Flixotide Nebules: new for chronic severe asthma

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Allen & Hanburys recently launched Flixotide Nebules for prophylactic management of severe chronic asthma in patients requiring high-dose inhaled or oral corticosteroid therapy.

Asthma affects an estimated 3.4 million people in the UK and causes some 1600 deaths (National Asthma Campaign, 1998). Fortunately, the vast majority of patients have mild to moderate disease which can be controlled with a combination of bronchodilator and anti-inflammatory therapy, administered by aerosol or dry powder devices, with minimal adverse effects. However, in line with recommendations in the most recent British Thoracic Society guidelines (British Asthma Guidelines Coordinating Committee, 1997), patients with chronic, severe symptoms are likely to require treatment with an oral corticosteroid (Step 5) such as prednisolone, in addition to high-dose inhaled steroids and regular bronchodilators.

Such an approach, while aimed at minimizing symptoms and limitations on daily activities, and maximizing lung function, is associated with an increased risk of bone degeneration and osteoporosis resulting from suppression of the hypothalamic–pituitary–adrenal axis (because of the usage of oral steroids). The risk of fractures has been shown to double in patients taking more than 7.5 mg prednisolone per day (Eastell, 1995) and, in one retrospective survey, vertebral or rib fractures were noted in 11% of patients over 40 years old who were dependent on oral steroids (Adinoff and Hollister, 1983).

As a result, the pharmaceutical industry has been actively involved in developing alternative ways of administering high doses of corticosteroid treatment directly into the lungs of patients with severe asthma, thus reducing the need for oral treatment with its accompanying systemic side-effects (Efthimiou et al, 1998). Nebulizers are preferred by some patietns as they are simpler to operate than spacers, and require less interation and less coordination.

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FLIXOTIDE NEBULES

In January 1999, Allen and Hanburys introduced a new addition to its Flixotide (fluticasone propionate) range of inhaled corticosteroid treatment. Flixotide Nebules are the nebulized form of fluticasone propionate, and they are indicated for the prophylactic management of chronic, severe asthma in adults requiring high dose inhaled or oral corticosteroid therapy.

Until recently, Flixotide has been available in a range of three aerosol and dry powder delivery devices — the metered dose inhaler (MDI), Diskhaler and Accuhaler —in dose units of 50–500 μg.

Flixotide Nebules have been formulated for nebulizer administration in adults and children over 16 years with chronic, severe asthma in a dose of 500–2000 μg twice daily. The manufacturers advise that for maintenance therapy, the drug should be titrated to the lowest dose at which effective control of asthma can be maintained. The dose does not need to be adjusted in elderly patients or those with hepatic or renal impairment.

Nebulized corticosteroids may be helpful in steroid-dependent asthmatic patients to reduce the maintenance dose of oral steroids. They should be administered as an aerosol produced by a jet nebulizer — use with ultrasonic nebulizers is not generally recommended because of problems with drug suspension which may not nebulize very well.

NEBULIZED CORTICOSTEROID

There is at present no randomized controlled trial of the effectiveness of nebulized corticosteroids

in adults with asthma, and the author is not aware of any intention to perform one in the future.

A group of patients with severe asthma may require maintenance of oral prednisolone in addition to a high dose inhaled corticosteroid — this can lead to adverse systemic effects. The effect of nebulized budesonide (2–8 mg/day) has been studied in this group and it is suggested that budesonide can reduce the requirement of oral corticosteroid. The study, however, did not compare the addition of nebulized budesonide with an increased dosage of budesonide by MDI and was not placebo controlled (Higgenbottom et al, 1994).

Fluticasone propionate is the first nebulized corticosteroid shown, in a placebo-controlled clinical trial, to reduce the amount of oral steroids which adult patients with chronic severe asthma need to take to keep their disease under control (Efthimiou et al, 1998).

In a 12-week, randomized, double-blind, placebo-controlled trial, 301 patients aged 17 and over with chronic severe oral steroid-dependent asthma were randomized to twice daily Flixotide Nebules added to existing treatment or placebo. On entry to the study, patients were receiving a mean oral steroid dose of 10 mg/day. The end-points measured in the study were oral prednisolone reduction/cessation, daily morning and evening peak expiratory flow rate, symptom scores, and clinical pulmonary function tests.

At the end of the study, the mean oral steroid dose in patients who received Flixotide Nebules 2 mg/ml was reduced by over 40%, while disease control was maintained. Oral steroids were completely discontinued in 37% of patients taking Flixotide Nebules compared to 17% of those in the placebo group (P=0.003). In addition, Flixotide Nebules improved the percentage of days free from shortness of breath (P=0.036), the median percentage of nights undisturbed by asthma (P=0.008), and the median percentage of days and nights free from wheeze (P=0.036 and P=0.021 respectively), when compared with placebo.

Currently, the only other inhaled corticosteroid available in nebule formulation is budesonide (Pulmicort Respules, Astra Pharmaceuticals Ltd, Kings Langley). There have, as yet, been no direct comparisons between nebulized fluticasone and budesonide. However, the oral steroid-sparing effects of fluticasone propionate and budesonide have been compared when administered via dry powder devices (Lundback et al, 1998).

COST CONSIDERATIONS

Flixotide Nebules are between 10 and 37% cheaper than equivalent doses of budesonide Respules.

CONCLUSIONS

Asthma patients with chronic, severe disease may require high doses of inhaled corticosteroids and regular oral steroids to control their symptoms, maintain their lung function and minimize the effects of their condition on their everyday life. However, the systemic effects of oral treatment are well documented and the risks of osteoporosis and bone fracture are high. The introduction of Flixotide Nebules — with their oral steroid-sparing effects — may provide a further option for patients who have difficulty using current delivery devices, or are at risk of systemic adverse effects.

Flixotide Nebules should be used on the recommendation of a respiratory specialist, who should review these cases. HM

Conflict of interest: Dr Mukherjee has received an honorarium from Allen & Hanburys and has attended seminars and meetings sponsored by Allen & Hanburys.

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KEY POINTS

- Flixotide Nebules are the latest addition to Allen and Hanburys' Flixotide range of asthma therapy.
- They can be used on the recommendation of a respiratory specialist for the prophylactic management of chronic, severe asthma in adults requiring high-dose inhaled or oral corticosteroid therapy.
- Flixotide Nebules are the first nebulized corticosteroid shown to reduce the need for oral steroids in a randomized, placebo-controlled trial.
- The manufacturers claim that Flixotide Nebules offer a cost saving when compared with nebulized budesonide.
- Patients should be reviewed by a respiratory specialist before they are prescribed.