Chapter

135 Finding the Correct Inhaled Corticosteroid Dose in Asthma

Randeep Guleria, Anant Mohan

INTRODUCTION

Inhaled corticosteroids (ICS) form the basis of maintenance therapy in subjects with asthma[1-3] in whom they target the airway inflammatory process and effectively reduce mortality and morbidity[4,5]. While the efficacy of ICS in asthma is well established[6-8], dosing remains problematic. For some outcomes the dose-efficacy curve is relatively flat and more than 90% of the benefit is achieved at low doses of ICS (for example, fluticasone propionate 250 µg/day)[6,9,10]. However, in clinical practice, very high doses of ICS are frequently prescribed[11] and there are now reports of significant side effects including acute adrenal crises with high dose ICS[12]. In addition, undertreatment of asthma could result when inadequate doses of ICS are used. Asthma guidelines recommend that maintenance ICS be given at the lowest effective dose according to the severity of the condition[1–3]. However, the optimal starting dose of ICS in asthma has not been established. This is an important issue since there is concern that patients started on an initial high dose of ICS may continue to receive this dose in the long-term and therefore be exposed to unnecessarily high ICS doses.

Asthma guidelines vary in their recommendations for starting ICS. The GINA guidelines recommend a wide range of starting doses ranging from 200 to 1000 µg beclomethasone (BDP) equivalent per day[2], the Australian guidelines recommend starting with a high dose of ICS and then reducing the dose (step down)[3], while the British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN) guidelines and the New Zealand guidelines recommend starting with moderate to low doses of ICS[1,13]. A recent meta analysis of thirteen studies comparing various doses and preparations of ICS was performed[14]. Of these, Budesonide (BUD) doses were compared in nine studies, fluticasone (FP) in three, and BDP in one. Seven studies compared high dose ICS with moderate dose ICS (n = 1579), six compared moderate dose ICS with low dose ICS (n = 1140), and four studies compared a step down dose with a constant ICS dose regimen (starting with a high dose and back titrating to either a moderate or low dose (n = 1197)). Two studies had three dosage arms of high, moderate and low dose ICS[15-17] and were included in both the high versus moderate and moderate versus low dose ICS comparisons.

HIGH VERSUS MODERATE DOSE ICS

A meta-analysis of the change in morning peak flow (PEF, l/min) from baseline found a non-significant improvement in favor of high dose ICS). The 95% confidence intervals of the effect size excluded a clinically important change in PEF. One additional study[18] found no treatment effect. Asthma symptoms were reduced in two studies with no significant difference between the treatment groups[17,19]. Two studies only reported significant dose response relationships for symptom scores but not in a form that could be used for meta-analysis[15,16]. There was no significant difference between high or moderate dose ICS for the change in daytime or night time symptom scores when the results of two studies (reporting symptom scores on the same 0–3 scale) were pooled in a meta analysis. There was no significant difference between ICS doses in rescue medication during the day or night. A meta-analysis was carried out of randomized, double blind clinical trials that compared the efficacy of adding salmeterol to moderate doses of ICS (fluticasone propionate 200 mcg/day or

equivalent) with increasing the ICS dose by at least twofold in symptomatic adult patients with asthma[20]. The main outcome measures were the number of subjects withdrawn from the study due to asthma and the number of subjects with at least one moderate or severe exacerbation. Twelve studies with a total of 4576 subjects met the inclusion criteria for the analyses. The number of subjects withdrawn due to asthma and with at least one moderate or severe exacerbation was higher in the high dose ICS group (odds ratios 1.58, 95% CI 1.12 to 2.24 and 1.35, 95% CI 1.10 to 1.66, respectively). For the secondary outcome variables (forced expiratory volume in 1 second, morning and evening peak expiratory flow, and daytime beta agonist use) there was significantly greater benefit in the salmeterol group. This meta-analysis shows that the addition of salmeterol to moderate doses of ICS (fluticasone 200 mug/day or equivalent) in patients with asthma symptomatic at that dose results in significantly greater clinical benefit than increasing the dose of ICS by twofold or more.

MODERATE VERSUS LOW DOSE ICS

Studies have compared the efficacy of low-dose ICS (e.g. Budesonide 100 mcg/day/Fluticasone 100 mcg/day) with moderated dose ICS (Budesonide 400 mcg/day/Fluticasone 200 mcg/day)[21,22]. There was a significant improvement in morning PEF from baseline in favor of the moderate dose ICS group. Night time symptom score and mean number of awakenings also reached significance favoring a moderate dose ICS. There was no significant difference between moderate and low dose ICS for other symptom scores, mean symptom free days, or change in score from baseline. There was a non-significant reduction in rescue β agonist use for moderate dose ICS, and one additional study reported no difference from baseline between moderate and low dose ICS in reduction in day or night β agonist use[21].

Evaluating the effects of starting ICS at a high dose (with or without a subsequent step down) compared with starting with a moderate or low dose ICS, has found no benefit of the step down approach when used as initial treatment.

In view of the differing guideline recommendations and the frequent prescription of high dose ICS with subsequent significant side effects, it is important to establish the optimal starting dose for ICS in asthma. It has previously been established that low to moderate ICS doses are highly effective as maintenance treatment for asthma[6,10]. There is still debate as to the optimum dose of ICS to be used as initial therapy. In most of the studies that compared varying doses, the efficacy was shown in both treatment arms for the majority of outcomes and there was no clear benefit for starting at a high ICS dose. A review of the seven studies that compared a constant high dose ICS with a moderate dose ICS showed that there was a non-significant improvement in the change in morning PEF from baseline. The upper 95% confidence interval of the effect size was 13 l/min, which is less than a clinically significant change in PEF. This suggests that, although there was a trend for a benefit of high dose ICS, it is unlikely to be clinically significant even with further studies. No differences were found between commencing with high or moderate dose ICS for asthma symptoms or rescue medication use. The small non-significant benefit in lung function needs to be considered against the risks of increased side effects with the use of constant high dose ICS[6,10]. One particular concern is that, unless patients attend for regular medication review, the initial dose prescribed becomes the long term maintenance dose. This could explain the ongoing use of very high ICS doses, even though most guidelines recommend back titration. Starting treatment with a moderate dose should minimize this problem.

For moderate dose ICS there was a significant improvement in the change in morning PEF from baseline and nocturnal symptoms in comparison with low dose ICS. There were also non-significant improvements in the reduction of rescue medication use from baseline, suggesting a superior effect for moderate dose ICS.

The practice of starting with high dose ICS to gain control of asthma and then stepping down to a moderate or low maintenance dose is recommended in some asthma management guidelines[3]. A review of the four studies that compared this practice with a constant moderate or low ICS dose found no significant benefit in the effect on lung function, symptoms, or rescue medications. These results suggest that constant ICS doses have similar clinical efficacy to the more complex regimen of high ICS doses followed by a step down. One reason for considering initial high dose therapy is to obtain rapid symptom control. It is likely that this can be achieved by the use of ICS in combination with a long acting β_2 agonist (LABA)[23].

In conclusion, current opinion and evidence support initiating treatment for mild to moderate asthmatics with low to moderate doses of ICS at a constant dose. The small non-significant benefits of commencing with a high dose of ICS are not of sufficient clinical benefit to warrant routine use when compared with moderate or low dose ICS. An initial moderate ICS dose appears to

be more effective than an initial low ICS dose. Starting ICS at a constant moderate or low dose is equally efficacious to starting at a high dose and then stepping down.

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