this report was retrospective and non-randomised and the finding requires confirmation in a prospective double-blind study. The cost-effectiveness of nebulised compared to inhaled steroid via an alternate delivery system in chronic severe asthma needs to be established, since the cost of one month's treatment with nebulised budesonide 4 mg daily is £250 compared to £103.60 when the same dose is administered by a turbulent flow inhaler.[30]

Studies on the cost-effectiveness of different add-on drugs have not been reported. This information is of interest in view of the difference in cost of one month's treatment with theophylline compared with other add-on therapies:[30]

- oral theophylline 800 mg daily (£7.32);
- salmeterol 100 mcg daily via accurate dose inhaler (£27.98);
- eformoterol fumarate 12 mcg daily via turbulent flow inhaler (£24.80);
- montelukast 10 mg daily (£25.69);
- zafirlukast 40 mg daily (£25.69).

TRANSITION TO INHALED STEROIDS VIA CFC-FREE INHALERS

General advice on managing the transition to CFC-free metered dose inhalers has been reviewed in this journal recently.[31] Some CFC-free steroid inhalers are equally effective as CFC steroid inhalers but at approximately half the dose. A step down of inhaled steroid dose will be required for those patients receiving this reformulation. It may be sensible to delay stepping down the steroid dosage for two weeks after switching to the CFC-free inhaler, but advising the patient that the new inhaler is more effective and that a reduction in dose will be undertaken shortly. The bronchodilator response to ß2-agonists such as salbutamol administered from a CFC-free inhaler is identical to that from a CFC-inhaler.

Other important points that need to be noted during the transition period include the following.

- Patient perceptions: the taste, oropharyngeal impact and shape of some CFC-free inhalers may differ from CFC-inhalers. Patients need to be reassured that the new inhalers are effective and safe as well as environmentally friendly.
- Generic and branded products: a more limited range of CFC-free inhalers will be available for use. Many generic inhalers will be withdrawn since CFC-free versions have not been developed.
- Continuity of prescriptions: it will be important to ensure that patients are not changed inadvertently between CFC-free and CFC inhalers e.g. after discharge from hospital.
- Instituting change: all those involved in asthma care will be involved in the change over to CFC-free inhalers. To avoid patients becoming confused during this process the advice given by these different groups must be similar.

CONCLUSIONS

Inhaled steroids have a central role in the management of adult asthma and a number of important issues remain unresolved about the most effective use of these drugs. The plateau in the dose-response relationship as regards efficacy for inhaled steroids and the potential risk of systemic side-effects from high-dose inhaled steroids made the addition of alternative treatment the preferred option for the majority of patients receiving low-dose or medium-dose inhaled steroids whose asthma control is inadequate. The choice of which drug or combination of drugs to add has not been clearly established. Further guidance must await the results of studies designed to compare the cost-effectiveness of long-acting inhaled ß2-agonists with other add-on therapies such as leukotriene receptor antagonists and oral theophyllines. It is important to recognise that some patients will benefit from high-dose inhaled steroids, but at present the only way of identifying these individuals is by a trial of therapy. The final decision on which drug combination to prescribe will be influenced not only by information on the efficacy and side-effects profile of each drug but also on cost, route of administration and patient preference. Future challenges in the use of inhaled steroids include identifying better methods of assessing the maximum therapeutic response in an individual asthmatic patient and the transition to CFC-free inhalers.■

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Review

Recommendations based on guidelines on the management of mild to moderately severe chronic obstructive pulmonary disease: some practical applications in primary care

C P van Schayck, C L A van Herwaarden, P J Barnes, K Jones, J A Knottnerus, D S Postma, C van Weel, E F M Wouters and P Vermeire

A variety of clinical guidelines on the management of asthma have appeared over the last ten years.[1-6] Guidelines for the management of chronic obstructive pulmonary disease (COPD) have also been published,[6-13] but these are mainly drawn up by thoracic societies and some parts are less relevant for patients with milder forms of COPD or those treated in primary care. The aim of this paper is to provide recommendations (evidence-based where possible) to guide primary care professionals in their management of adult patients with COPD.

A Medline search has been performed over the past 10 years with the combined MESH headings 'COPD' and 'guidelines'. In total 32 published papers were found. Only guidelines for the managment of COPD which were published in English were selected. Only 10 publications met these criteria[6-16] and none of them were specifically aimed at patients treated in primary care. Based on these publications and on the consensus of the authors, the following guidelines for the management of mild to moderate COPD in primary care are suggested.

In drawing up a plan for the management of patients with COPD, there are a number of important considerations. Firstly, the treatment of the patients should be based on the underlying pathophysiology mechanisms. In this respect there are significant differences between COPD and asthma that have obvious consequences for treatment.[6] COPD is a generic term for chronic bronchitis, emphysema and a disorder of the peripheral airways, of which chronic progressive irreversible airflow obstruction is the