Inhaled Corticosteroid Therapy in Adult Asthma

Time for a New Therapeutic Dose Terminology

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Abstract

The Global Initiative for Asthma guidelines use the traditional terminology of "low," "medium," and "high" doses of inhaled corticosteroids (ICS) to define daily maintenance doses of 100 to 250 μg, >250 to 500 μg, and >500 μg, respectively, of fluticasone propionate or equivalent for adults with asthma. This concise clinical review proposes that this terminology is not evidence based and that prescribing practice based on this terminology may lead to the use of inappropriately excessive doses of ICS. Specifically, the ICS dose that achieves 80–90% of the maximum obtainable benefit is currently classified as a low dose, with the description of two higher dose levels of medium and high, which are associated with significant risk of systemic adverse effects. Asthma guidelines and clinician prescribing practice need to be modified in accordance with the currently available evidence of the dose–response relationship of ICS in adult asthma. We propose a reclassification of ICS doses based on a "standard daily dose," which is defined as 200–250 μg of fluticasone propionate or equivalent, representing the dose at which approximately 80–90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity. It is recommended that ICS treatment be started at these standard doses, which then represent the doses at which maintenance ICS are prescribed at step 2 and within ICS/long-acting β-agonist combination therapy at step 3. The opportunity is available to prescribe higher doses within ICS/long-acting β-agonist maintenance therapy in accordance with the stepwise approach to asthma treatment at step 4.

Keywords: asthma; inhaled corticosteroids; dose–response relationship

Inhaled corticosteroids (ICS) are the mainstay of asthma management in adults (1). The latest Global Initiative for Asthma guidelines recommend their use in all patients who experience asthma symptoms or self-administer a short-acting β-agonist (SABA) twice or more per month, in those who awaken because of asthma once or more per month, or in those with less frequent symptoms with one or more risk factors for an exacerbation (2). Indeed, the recent British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines recommend ICS therapy in all patients once the diagnosis of asthma is confirmed (3). It has also been proposed that ICS should become a universal treatment, by replacing SABA reliever therapy with combination ICS/SABA or ICS/fast-onset long-acting β-agonist (LABA) reliever therapy (4, 5), in part because of concerns about the long-term safety/efficacy profile of SABA reliever therapy (4–7).

In order for ICS to be recommended as a mainstay of asthma treatment, there is a responsibility to ensure they are prescribed in accordance with their known dose–response relationships. Many (2, 3, 8, 9) but not all (10) guidelines use the traditional terminology of "low," "medium," and "high" doses of ICS to define daily maintenance doses of 100–200 μg, 250–500 μg, and >500 μg of fluticasone propionate (FP) or equivalent for adults with asthma (3, 8) or 100–250 μg, >250 to 500 μg, and >500 μg, respectively (Table 1) (2, 9). In accordance with the stepwise approach to the pharmacological management of asthma, the guidelines recommend that the dose of ICS be increased, with or without concomitant LABA therapy, to achieve "asthma control" and reduce the risk of exacerbations, with the option to reduce the dose after a period of prolonged control (2, 3, 8–10). The provision of these three dose categories suggests incremental benefit as the dose is escalated.

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Table 1. Low, Medium, and High Doses of Inhaled Corticosteroids in Adults and Adolescents, Defined by Global Initiative for Asthma Guidelines

Inhaled Corticosteroid	Dose (μg/d)			Bioequivalence*
	Low	Medium	High	
Beclomethasone dipropionate (CFC)	200–500	>500–1,000	>1,000	1.0
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400	2.5
Budesonide (DPI)	200–400	>400–800	>800	1.25
Ciclesonide (HFA)	80–160	>160–320	>320	3.125
Fluticasone propionate (HFA)	100–250	>250–500	>500	2.0
Fluticasone furoate (DPI)	100	NA	200	5.0
Mometasone furoate	110–220	>220–440	>440	2.25

Definition of abbreviations: CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; NA = not applicable.
*Bioequivalence compared with beclomethasone dipropionate, derived from the stated "high dose." From reference 2.

In this article, we critically review the therapeutic dose–response relationship of ICS in adult asthma, with specific reference to the terminology of low, medium, and high ICS doses, from six perspectives:

1. What is the therapeutic dose–response relationship of maintenance ICS when treatment is initiated in a steroid-naive adult with asthma?
2. What is the therapeutic dose–response relationship of maintenance ICS in adults with moderate to severe disease?
3. What factors influence the variability in response, and how might this knowledge be used to personalize ICS treatment?
4. What is the effect of reducing the ICS dose in adults with stable asthma?
5. What is the ICS dose–response relationship in terms of adverse systemic effects such as cataracts, adrenal insufficiency, osteoporosis, and diabetes?
6. What is the dose–response relationship of ICS when prescribed as maintenance ICS/LABA combination therapy?

The findings from relevant systematic reviews and meta-analyses of randomized controlled trials are preferentially examined, and clinical variables are considered in terms of both statistical and clinical significance, with reference to minimal clinically important differences (11).

Starting Dose

A systematic review and meta-analysis of randomized controlled trials compared the inhalation of two doses of the same ICS in steroid-naive adults with asthma (12). Efficacy comparisons were presented between "high" (⩾800 μg/d beclomethasone propionate chlorofluorocarbon propellant [BDP CFC] or equivalent) and "moderate" (400 μg/d BDP CFC or equivalent), between "moderate" and "low" (⩽200 μg/d BDP CFC or equivalent), and between "high then step-down" and a constant "moderate/low" dose. There were no statistically or clinically significant differences in lung function or symptoms between "high" and "moderate" doses of ICS or between the "high then step-down" versus "moderate/low" doses of ICS. There were statistically but not clinically significant improvements in lung function and symptoms with moderate versus low doses of ICS. No standardized data on severe exacerbations were presented. As a result, the top of the dose–response curve for therapeutic efficacy with the initiation of ICS is around 400 μg/d BDP (200 μg of FP equivalent), which is currently classified as a low ICS dose.

Moderate to Severe Asthma

A series of systematic reviews and meta-analyses has determined the dose–response relationship of therapeutic efficacy of the most commonly used ICS in adolescents and adults with moderate to severe asthma. The most comprehensive data are available from randomized controlled trials of FP (13, 14) and budesonide (15). In randomized placebo-controlled trials of FP in adolescents and adults with asthma, 80% of the benefit obtained at 1,000 μg/d was achieved at doses of 70–180 μg/d and 90% at a dose of 100–250 μg/d (Figure 1 and Table 2). These findings apply to all major clinical outcomes, including severe exacerbations, night awakenings, use of rescue medications, FEV_1, and morning and evening peak flow. The maximum achievable efficacy was obtained with FP doses of around 600 μg/d. The odds ratio for patients remaining in a study at an FP dose of 200 μg/d compared with higher doses was 0.73 (95% confidence interval [CI], 0.49–1.08). To allow for better determination of the dose–response relationship at higher doses, this analysis was followed by a systematic review and meta-analysis of double-blind randomized controlled trials of FP that did not require a placebo group (14). For all outcome variables, there were no significant differences between doses of 200 and 500 μg/d, 200 and ⩾500 μg/d, and 200 and 1,000 μg/d, although the point differences favored the higher doses (Table 3).

In a related systematic review and meta-analysis of randomized placebo-controlled trials of budesonide in adults and adolescents with moderate to severe asthma, authors reported that 80–90% of the maximum therapeutic benefit of budesonide was achieved with a dose between 200 and 600 μg/d, and the maximum effect was obtained with budesonide doses between 900 and 1,100 μg/d (15). The odds ratio for withdrawals with 200 μg/d compared with ⩾500 μg/d was 1.27 (95% CI, 0.78–2.07). In the FACET (Formoterol and Corticosteroids Establishing Therapy) study, budesonide at a dose of 800 μg/d resulted in a 49% reduction in severe exacerbations compared with 200 μg/d (16). The ICS doses in this study encompass the steepest part of the dose–response curve for budesonide, so these findings are consistent with the known dose–response relationship of budesonide presented above. Two randomized non–placebo-controlled trials in which researchers examined budesonide doses >800 μg/d indicated that there was minimal, if any, additional clinical benefit derived from a dose of 3,200 μg/d compared with 1,600 μg/d (17) or 1,600 μg/d compared with 400 μg/d (18).

A further related systematic review and meta-analysis of mometasone in adolescents and adults with predominantly moderately severe asthma showed that 400 μg/d was superior to 200 μg/d with differences of 0.09 L (0.04–0.13) in FEV_1 and 0.6 (95% CI, 0.4–1.1) for risk of dropout owing to treatment failure (19). Data on doses >400 μg/d were limited but did not support the superiority of 800 μg/d to 400 μg/d. Thus, there is consistency between the therapeutic

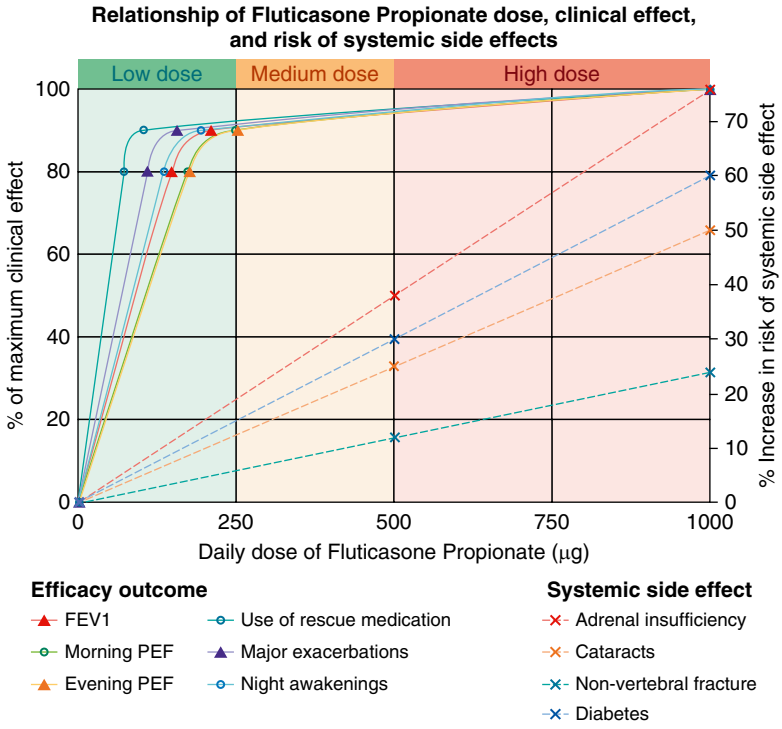

Figure 1. Schematic dose–response curves for different outcomes for efficacy and adverse effects with inhaled corticosteroids, expressed as fluticasone propionate in μg/d, derived from Tables 2 and 5. PEF = peak expiratory flow.

dose–response relationships of FP, budesonide, and mometasone in adolescents and adults with moderate and severe asthma when the dose bioequivalence of budesonide, FP, and mometasone is considered.

Similar dose–response findings were observed in an epidemiological study of the risk of mortality with the long-term use of ICS in a broad population with asthma (20). An estimated 80% reduction in mortality risk is achieved at a dose of approximately 220 μg/d of BDP (Figure 2). Although these findings relate primarily to compliance and continuity of use of ICS, they do show that the dose–response relationship of the effect of ICS on mortality is similar to other clinical outcome variables.

Bronchial hyperresponsiveness (BHR) is a physiological marker of asthma severity relevant to this review. However, the findings of the two major systematic reviews and meta-analyses are conflicting and do not inform the BHR dose–response relationship of ICS within the therapeutic range (21, 22).

It could be argued that the dose–response relationship of ICS on airway inflammation is different and clinically important. However, bronchial biopsy studies of the effect of FP on airway inflammation show suppression of airway inflammation that is optimal at a dose of 500 μg/d, with no significant further benefit at 2,000 μg/d (23), or at a dose of 400 μg/d compared with 1,000 μg/d of FP (24), respectively. This suggests that the dose–response relationship for antiinflammatory effects is comparable to clinical efficacy.

An important clinical consideration is the dose–response relationship of the steroid-sparing effect of high-dose ICS in oral steroid–dependent asthma. Studies of BDP, budesonide, and FP have shown variable and small differences in oral corticosteroid–sparing effect between low/medium and high doses and also between high and very high doses (25–31) (Table 4). Together, these findings suggest that high and "very high" ICS doses only have modest and variable efficacy above medium-dose ICS, which are likely to be predominantly owing to the effects resulting from their systemic absorption. In summary, it can be concluded that the ICS dose that achieves at least 80–90% of the maximum achievable clinical benefit is classified as a low ICS dose.

Table 2. Doses of Fluticasone Propionate at Which 80% and 90% of Maximum Effect Are Achieved, as Derived from a Negative Exponential Model

Outcome Measure	80% of Maximum Effect Achieved	90% of Maximum Effect Achieved
FEV_1	146	209
Morning PEF	172	247
Evening PEF	175	251
Use of rescue medication	71	102
Major exacerbations	108	155
Night awakenings	135	193

Definition of abbreviation: PEF = peak expiratory flow.
The effect obtained with 1,000 μg/d of fluticasone propionate was considered to be the "maximum effect" for the purposes of this analysis.
Derived from Reference 13.

Variability in Response

There is considerable individual variability in the response to ICS in adult asthma, and a number of clinical characteristics have been identified that predict steroid responsiveness. These include biomarkers of type 2 inflammation such as high fractional exhaled nitric oxide (F_{ENO}), elevated blood or sputum eosinophils, high bronchodilator reversibility, low FEV_1/FVC ratio, greater BHR, onset of asthma in childhood compared with adult life, shorter duration of symptoms before starting ICS treatment, and nonsmoking status (32–35). Consideration of such predictors of responsiveness raises a number of clinical issues.

The first is whether different dose–response relationships exist in

Table 3. Pooled Differences according to Systematic Review and Meta-analysis Using Weighted SD for Outcome Measures Relating to Fluticasone Propionate Use

Outcome Measure	200 vs. 500 μg/d	200 vs. ⩾500 μg/d	200 vs. 1,000 μg/d
FEV_1, L	0.02 (−0.07 to 0.11)	0.07 (−0.01 to 0.14)	0.13 (0.03 to 0.24)
Morning PEF, L/min	2.9 (−8.2 to 14.9)	5.9 (−3.0 to 15.3)	10.4 (−1.4 to 22.6)
β-Agonist use, puffs/d	0.07 (−0.38 to 0.53)	−0.05 (−0.34 to 0.25)	−0.23 (−0.65 to 0.18)

Definition of abbreviation: PEF = peak expiratory flow.
The minimal patient perceivable improvement for FEV_1 is 0.23 L, PEF is 18.8 L/min, and β-agonist use is −0.81 puffs per day (11).
Derived from Reference 14.

patients with different clinical characteristics that predict ICS responsiveness. The second is that the titration of maintenance ICS dose in accordance with changes in biomarkers of responsiveness may represent the optimal approach to ICS dosing in individual patients. There is evidence in support of this approach, particularly with biomarkers of type 2 inflammation and BHR in asthma. When ICS and oral corticosteroid dose is titrated in response to sputum eosinophils (35–37), Fe_{NO} (37), or BHR (38), a greater reduction in severe exacerbations is achieved than with the standard guideline-mandated stepwise approach to pharmacological treatment. In the case of sputum eosinophil–based titration of ICS dose, this may result in relatively high doses of ICS being prescribed to patients with the "biomarker-high" phenotype and lower doses to those with other phenotypes (35). Third, the ability of Fe_{NO} to predict individual ICS responsiveness in adults with symptoms and lung function suggestive but not diagnostic of asthma indicates that Fe_{NO} measurements may be sufficient to determine whether ICS should be prescribed (39–41). Further long-term studies to determine the optimal approach for type 2 inflammation–guided treatment are a priority.

Systemic Adverse Effects

In comparison with efficacy outcomes, there is a different ICS dose–response relationship for systemic adverse effects such as risk of adrenal suppression, cataracts, fractures, and diabetes. A series of systematic reviews and meta-analyses of randomized controlled trials has shown that there is a progressive increase in risk of adrenal suppression (42), cataracts (43), fractures (44), and diabetes (45) with increasing ICS dose, without a plateau in effect as occurs with efficacy outcomes. The magnitude of the increased risk is probably clinically significant for doses ⩾250 to 500 μg/d of FP or equivalent (Figure 1 and Table 5). It is acknowledged that the interpretation of these studies has been limited by many factors, including a paucity of long-term studies, in particular those with high ICS doses, methodological issues, and confounding by other risk factors, such as the association between asthma severity and exposure to systemic steroids. Despite these limitations, available evidence suggests that adults with asthma who are prescribed medium or high ICS doses are at risk of clinically important systemic side effects.

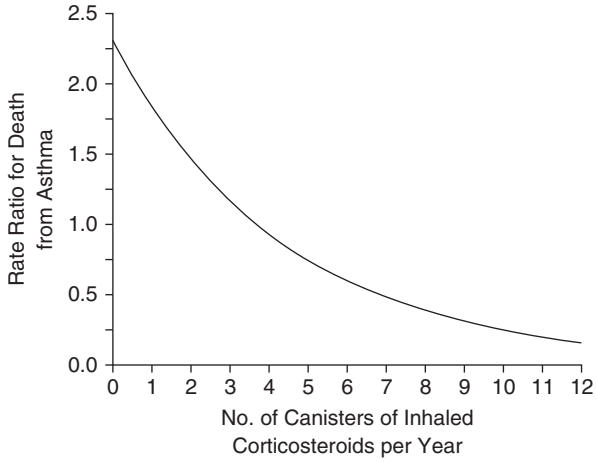

Figure 2. Rate ratio for death resulting from asthma according to number of canisters of inhaled corticosteroid used the year before the index case. In total, 93% of prescribed canisters of inhaled corticosteroid contained beclomethasone, 200 puffs per canister, with 50 μg of beclomethasone delivered per puff. An 80% reduction in risk of death corresponds to about eight canisters per year, which is the equivalent of approximately 220 μg of beclomethasone per day. Reproduced by permission from Reference 20.

Step Down

The relevant Cochrane systematic review analyzed the risk of severe exacerbations after reducing ICS in adults with well-controlled asthma who were already receiving a medium to high ICS dose (46). The clinical trials randomized adults to either a 50–60% reduction in ICS dose or no changes in ICS dose, and analysis was undertaken in subgroups defined by whether patients were receiving concomitant LABA therapy. The meta-analysis was limited by the poor quality of the data and the small number of studies contributing to each comparison. Although there were no significant or clinically significant differences between groups for any of the primary or secondary outcome variables, the data were insufficient to rule out benefit or harm. For the two studies without concomitant LABA, the odds ratio for severe exacerbations with ICS reduction was 1.86 (95% CI, 0.16–21.09), and in the two studies with concomitant LABA therapy, the odds ratio was 1.31 (95% CI, 0.82–2.08). As a result, this analysis cannot inform the therapeutic dose–response relationship in adult asthma or the benefit or harm with reducing the dose of ICS.

ICS/LABA Therapy

Because ICS are commonly prescribed as a combination ICS/LABA inhaler, it is also

Table 4. Oral Corticosteroid-Sparing Effects of Different Inhaled Corticosteroid Doses in Corticosteroid-Dependent Asthma

Study	ICS Daily Dose (μg)	Mean Change in Prednisolone Dose (mg) Compared with Baseline	Difference in Prednisolone-Sparing Effect (mg) between Lower and Higher ICS Doses
Budesonide			
Miyamoto *et al.*, 2000 (25)	1,600	−7.14	2.9
	800	−4.24	
	Placebo	−0.92	
Nelson *et al.*, 1998 (26)	1,600	−15.1	−1.1
	800	−16.2	
	Placebo	−5.4	
Laursen *et al.*, 1986 (27)	1,600	−7.5	2.1
	400	−5.4	
BDP			
Hummel *et al.*, 1992 (28)	1,500	−5.0	−0.2
	300	−5.2	
Tarlo *et al.*, 1988 (29)	2,000	−5.8	1.3
	800	−4.5	
Fluticasone			
Noonan *et al.*, 1995 (30)	2,000	−9.3	2.7
	1,500	−6.6	
	Placebo	1.6	
Nelson *et al.*, 1999 (31)	2,000	−13.0	1.0
	1,000	−12.0	
	Placebo	−5.2	

Definition of abbreviations: BDP = beclomethasone dipropionate; ICS = inhaled corticosteroid.
A positive difference in prednisolone-sparing effect represents a greater reduction in prednisolone dose with the higher ICS dose than with the lower ICS dose.

relevant to review the dose–response relationship of ICS when received as ICS/LABA maintenance therapy. There is insufficient evidence to determine the dose–response relationship of increasing doses of FP or budesonide within combination FP/salmeterol or budesonide/formoterol inhalers. However, the research program of the novel fluticasone furoate/vilanterol product does investigate this issue, and it shows no clinically significant difference in efficacy outcomes between the fluticasone furoate 100 μg/vilanterol 25 μg and fluticasone furoate 200 μg/vilanterol 25 μg preparations in adult asthma (47–49). Considering the bioequivalence of fluticasone furoate to FP (50), this suggests that the dose–response relationship of ICS within ICS/LABA maintenance therapy is similar to ICS maintenance alone.

Table 5. Risk of Systemic Side Effects of Inhaled Corticosteroids

	Adrenal Insufficiency*	Cataracts	Nonvertebral Fracture	Diabetes†
500 μg/d increase in dose of FP or equivalent	1.38 (1.01–1.59)	1.25 (1.14–1.37)	1.12 (1.00–1.26)	1.30 (1.25–1.35)

Definition of abbreviation: FP = fluticasone propionate.
Derived from References 42–45. Data are shown as odds ratio (95% confidence interval) unless otherwise indicated.
*Adrenal function below the lower limit of the normal range.
†Adjusted rate ratio (95% confidence interval) determined for medium/moderate doses of 500–999 μg/d of FP.

Conclusions

The classification of ICS by dose level using the current terminology of "low," "medium," and "high" is not evidence based, and clinical practice based on this terminology may lead to the prescription of inappropriately excessive doses of ICS, resulting in unnecessary systemic adverse effects and cost. The extent of this prescribing practice is shown with the example of Australia, in which it was reported that over two-thirds of the defined daily dose of ICS was supplied in the highest-dose preparations of budesonide and FP (51), and by data from Scotland, in which over half of patients prescribed an ICS/LABA for the first time were prescribed high-dose combination therapy (52). We are not aware of any other medication for which the dose that achieves the maximum obtainable benefit in the initiation of treatment and 80–90% of the maximum obtainable benefit in the long-term treatment of moderate and severe disease is classified as a low dose, with the description of two higher-dose levels as medium and high doses.

The considerable variability of response depending on clinical characteristics such as type 2 inflammation has implications in terms of the decision whether to treat with ICS and subsequent dose titration in clinical practice. A research priority is to determine the dose–response relationship of ICS in phenotypes defined by clinical characteristics such as type 2 biomarker status and to better define how to titrate the ICS dose in accordance with changes in type 2 biomarkers in asthma, in particular to determine which patients require relatively higher doses.

We acknowledge that prescribing practice is influenced by numerous factors, including pharmaceutical marketing; however, we propose that evidence-based classification of ICS terminology in guidelines represents a crucial initiative in addressing the current practice of entrenched prescription of unnecessarily high doses of ICS. For this reason, we suggest that national and international guidelines need to be modified in accordance with the currently available evidence of the dose–response relationship of ICS in adult asthma. We propose a reclassification of ICS doses based on the "standard daily dose," which is defined as 200–250 μg of FP or equivalent, representing the dose at which about 80–90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity.

It is recommended that ICS treatment be started at these standard doses, which then represent the doses at which maintenance ICS are prescribed at step 2 and within ICS/LABA combination therapy at step 3. The opportunity is available to prescribe higher doses within ICS/LABA maintenance therapy in accordance with the stepwise approach to asthma treatment at step 4.

Search Strategy and Selection Criteria

The sources of reference material for this review were PubMed and the Cochrane Database of Systematic Reviews, which were searched using the terms "inhaled corticosteroids" and "asthma." We searched the references of retrieved articles for further articles. We restricted our literature review to articles that included adults and were published in English. Relevant systematic reviews and meta-analyses of randomized controlled trials were preferentially examined, and they were considered for inclusion if they dealt with at least one of the six key questions.

The Evidence

1. The top of the dose–response curve for therapeutic efficacy with the initiation of ICS is around 200 μg/d of FP or equivalent, which is currently classified as a low ICS dose.
2. The ICS dose that achieves at least 80–90% of the maximum achievable clinical benefit in moderate to severe asthma is around 200 μg/d of FP or equivalent, which is currently classified as a low ICS dose.
3. The considerable variability of response to ICS owing to factors such as type 2 inflammation has clinical implications in terms of the decision whether to treat with ICS and subsequent dose titration in clinical practice.
4. There is a progressive increase in risk of adrenal suppression, cataracts, fractures, and diabetes with increasing ICS dose, with clinically significant risk with doses ⩾250 to 500 μg/d of FP or equivalent.
5. The available evidence suggests that the dose–response relationship of ICS within ICS/LABA maintenance therapy is similar to ICS maintenance therapy alone.

Key Messages

1. The classification of ICS by dose level using the current terminology of "low," "medium," and "high" is not evidence based, and clinical practice based on this terminology may lead to the prescription of inappropriately excessive doses of ICS, resulting in unnecessary systemic adverse effects.
2. Different dose–response relationships are likely to exist in patients with different clinical characteristics that are predictors of responsiveness.
3. The titration of maintenance ICS dose in accordance with changes in biomarkers of type 2 responsiveness may represent the optimal approach to ICS dosing in individual patients.
4. An alternative classification is proposed whereby ICS doses are based on the "standard daily dose," which is defined as 200–250 μg of FP or equivalent, representing the dose at which about 80–90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity. ■

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