

INHALED CORTICOSTEROIDS FOR ASTHMA IN ADULTS AND CHILDREN OVER TWELVE YEARS

In both adults and children over 12 inhaled corticosteroids are the most important treatment for chronic asthma. This is because their clinical effects are essential in achieving the goals of asthma management as set out in national and international guidelines; that is eliminating or reducing chronic symptoms of asthma, preventing exacerbations, maximising lung function, reducing the need for rescue beta₂ agonists, enabling normal activity including exercise and doing so in a safe manner. All of these attributes have been demonstrated in numerous well conducted controlled clinical trials. In addition there is evidence from a limited number of clinical trials and a huge number of database studies that inhaled corticosteroids reduce hospitalisations due to asthma. Database and ecological studies strongly indicate that inhaled corticosteroids markedly reduce the asthma death rate. In this regard they are the only treatment for chronic asthma which has been shown to reduce asthma deaths.

There are five inhaled steroids currently available in the UK.(Beclomethasone dipropionate (BDP), budesonide (Bud), fluticasone dipropionate (FP), mometasone furoate (MF) and ciclesonide). They are available in a large variety of metered dose inhalers and dry powder inhalers. All inhaled steroids work by binding to a common glucocorticoid receptor so the basic pharmacology and clinical studies would indicate that the same clinical effect can be achieved with all inhaled steroids though not at the same microgramme dose. At doses of inhaled steroids with equal clinical effect there are differences in the side effect profile of inhaled corticosteroids, the importance of which is a subject of considerable debate. The equitherapeutic activity of different inhaled steroids varies between delivery device.

The relative efficacy of different inhaled corticosteroids has been the subject of considerable dispute and debate. However, Cochrane reviews and a completely different methodology used by the pharmacology section of the BTS/SIGN Asthma Guidelines came to very similar conclusions, that is that BDP and budesonide were equiactive and F.P. was active at half the microgramme dose. Equiactive doses for newer inhaled steroids are more difficult to determine, evidence would suggest that mometasone is approximately equipotent to F.P. and that ciclesonide falls somewhere between BDP and F.P. A further complication is added by the introduction of HFA-BDP (Qvar). This is claimed to be active at half the metered dose of CFC-BDP. However, the evidence would suggest that although more active than CFC-BDP, it is difficult to be certain about an exact dosage ratio of 2:1. Indeed, the USFDA concluded that although more clinically active than CFC-BDP an exact doses ratio for HFA-BDP could not be determined.

Threshold for starting inhaled corticosteroids

The exact threshold for starting inhaled corticosteroids is difficult to determine. Examination of the inclusion criteria and patient characteristics of two large clinical trials of inhaled corticosteroids versus placebo (START and OPTIMA) in patients with mild asthma led to the BTS/SIGN Guideline recommendation that inhaled steroids should be considered in patients waking at least one night a week, being symptomatic or using their beta₂ agonist three times or more a week and having an exacerbation of asthma requiring treatment with oral corticosteroids within the last

two years. Benefit was seen even in patients with an FEV1 of 90% of predicted. In this mild group of patients the most important clinical effect is a reduction in exacerbations of asthma and a numeric trend, though not statistically significant to a reduction in fatal and near fatal asthma. The exact starting dose of inhaled corticosteroids is not clear. Previous UK Guidelines has suggested the strategy of starting with high doses of inhaled steroids to rapidly gain control of asthma and then stepping the dose down. This strategy has been compared with starting with a modest dose of inhaled steroids in a number of studies in both primary and secondary care and these studies have shown no evidence of any benefit from a high dose step down strategy. This has led to the recommendation in the guidelines to commence inhaled steroids at a dose of 400 micro grams BDP equivalent per day.

Step 3 - Add-on for inhaled steroids

In patients not completely controlled on inhaled corticosteroids there is some controversy over the best treatment option to use and the dose of inhaled corticosteroids at which additional treatment should be introduced. UK asthma guidelines in the mid 1990s advocated increasing doses of inhaled corticosteroids to between 1000 and 2000 micro grams per day prior to the introduction of inhaled long acting beta₂ agonists. The UK Guidelines have systematically investigated the various options in patients poorly controlled on low to moderate doses of inhaled corticosteroids. Five options have been shown to produce clinical benefit, these are addition of an inhaled long acting beta₂ agonist, increased dose of inhaled corticosteroids, addition of oral theophyllines, addition of leukotriene receptor antagonists and addition of oral slow release beta₂ agonists. Of these options the most effective is the addition of inhaled long acting beta₂ agonists. Numerous studies have now been performed comparing on the background variety of doses of inhaled corticosteroids who are not completely controlled whether the strategy of doubling the dose of inhaled corticosteroids or the addition of a long acting beta₂ agonist is superior. In general these studies and Cochrane reviews have shown that the addition of a long acting beta₂ agonist is superior.

However, the dose of inhaled corticosteroids at which these studies were performed varies between 200 and 1000 micro grams (BDP equivalent) per day. Furthermore it is clear that the dose response relationship of individuals for inhaled steroids is highly variable with some individuals having a maximum response at 200 micro grams and others having maximum response at greater than 1000 micro grams per day. These studies are also difficult to analyse because it is clear that the dose response relationship for inhaled steroids varies according to the outcome measure used. There is good evidence that the maximum improvement in lung function occurs at lower doses of inhaled steroids than that needed to control asthma exacerbations. For these reasons the UK Guidelines give a range of doses of inhaled steroids between 200 and 800 micro grams (BDP equivalent) per day over which clinicians may wish consider adding additional treatment. The UK Guidelines strongly recommend that before inhaled corticosteroids are increase above 800 micro grams per day. additional therapy is added. This recommendation is based on the observations that above 800 micro grams per day only a minority of patients show improvement when doses of inhaled corticosteroids are increased whereas it is above 800 micrograms a day that biochemical tests of adrenocortical suppression show changes, though the clinical significance of these changes is unclear.

There is some controversy at present over the safety of long acting beta₂ agonists. However, much of the data causing concern about the safety of long acting beta₂ agonists is generated from a US trial where patients were enrolled into the study and allowed to take long acting beta₂ agonists without concomitant inhaled corticosteroids. In asthma long acting beta₂ agonists should never be prescribed without concomitant inhaled corticosteroids and it is doubtful that this data has much relevance to the UK situation.

Step 4 of the UK Guidelines

In patients who are inadequately controlled on inhaled steroids at a dose of 800 micro grams per day plus a long acting beta₂ agonists there is a paucity of evidence for the best strategy, the Guidelines recommend treatment trials of increased doses of inhaled steroids, an addition of oral theophyllines or an addition of leukotriene receptor antagonists. There are no active comparative studies between these different strategies. Currently the best evidence is probably for an increased dose of inhaled corticosteroids though even this evidence is weak.

Step 5 – Oral Steroid Requiring Asthma

One of the first ways in which the efficacy of inhaled corticosteroids was demonstrated was in the 1970's when trials showed that they could eliminate the requirement for oral corticosteroids in the majority of patients. Since then the number of patients requiring long term oral corticosteroids has decreased markedly due to better care, principally with inhaled corticosteroids. However, for the minority of patients (estimated to be between 1% and 2% of the total asthmatic population) who are on long term oral corticosteroids, high dose inhaled steroids are important in reducing or eliminating the requirement for oral steroids. Although more expensive than oral corticosteroids, high dose inhaled steroids markedly reduce corticosteroids side effects including particularly weight gain, diabetes, hypertension and osteoporosis. As fluticasone can be given up to doses of 2000 microgrammes per day it is often of particular benefit at high dose in reducing oral steroids requirement.

Side effects of inhaled corticosteroids

The side effects of inhaled corticosteroids can be divided into local and systemic. Local side effects are oral candidiasis which is now rarely a problem in clinical practice and can be overcome by gargling and, if necessary, topical anticandidal drugs. Cough is a problem with inhaled steroids, particularly metered dose inhalers, but can usually be overcome by changing delivery device. The local side effect which is most difficult to overcome is hoarse voice. Hoarseness and voice changes occur more frequently with dried powder inhalers than metered dose inhalers. As the hoarseness is caused by the drug impacting on the vocal cords it is the most difficult side effect to overcome, it is dose related. There is evidence that ciclesonide causes less hoarseness and local side effects

The systemic side effects which may potentially occur in adults are biochemical adrenocortical suppression and effects on bone metabolism, other potential side effects such as weight gain and increased incidence of diabetes do not seem to occur clinically. There is a rare incidence of clinically apparent adrenocortical suppression in adults. The effect of inhaled corticosteroids in adults on bone

metabolism is very controversial. Markers of bone metabolism have no predictive value for clinical effects on bone. Database studies of the effects of inhaled corticosteroids on bone density produce contradictory results, some show no effect of inhaled corticosteroids under 2000 micro grams per day whereas others show effects on bone density and fracture rates at doses above 800-1000 micro grams per days. There are a number of prospective trials which have measured bone density and fracture rate and there is a Cochrane review on bone density and fracture rate. The Cochrane review is problematic due to small numbers in the studies. The best data comes from looking at some of the large studies in COPD, particularly the unpublished TORCH Study. This has been presented in abstract form and has shown no change in bone density or fracture rate in a large cohort of COPD patients over a three year period treated with F.P. 1000 micro grams per day. A reasonable consensus view would be that there is no appreciable problem at doses up to 800 microgrammes per day, there may be an effect at doses over this but the jury is still out. It should be noted that patients taking over 800 microgrammes per day of inhaled steroids often do so because of poorly controlled asthma with frequent exacerbations requiring oral corticosteroids and it is likely that the beneficial effect of inhaled corticosteroids in preventing the requirement for courses oral corticosteroids outweighs any deleterious effect on bone that they have.

The above discussion applies to BDP budesonide, fluticasone and mometasone. The new inhaled corticosteroid, ciclesonide, currently available only at low dose in the UK, has a more favourable efficacy to safety ratio. There is reasonable evidence that it has less topical effect in causing candidiasis and voice hoarseness and has less systemic effects. However, at the licensed doses, the therapeutically equivalent of conventional inhaled steroid will not have any effect on adrenocortical function either. If ciclesonide was available at higher doses it's more favourable efficacy to side effect ratio may be of importance in some patients.

Compliance with inhaled steroids

One of the most important clinical problems with inhaled corticosteroids is poor compliance, it is estimated that compliance with inhaled corticosteroids is probably at most 40%. There is little evidence that compliance is related to disease severity i.e. those with mild and those with bad asthma are equally likely to be compliant. The data on inhaler specific factors influencing compliance is poor. However, clinicians will frequently change delivery devices in order to find one which a patient likes with the hope of improving compliance.

Inhaler device choice

In comparison with other European countries the UK still has high usage of metered dose inhalers. Metered dose inhalers are convenient and easy to use. Side effects can be decreased and efficacy improved to some extent with the use of large volume spacers. The problems with metered dose inhalers are that only about 50% of patients can use them efficiently, even after instruction. Large volume spacers are inconvenient to carry and are really therefore confined to patients taking their treatment at home. A variety of breath actuated metered dose inhalers and dry powder inhalers are available for patients unable to take metered dose inhalers. All have there advantages and disadvantages and none has overwhelming advantages which make it dominant. Although potentially confusing the availability of this wide

variety of inhalation devices does mean that for most patients a delivery device suitable for them can be found. For clinicians overly restrictive guidance on the use of delivery devices would give problems in a significant percentage of patients.

Steroids are available as nebulisers, this is a relatively small market in the UK. There is no evidence that nebulised steroids are any more effective than the same dose given by a conventional inhaler. I personally hardly ever use nebulised steroids. The only patients I have on nebulised steroids are two patients with cerebral palsy and asthma who cannot take any other form of inhaled therapy apart from nebulisers.

Combination Therapy

The pharmacology section in the UK Guidelines has looked at the issue of whether it is best to use a combination inhaler such as Seretide or Symbicort or the two drugs in separate inhalers. The trials which have compared the two drugs in same inhaler versus in separate inhalers have shown no difference. However, it needs to be noted that these were efficacy studies often performed to enable the drug to be registered and compliance was likely to have been in the order of 80%. One of the major benefits of combination therapy is likely to be improve compliance though the formal evidence to support this is poor. Nevertheless, most clinicians would recognise patients in whom switching to combination inhaler has led to an improvement in asthma control and it is most likely that this relates to improved compliance. Given that compliance is such a major problem in the management of asthma to lose the ability to use a combination inhaler would be clinically disadvantageous. In head to head clinical trials of the two long acting beta₂ agonists available, Salmeterol and Formoterol, no difference has been apparent.

AstraZeneca have devised a new strategy with Symbicort known as SMART therapy. Rather than the traditional use of short acting beta₂ agonists as rescue medication, the SMART strategy uses a Symbicort inhaler as rescue medication. The UK Asthma Guidelines have not yet formally looked at the SMART strategy which was only licensed in late 2006. They have looked at the previous strategy known as Adjustable Maintenance Dosage and the provisional conclusion is that, while it does not disadvantage patients compared with conventional strategy of stable dose of inhaled corticosteroids, there is no evidence that it produces any extra benefit. As we have not yet looked at the SMART strategy it would be inappropriate to make detailed comments on this. However, it is likely that in clinical practice some patients will find this approach helpful whereas others will prefer a stable dose strategy and it will be down to clinicians and patients to negotiate the best solution for each individual. It should be noted that the Adjustable Maintenance Dosage and SMART strategy have not been investigated with other combinations of inhaled steroids, particularly Seretide and the more recently available FOSTER (combination of BDP and formoterol). It is also the case that, with the SMART strategy, the baseline dose of drug that should be routinely used is still a matter of some debate. Studies looking at giving Symbicort once daily do not seem to have produced such effective control and it is almost certainly possible that the maintenance dose will vary according to disease severity.