Safety of Inhaled Corticosteroids in the Treatment of Persistent Asthma

Stephen P. Peters, MD, PhD
Winston-Salem, North Carolina

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Objective: Inhaled corticosteroids (ICSs) are the most effective medications available for patients with persistent asthma of all severities and currently are recommended as the preferred asthma controller therapy by the National Heart, Lung and Blood Institute. Nevertheless, lingering concerns about potential adverse systemic effects of ICSs contribute to their underuse. This review discusses the safety of ICSs with respect to potential systemic effects of most concern to physicians and patients.

Methods: Articles reporting on the safety of ICSs in children and adults with persistent asthma were identified from the Medline database from January 1966 through December 2003, reference lists of review articles and international respiratory meetings.

Results: Ocular effects of ICSs and ICS effects on bone mineral density and adrenal function are minimal in patients maintained on recommended ICS doses. One-year growth studies in children have shown decreased growth velocity with ICSs, but long-term studies with inhaled budesonide and beclomethasone show no effect on final adult height, suggesting that these effects are transient. In addition, extensive data from the Swedish Medical Birth Registry show no increased risk of adverse perinatal outcomes when inhaled budesonide is administered to pregnant women with asthma.

Conclusions: ICSs have minimal systemic effects in most patients when taken at recommended doses. The benefits of ICS therapy clearly outweigh the risks of uncontrolled asthma, and ICSs should be prescribed routinely as first-line therapy for children and adults with persistent disease.

Key words: asthma ■ inhaled corticosteroid ■ safety ■ pregnancy

 Send correspondence and reprint requests for *J Natl Med Assoc.* 2006;98:851–861 to: Dr. Stephen P. Peters, Wake Forest University Health Sciences, Center for Human Genomics, Medical Center Blvd., Winston-Salem, NC 27157; phone: (336) 713-7500; fax: (336) 713-7566; e-mail: sppeters@wfubmc.edu

OBJECTIVES

After reading this article, "Safety of Inhaled Corticosteroids in the Treatment of Persistent Asthma," the learner should be able to better understand the minimal risk of adverse systemic effects associated with inhaled corticosteroid therapy for patients with persistent asthma. Readers also should be able to recognize that the benefits of this preferred therapy clearly outweigh these risks. Finally, the learner should be able to complete the quiz and evaluation questions listed at the end of this article.

EXPIRATION

The quiz must be completed, postmarked and mailed, scanned and e-mailed, or faxed by July 1, 2006 for eligibility to receive continuing medical education credit for this CME activity.

INTRODUCTION

Clinical guidelines for the management of asthma currently recommend controller therapy for children and adults with persistent asthma. Inhaled corticosteroids (ICSs) are the preferred controllers for mild, moderate and severe persistent asthma.[1] Minimum criteria for persistent asthma (i.e., mild persistent asthma) include daytime symptoms >2 per week and nighttime symptoms >2 per month. For patients aged >5 years, peak expiratory flow (PEF) or forced expiratory volume in one second (FEV_1) of ≥80% and PEF variability of 20–30% also indicate mild persistent disease. ICS therapy is highly effective in reducing airway inflammation, improving pulmonary function and asthma symptoms, and reducing asthma exacerbations. Moreover, regular use of ICS therapy has been associated with substantial reductions in the rates of hospital admissions and readmissions for asthma, and in the rate of deaths from asthma. A population-based study of >30,000 patients with asthma in the Saskatchewan health system databases showed a reduction of 31% and 39% in the rate of hospitalizations and readmissions for asthma, respectively,[2] and an approximate 50% reduction in the rate of asthma-related deaths,

with regular ICS use.[3] When administered regularly, ICS therapy not only reduces the need for supplemental medication and emergency healthcare but also decreases the cost of asthma management.[4]

Comparative low-, medium- and high-dose estimates for available ICSs are shown in Table 1.[1] High-dose ICSs are the preferred controller therapy for patients with severe persistent asthma, whereas low- to medium-dose ICSs are recommended for patients with mild and moderate persistent disease. For patients with moderate disease, a long-acting β_2-adrenergic agonist can be added to decrease the ICS dose needed for optimal disease control.[1] Despite recommendations for the daily use of ICSs for patients with any severity of persistent asthma, unsubstantiated concern about the potential for adverse systemic effects may be sufficient to reduce physician prescribing of ICSs and patient adherence to therapy. This review discusses ICS safety with respect to systemic effects of most concern to physicians and their patients.

SAFETY CONCERNS OF LONG-TERM INHALED CORTICOSTEROID USE

Growth

Studies assessing the effects of ICSs on growth in children for relatively short periods (≤1 year) have reported variable effects. In a 12-month, randomized, double-blind study, children aged 6–16 years with asthma who received beclomethasone dipropionate 84 µg four times daily experienced slower growth velocity (4.2 cm/year) compared with children given theophylline twice daily at doses adjusted for optimal asthma control and with a target blood level of 8–15 µg/ml 12 hours after dosing (5.5 cm/year; P=0.005).[3] Another study showed that children aged 7–9 years randomized to beclomethasone 200 µg twice daily exhibited less growth at the end of seven months of double-blind treatment compared with children who received placebo (mean growth, 2.66 ± 0.78 vs. 3.66 ± 0.77 cm; P<0.0001).[6] Similar results were reported in two one-year, randomized, double-blind studies comparing beclomethasone 200 µg twice daily with salmeterol 50 µg twice daily in children.[7,8] Meta-analysis of these four beclomethasone studies by Sharek and Bergman showed a reduction in growth velocity of about 1.51 cm/year with beclomethasone (328–400 µg/day) compared with a reduction of 0.43 cm/year during a one-year study of fluticasone propionate (200 µg/day) administered via dry-powder inhaler.[9] In this study, children receiving fluticasone propionate grew at rates similar to those receiving placebo and at rates consistent with their age.[10] A more recent comparison study of fluticasone (200 µg/day) and nedocromil (8 mg/day) (with maximum allowed doses of 400 µg/day and 16 mg/day for uncontrolled asthma) in 174 children aged 6–14 years with asthma reported by Roux et al. showed similar rates of growth between fluticasone and nedocromil (6.1 cm and 5.8 cm/year, respectively).[11] One report of growth suppression in six children with severe persistent asthma who were switched from high-dose beclomethasone or budesonide (≥800 µg/day) to fluticasone administered by dry-powder inhaler (≥1,000 µg/day) suggests that high fluticasone doses may lead to growth suppression in some children.[12]

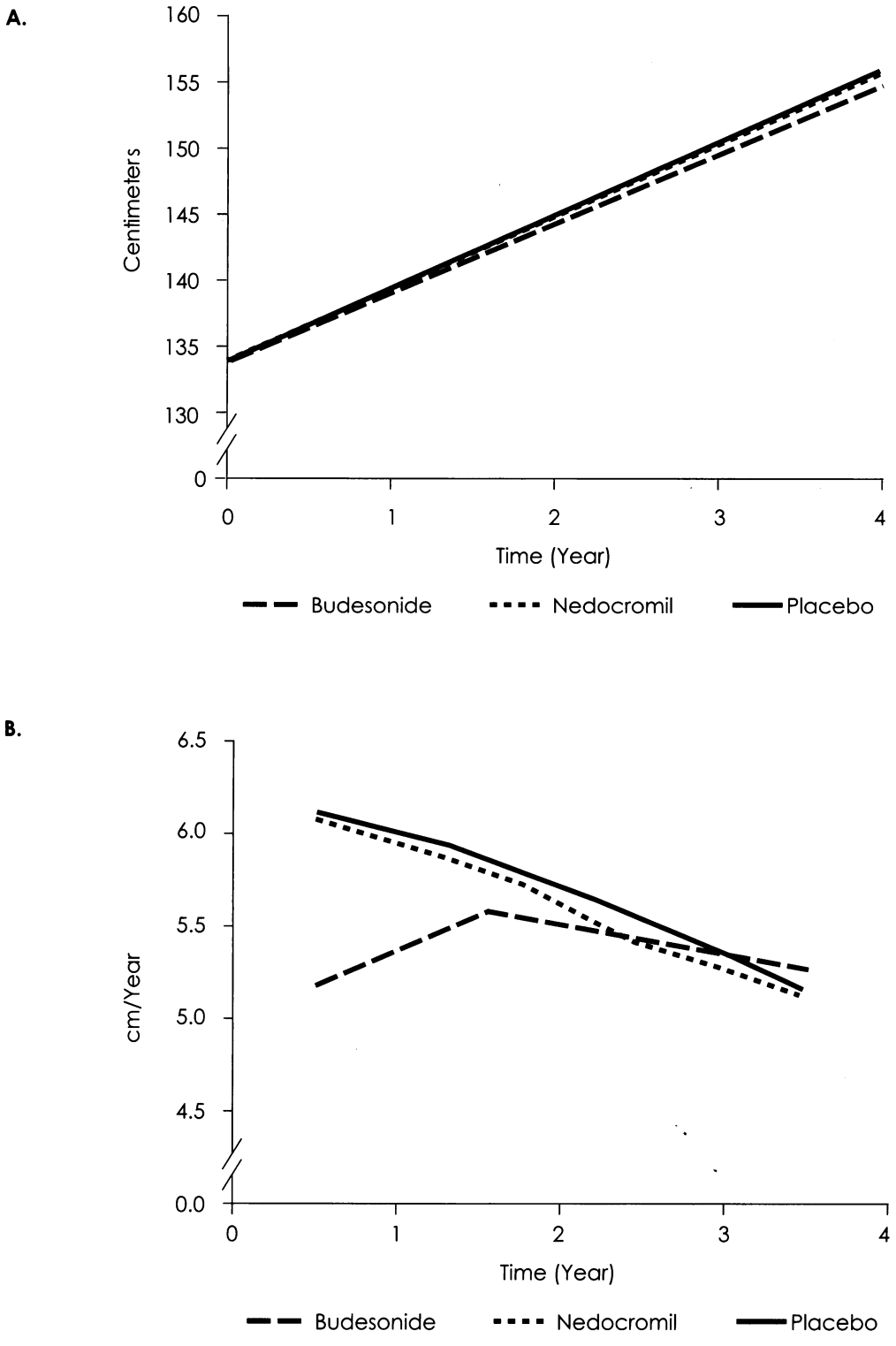
Three 52-week, randomized, open-label exten-

Table 1. Estimated comparative daily inhaled corticosteroid doses

	Low Daily Dose		Medium Daily Dose		High Daily Dose	
Drug	**Adult**	**Child***	**Adult**	**Child***	**Adult**	**Child***
Beclomethasone CFC 42 or 82 µg/puff	168–504 µg	84–336 µg	504–840 µg	336–672 µg	>840 µg	>672 µg
Beclomethasone HFA 40 or 80 µg/puff	80–240 µg	80–160 µg	240–480 µg	160–320 µg	>480 µg	>320 µg
Budesonide DPI 200 µg/inhalation	200–600 µg	200–400 µg	600–1,200 µg	400–800 µg	>1,200 µg	>800 µg
Budesonide suspension for nebulization	—	0.5 mg	—	1.0 mg	—	2.0 mg
Flunisolide 250 µg/puff	500–1,000 µg	500–750 µg	1,000–2,000 µg	1,000–1,250 µg	>2,000 µg	>1,250 µg
Fluticasone MDI 44, 110 or 220 µg/puff	88–264 µg	88–176 µg	264–660 µg	176–440 µg	>660 µg	>440 µg
Fluticasone DPI 50, 100 or 250 µg/inhalation	100–300 µg	100–200 µg	300–600 µg	200–400 µg	>600 µg	>400 µg
Triamcinolone acetonide 100 µg/puff	400–1,000 µg	400–800 µg	1,000–2,000 µg	800–1,200 µg	>2,000 µg	>1,200 µg

CFC: chlorofluorocarbon; DPI: dry-powder inhaler; HFA: hydrofluoroalkane; MDI: metered-dose inhaler; * Children aged ≤12 years. From the National Asthma Education and Prevention Program.[1]

Figure 1. Mean value for standing height (A) and standing-height velocity (B) during four years of treatment with inhaled budesonide, nedocromil or placebo



sion studies from 12-week, randomized, controlled studies (N=1,018)[13-15] compared the safety of budesonide inhalation suspension (BIS) with conventional asthma therapy, which could include ICSs in two studies, in 670 children aged six months to eight years.[16] Children randomized to BIS were initially treated with 0.5 mg once or twice daily. Attempts were made to reduce BIS dosing to the minimal effective dose throughout the study. One of these studies enrolling 350 patients demonstrated a significant difference in growth velocity between treatments: 6.55 ± 2.08 cm/year in children treated with BIS (median daily dose, 0.5 mg) compared with 7.39 ± 2.52 cm/year in children treated with conventional therapy (P=0.002). In the remaining two studies, growth velocities with BIS (median daily doses, 0.5 mg and 0.8–1.0 mg) were not different from conventional asthma therapy.[16] Analysis of pooled data from the three studies showed no statistically significant differences in growth velocity, standard median heights or skeletal age between BIS and conventional asthma therapy.[16] Overall mean growth velocities were 6.64 ± 2.28 and 6.45 ± 2.52 cm/year for children receiving BIS and conventional therapy, respectively. An earlier open-label study in children aged <3 years did not reveal an effect of BIS (1–4 mg/day) on growth measured over a period of six or more months.[17]

Findings of Heuck et al. suggest that reducing the frequency of dosing with ICSs to once daily may have a sparing effect on short-term growth suppression. In children aged 5–12 years, mean lower leg growth rate was reduced with budesonide 400 μg administered twice daily via metered-dose inhaler for four weeks compared with budesonide 800 μg administered once daily in the morning for four weeks (0.27 ± 0.04 vs 0.38 ± 0.05; P=0.04).[18]

Recent results from two large randomized studies suggest that the effects of ICSs on growth observed over periods of up to one year are not sustained with longer-term therapy.[19,20] In the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study, 7,241 patients aged 5–66 years with recent-onset, mild persistent asthma were randomized to receive budesonide (200 μg/day for children aged ≤11 years, 400 μg for others) or placebo, plus usual asthma therapy.[19] Reductions in growth velocity in children aged <11 years were apparent over the three years of treatment with budesonide but were greatest in the first year. The reductions in the first, second and third years of the study were 0.58 cm (P<0.0001), 0.43 cm (P<0.0001), and 0.33 cm (P=0.0005), respectively. The Childhood Asthma Management Program (CAMP) study compared the effects of inhaled budesonide 200 μg, nedocromil sodium 8 mg and placebo administered twice daily for 4–6 years in 1,041 children aged 5–12 years.[20] At the end of the study, the mean increase in height for children treated with budesonide was 1.1 cm less than that in the placebo group (Figure 1A). However, this difference resulted primarily from reduced growth velocity during the first year of treatment (Figure 1B). At the study's end, growth velocity and projected final height in children treated with budesonide were similar to those in children treated with nedocromil and placebo. Similar findings were reported in a separate prospective study by Agertoft and Pedersen that examined the effects of long-term budesonide therapy on final adult height in children.[21] Although growth rates in children treated with budesonide (mean daily dose, 412 μg) were significantly reduced during the first two years of treatment compared with untreated controls and healthy siblings, measures obtained after a mean of 9.2 years of treatment revealed no significant effects of budesonide on final adult height. The difference between measured and target adult height did not correlate with either duration of budesonide treatment or cumulative dose. In an earlier study by Balfour-Lynn, long-term treatment with beclomethasone (mean duration, 5.8 years) in 26 children with asthma at doses of up to 600 μg/day before puberty and 400 μg/day during puberty had no effect on the attainment of predicted final height.[22] Thus, children do achieve their predicted adult height after long-term ICS treatment, and transient decreases in growth rates are not reliable predictors of final height.

Bone Mineral Density

In general, low-to-medium-dose ICSs do not have significant effects on bone mineral density in children.[1] No statistically significant differences in measurements of BMD were found in a study of children aged 4–17 years with asthma who had been treated with beclomethasone (300–800 μg/day) for a mean duration of 25 months compared with children with asthma who were not treated with corticosteroids.[23] In another study, bone mineral density in 44 children aged 5–10 years treated with beclomethasone (mean dose, 319.3 μg/day) for 6.7 ± 1.3 months was similar to that of 20 age-matched children treated with cromolyn sodium.[24] In the study by Roux et al., increases in bone mineral density with fluticasone (200–400 μg/day) and nedocromil (8–16 mg/day) were similar at the lumbar spine (11.6% vs. 10.4%) and femoral neck (8.9% vs. 8.5%) after 24 months of treatment.[11] Similarly, a cross-sectional study assessing the effects of long-term budesonide treatment (mean duration, 13 months) on bone mineral density in 74 children aged 3–10 years with asthma failed to show significant differences between children receiving low- or high-dose budesonide (range 200–800 μg/day) and those

who were ICS naïve.[25] Furthermore, bone mineral density did not correlate with treatment duration or cumulative budesonide dose. In the previously described CAMP study, investigators observed no effects of inhaled budesonide on bone mineral density in children treated with budesonide over 4–6 years.[20] In contrast, an increased risk of fracture is seen with as few as four short courses of oral corticosteroids in children aged 4–17 years [odds ratio (OR)=1.32; 95% confidence interval (CI)=1.03–1.69].[26] These findings support the long-term use of ICSs, in terms of safety, compared with intermittent use of oral corticosteroids.

There have been conflicting reports regarding the effects of ICSs on bone mineral density in adults. Initial studies reported decreased bone mineral density in small numbers of patients receiving high doses of budesonide or beclomethasone (800–2,000 μg/day).[27-29] Patients received ICSs for a mean of 40 ± 43.1 months (range 3–180 months) and 29.8 ± 19.5 months in the studies by Ip et al.[28] and Hanania et al.,[27] respectively. In the study by Packe et al., patients received ICSs for 1–10 years (median 3 years for beclomethasone and 4.5 years for budesonide).[29] A more recent three-year study in 109 premenopausal women receiving triamcinolone acetonide demonstrated a yearly dose-related decline in bone mineral density of 0.00044 g/cm^2 per puff (100 μg/puff) at both the hip (P=0.01) and trochanter (P=0.005), but no decline at the femoral neck or spine. Significant declines at the hip and trochanter were apparent even in those women who received no oral or parenteral corticosteroids.[30] Several other studies in adults failed to demonstrate significant effects of ICSs on bone mineral density or bone metabolism,[31-35] although studies have shown an association between ICS dose and decreases in bone mineral density.[31,35] Boulet et al. reported no significant differences in bone mineral density or bone metabolism over three years between patients (N=51) receiving high-dose beclomethasone or budesonide (>800 μg/day) and those receiving low-dose (<500 μg/day) or no ICS.[31] There were likewise no significant changes in bone mineral density or markers of bone metabolism reported among 374 patients randomized to budesonide (median 389 μg/day), beclomethasone (median 499 μg/day) or noncorticosteroid therapy over two years by Tattersfield et al.[35] In two additional studies, no apparent loss of bone mineral density and no significant changes in markers of bone metabolism were evident over one year among patients (N=59) receiving fluticasone 1,000 μg/day or budesonide 1,600 μg/day in the first study,[33] or among patients (N=69) receiving fluticasone at doses of 400 and 750 μg/day or beclomethasone at doses of 800 and 1,500 μg/day in the second study.[34] Finally, bone mineral density was not significantly different between 106 postmenopausal women exposed to ICS therapy (mean dose 853 μg/day) for a mean of 8.2 ± 5.03 years and 674 women not exposed to corticosteroids.[32] Based on a meta-analysis of seven studies on the effects of ICSs in patients with asthma or mild chronic obstructive pulmonary disease, the Cochrane Airways Group concluded that the use of ICSs at conventional doses for 2–3 years does not affect bone mineral density.[36] In contrast, a more recent meta-analysis, based on the results of 11 studies of ICS use and bone mineral density in patients with asthma and chronic obstructive pulmonary disease, reported that the use of ICSs at pharmacologic doses for a mean duration of 2.33 years is associated with decreased bone mineral density.[37] The authors attribute the disparity between their findings and those of previous meta-analyses to the inclusion of two recent studies involving triamcinolone. Both studies showed that inhaled triamcinolone adversely affects bone mineral density.[30,38] Of the ICSs studied, budesonide (mean daily dose 686 μg) had the least deleterious effects on bone mineral density; triamcinolone (mean daily dose 1,000 μg) had the most deleterious effects followed by beclomethasone (mean daily dose 703 μg).[37] Compared with control patients, bone losses of 0.010% per month in patients receiving budesonide, 0.016% in patients receiving beclomethasone and 0.028% in patients receiving triamcinolone were observed. Available data for fluticasone were insufficient to provide a value for comparison.

Although unclear, the reasons for conflicting results among studies addressing the effect of ICSs on bone mineral density may be related to differences in oral corticosteroid use, numbers of postmenopausal women with age-related bone loss, or asthma severity.[28] It remains to be determined whether reductions in bone mineral density associated with ICS therapy in adults are clinically significant. One retrospective database analysis reported a significant dose-related increase in the risk of hip fracture in older patients with recent ICS use (median daily dose 249 μg; OR=1.19; 95% CI=1.10–1.28) after adjusting for oral corticosteroid use (P=0.007).[39] However, studies suggest that corticosteroid-related bone loss may be easily prevented with dietary supplements. One study found that bone loss associated with long-term use of high-dose budesonide or beclomethasone (>1.5 mg/day for up to 18 months) can be prevented with calcium supplements administered daily with or without cyclical sodium etidronate.[40] Evidence also suggests that osteoporosis induced by oral corticosteroid use can be effectively managed using bisphosphonates, with concomitant administration of vitamin D.[41]

Hypothalamic Pituitary Adrenal Axis Function

The hypothalamic pituitary adrenal (HPA) axis is very sensitive to the systemic activity of corticosteroids and is thus a useful indicator of systemic activity of ICSs; however, the clinical relevance of minor changes in the HPA axis is unclear. A decrease in endogenous cortisol production is expected, with systemic exposure to exogenous corticosteroids due to negative feedback inhibition from the HPA axis.

The effects of ICSs on HPA axis function have been assessed in healthy subjects and patients with asthma using a variety of measures, including morning plasma cortisol, integrated 12- or 24-hour area-under-the-curve plasma cortisol levels, 24-hour urinary free cortisol, adrenocorticotrophic hormone levels and adrenocorticotrophic hormone-stimulated cortisol.[42] Integrated plasma cortisol levels, overnight or 24-hour urinary cortisol, and low-dose adrenocorticotrophic hormone-stimulation tests are the most sensitive measures of HPA axis function.[43] Single morning cortisol levels are insensitive measures of HPA axis function due to wide variation within individual patients.[42]

In one 52-week study, open-label treatment with budesonide dry-powder inhaler (200–1,600 μg/day) demonstrated no evidence of suppressed adrenal cortisol synthesis in 1,133 patients with mild-to-severe persistent asthma based on adrenocorticotrophic hormone-stimulated cortisol levels.[44] However, effects on HPA axis function can vary depending on the ICS as well as the inhalation device used to deliver the ICS. For example, fluticasone administered via metered-dose inhaler plus spacer has resulted in about fivefold greater systemic bioactivity (and, consequently, greater suppression of adrenal cortisol synthesis) than the same dose of the drug administered via dry-powder inhaler.[45]

ICSs suppress adrenal cortisol synthesis in a dose-related manner. A recent study comparing the systemic effects of different ICSs reported substantial variation in effects on 12-hour area-under-the-curve plasma cortisol values.[46] The ICS-labeled dose that produced a 10% decrease from baseline in plasma cortisol ranged from 111 μg for fluticasone administered by metered-dose inhaler to 936 μg for flunisolide via metered-dose inhaler. A meta-analysis of studies examining systemic effects of ICSs on overnight urinary cortisol levels (21 studies) and on morning plasma and serum cortisol levels (13 studies) showed that the dose-response gradients for suppression of adrenal cortisol synthesis are steeper for fluticasone via metered-dose inhaler than for budesonide, beclomethasone or triamcinolone.[47] In a study comparing the efficacy and adverse systemic effects of fluticasone and beclomethasone administered via metered-dose inhaler in patients with mild-to-moderate persistent asthma, Szefler et al. concluded that near-maximal improvement in pulmonary function can be achieved at low and medium doses of fluticasone and beclomethasone, respectively, but that use of high-dose therapy, especially fluticasone via metered-dose inhaler, increased systemic activity as measured by overnight plasma cortisol excretion, without providing greater efficacy.[48]

Although the clinical significance of these effects on HPA axis function may be limited at low-to-medium ICS doses,[49] high doses may lead to acute adrenal insufficiency in very rare cases. A recent survey conducted in the United Kingdom reported acute adrenal crisis in 33 patients who were receiving ICSs at doses of 500–2,000 μg/day.[50] Twenty-three cases presented with acute hypoglycemia, with reduced consciousness, coma or convulsions. One patient died as a result of adrenal insufficiency. Notably, 94% of the adrenal insufficiency cases occurred with the use of fluticasone, even though this ICS was the least frequently prescribed by surveyed physicians. Based on these findings, the authors suggested confirming the diagnosis of asthma and using alternative therapeutic avenues before prescribing fluticasone at doses >400 μg/day in children and >1,000 μg/day in adults. With any ICS, efforts should be made to step down to the lowest effective dose.

Table 2. Food and Drug Administration pregnancy categories for inhaled corticosteroids

Pregnancy Category	Classification Criteria	Inhaled Corticosteroid
B	No evidence of risk in humans. Either animal studies show risk, but human findings do not or, if no adequate human studies have been performed, animal findings are negative for risk.	Budesonide
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify potential risk.	Beclomethasone Flunisolide Fluticasone Triamcinolone

Cataracts, Ocular Hypertension and Glaucoma

Systemic corticosteroid use is a documented risk factor for the development of cataracts,[51] but pediatric and adult study data argue against a large effect of ICS use on cataract development.[1] In children, analysis of data from the CAMP study demonstrated the presence of one posterior subcapsular cataract among 311 children who received inhaled budesonide, and this finding was reported as questionable.[20] Cataract formation could not be directly attributed to ICS use in this case because the child also received oral and intranasal corticosteroids during the study. Cataracts also were not reported in children with persistent asthma enrolled in the previously mentioned three U.S. 12-week studies of BIS administered at doses of 0.25–2.0 mg/day, their one-year open-label extensions (N=670) or five non-U.S. studies (N=333).[52] Moreover, only three reports of cataracts in children were identified in postmarketing surveillance of BIS from 1990 through June 2002. Of these reports, two were complicated by prematurity and history of congenital cataracts.

Similar to studies in young children, several studies in adolescents and adults suggest that long-term ICS use does not increase the risk of cataracts, even at high doses.[53-56] However, one study conducted in patients aged 49–97 years with asthma demonstrated a higher prevalence of nuclear (relative prevalence 1.5, 95% CI=1.2–1.9) and posterior subcapsular (relative prevalence 1.9; 95% CI=1.3–2.8) cataracts in patients currently or previously using ICSs compared with those who were ICS naïve.[57] Patients with higher cumulative lifetime doses of beclomethasone (≥1,000 mg) were at greater risk for the development of posterior subcapsular cataracts (P<0.001). A subsequent case-control study based on insurance claims data indicated that high-dose ICSs (>1 mg/day) increased the risk of cataract extraction in elderly patients after two years of treatment.[58] An increased risk for ocular hypertension or open-angle glaucoma was reported in another study involving patients aged ≥66 years prescribed high doses of ICSs (defined as an average daily dose ≥1,500 μg for flunisolide and ≥1,600 μg for beclomethasone, budesonide and triamcinolone) for ≥3 months (OR=1.44; 95% CI=1.01–2.06).[59] Postmarketing surveillance for BIS has shown no increased risk of ocular toxicity in adult or elderly patients.[60,61] In a recent population-based case-control study using the General Practice Research Database in the United Kingdom, the association between exposure to ICSs and cataracts was evaluated in 15,479 patients with cataracts and 15,479 controls.[62] The adjusted OR for cataract development with ICS doses of up to 400 μg/day was 0.99 (95% CI=0.87–1.13) compared with that of 1.69 (95% CI=1.17–2.43) with doses >1,600 μg/day.

These findings suggest that ocular effects from ICSs are minimal in children and most adults but that the risk of cataracts, glaucoma or ocular hypertension with long-term use of high ICS doses may be higher in older patients. In any event, routine ophthalmologic follow-up to detect ocular hypertension and glaucoma at an early stage is an important part of routine healthcare for everyone, patients with and without asthma alike.

SAFETY FOR THE PREGNANT WOMAN AND FETUS

Up to 8.4% of pregnant women may be affected by asthma,[63] which, if uncontrolled, can lead to adverse perinatal outcomes.[64] Although National Asthma Education and Prevention Program Guidelines recommend the use of ICSs for the treatment of all severities of persistent asthma during pregnancy,[65,66] few studies have assessed the safety of ICSs in pregnant women. Substantial data from the Swedish Medical Birth Registry showed a rate of congenital malformations among 2,534 children of women who used budesonide during early pregnancy equal to that observed in the general population (3.6%).[67] A subsequent analysis of registry data demonstrated normal gestational age, normal birthweight and length, and no increased risk of multiple births or stillbirths among infants born to 2,968 mothers who used budesonide during early pregnancy.[68] Among studies of beclomethasone, one prospective study reported rates of adverse outcomes in infants of 64 women exposed to ICSs (primarily beclomethasone) during pregnancy that were not significantly different from rates observed in infants of women who were not exposed to ICSs.[69] A second, observational study revealed a rate of congenital malformations with beclomethasone that was within the normal range.[70]

In their joint consensus statement, the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma and Immunology recommend the use of budesonide or beclomethasone for women with persistent asthma who are initiating ICS treatment during pregnancy.[71] Budesonide is recommended for pregnant patients with high ICS dose requirements. According to the U.S. Food and Drug Administration, only inhaled budesonide meets the criteria for adequate and well-controlled studies in pregnant women to justify a pregnancy category-B rating (Table 2).[72] Other ICSs have been rated pregnancy category C, which signifies that human pregnancy studies are lacking and animal reproduction studies are either positive for fetal risk or lacking; however, the potential benefits of treatment may justify any potential risks.

Continuing Medical Education (CME) Quiz and Evaluation—
Safety of Inhaled Corticosteroids in the Treatment of Persistent Asthma
A CME activity sponsored by the National Medical Association (NMA)

Accredidation: NMA is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. The *Journal of the National Medical Association* (*JNMA*) has been approved by the American Academy of Family Physicians (AAFP) as having educational content acceptable for five prescribed credit hours. NMA designates this continuing medical education activity for one credit hour in category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. Term of approval is from January 1, 2006 through December 31, 2006. Credit may be claimed for one year from date of individual use.

Instructions: Select the correct answer to each question and mark in the corresponding boxes provided. Mail, scan and e-mail, or fax the completed test and evaluation questions to *JNMA*, 1012 Tenth St. NW, Washington, DC 20001; (202) 371-1162; ktaylor@nmanet.org. You will receive notification of your test results within one month. If you have successfully completed the test (≥7 correct answers), you will receive via fax a certificate for one credit hour in category 1 of the Physician's Recognition Award or one Prescribed AAFP credit hour. There is no fee for participating in this CME activity.

Name _____ Medical license number _____

1. Suppression of growth velocity with ICS use in children appears to be transient, with no effect of long-term use on final adult height.
   A. True B. False

2. In general, the use of low-to-medium doses of ICSs has no significant effect on bone mineral density in children, whereas the intermittent use of oral corticosteroids (≥4 courses/year) can increase the risk of bone fracture.
   A. True B. False

3. Conflicting reports on the effects of ICSs on bone mineral density in adults may reflect:
   A. The ICS used
   B. Asthma severity
   C. Age-related bone loss in postmenopausal women
   D. A and C
   E. A, B, C

4. Which of the following is the least sensitive measure of HPA axis function?
   A. 24-hour urinary cortisol
   B. Integrated plasma cortisol level
   C. Morning cortisol level
   D. Adrenocorticotrophic hormone-stimulation test

5. ICS effects on HPA axis function depend on:
   A. The ICS used
   B. ICS dose
   C. Delivery device
   D. All of the above

6. High-dose ICS therapy may, in very rare cases, lead to acute adrenal insufficiency.
   A. True B. False

7. Studies suggest which of the following might increase the risk of cataract development with ICS use?
   A. High daily dose (>1,000 µg)
   B. High cumulative lifetime dose (≥1,000 mg)
   C. Older age
   D. All of the above

8. The National Asthma Education and Prevention Program recommends ICS use for the treatment of all severities of persistent asthma in pregnant women.
   A. True B. False

9. Inhaled budesonide has an FDA pregnancy category-B rating based on safety demonstrated in adequate and well-controlled studies in pregnant women.
   A. True B. False

10. The lowest effective ICS doses should be used, especially for higher-potency ICSs, to reduce any potential for adverse systemic effects.
    A. True B. False

Look for answers to this quiz in the July issue of *JNMA* below the table of contents.

CONCLUSIONS

ICSs improve pulmonary function and reduce asthma symptoms and asthma exacerbations more effectively than any other class of asthma-controller medication. This superior efficacy has contributed to the current status of ICSs as the preferred first-line therapy for the management of persistent asthma.[1] ICSs as a class are safe and well tolerated at recommended doses, and the benefits of their long-term use clearly outweigh the risks of uncontrolled asthma.

Most studies clearly demonstrate the safety of low and moderate doses of ICS therapy in terms of bone mineral density, adrenal function and ocular effects. In terms of growth, long-term data for budesonide suggest that the initial growth suppression demonstrated with ICSs does not affect final adult height. Moreover, analyses of Swedish Medical Birth Registry data have shown no increased risk of adverse perinatal outcomes with budesonide when administered to pregnant women. Some patients may be more susceptible to systemic effects of long-term, high-dose ICS therapy, but the clinical significance of this susceptibility is uncertain.

Although the risks of adverse effects due to ICS therapy are generally low, the potential for systemic effects can be reduced by titrating ICSs down to the lowest effective dose after asthma control has been achieved. It is particularly important to use the lowest effective dose to limit potential systemic effects of higher-potency ICS formulations.[47,73,74] Combining recommended asthma management strategies with appropriate ICS dosing is a safe and effective treatment approach for adults and children with persistent asthma.

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The program evaluation below must be completed to process your exam. Your responses to the following questions will have no effect on the grading or results of the CME quiz.

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