

Local and Systemic Safety of Intranasal Corticosteroids

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■ Abstract

The safety and efficacy of intranasal corticosteroids (INCs) are well established for the management of allergic rhinitis, rhinosinusitis, and nasal polyps. As seen in numerous studies, INCs demonstrate markedly reduced systemic bioavailability compared with oral and even inhaled corticosteroids and have shown an excellent safety profile over 3 decades of use. Nonetheless, concerns remain among some prescribers and patients that these agents may reach the systemic circulation in sufficient concentration to produce adverse effects (AEs). Available evidence does not support these concerns. A review of the published literature indicates that the side effect profiles of INCs consist primarily of a low incidence of mostly mild and often transient local AEs, such as nasal irritation and epistaxis. The second-generation INC agents currently in use (mometasone furoate nasal spray, fluticasone propionate, ciclesonide, and fluticasone furoate) have favorable pharmacokinetic characteristics that further minimize systemic bioavailability (<1%) compared with older INCs and compared with oral agents, thereby limiting the risk for systemic adverse events.

Key words: Glucocorticoids. Seasonal allergic rhinitis. Drug safety. Mometasone furoate. Fluticasone. Ciclesonide.

■ Resumen

La seguridad y eficacia de los esteroides intranasales (INCs) está claramente definida para el tratamiento de la rinitis alérgica, la rinosinusitis o la poliposis nasal. Como se ha demostrado en numerosos estudios, los INCs han demostrado tener una muy reducida biodisponibilidad en comparación con los corticoides orales o incluso los inhalados, al igual que han demostrado un excelente perfil de seguridad durante tres décadas de uso. No obstante, algunos prescriptores y pacientes tienen dudas sobre si estos productos pueden alcanzar la circulación sistémica en suficiente concentración para causar efectos adversos (AEs). Las pruebas disponibles no avalan estas dudas. Una revisión de la literatura científica sobre el tema indica que los efectos adversos de los INCs tienen una baja incidencia y son principalmente leves y a menudo transitorios, como irritación nasal y epistaxis. Los INCs de segunda generación actualmente en uso (furoato de mometasona, propionato y furoato de fluticasona, ciclesonida en forma de nebulización nasal) tienen unas características farmacocinéticas favorables que minimizan la biodisponibilidad sistémica (<1%) en comparación con los antiguos INCs o con los medicamentos en forma oral. Por lo tanto, se limita el riesgo de AEs sistémicos con el uso de los INCs de segunda generación.

Palabras clave: Glucocorticoides. Rinitis alérgica estacional. Seguridad de medicamento. Furoato de mometasona. Fluticasona. Ciclesonida.

Introduction

Although the efficacy and safety of intranasal corticosteroids (INCs) are well established for the management of allergic rhinitis, rhinosinusitis, and nasal polyps, concerns remain among some patients, caregivers, and health care providers that these agents may reach the systemic circulation in sufficient concentration to produce adverse effects (AEs) [1]. These concerns derive mainly from systemic adverse effects

reported with oral and some high-dose inhaled corticosteroids (ICS). These side effects include growth inhibition induced by hypothalamus-pituitary-adrenal (HPA) axis suppression, decreased bone mineral density, myopathy, cataract, glaucoma, hypertension, hyperglycemia, and thin or easily bruised skin [2]. The misconception that consistent use of INCs will cause systemic effects can be attributed to several factors [3]: infrequent reports of systemic AEs with some of the older INCs; concomitant use of INCs with ICS, which have greater systemic

absorption than INCs [4], for treatment of comorbid asthma, resulting in the perception of an additive inhibitory effect on the HPA that is more pronounced than the suppression seen with ICSs alone (a perception not supported by the few studies examining this question to date) [5-7]; and increasing chronic use of INCs in a broader patient population, raising concern among some health care providers regarding the long-term effects of these agents. This article examines data from clinical trials to investigate the safety profile of these agents and provides an overview of relevant pharmacokinetic differences between older and newer INCs.

Pharmacokinetic Differences

The systemic bioavailability of INCs reflects the sum of nasal and intestinal absorption, as well as clearance by first-pass hepatic metabolism [8]. The second-generation INC agents currently in use (mometasone furoate nasal spray [MFNS], fluticasone propionate [FP], ciclesonide, fluticasone furoate [FF]) have pharmacokinetic characteristics that minimize their systemic bioavailability (<1%) compared with both older INCs (eg, triamcinolone acetonide [TAA], flunisolide, beclomethasone, dexamethasone) and oral agents (eg, prednisone, methylprednisolone), thereby minimizing the risk of systemic adverse events (Table 1) [1,2,8-14]. With each dose of a second-generation INC, approximately 30% is deposited in the nose, where the agent binds with the glucocorticoid receptor. The remaining 70% is swallowed and subject to first-pass hepatic metabolism, the degree of which varies in available agents, from approximately 80% to 90% for TAA and 90% for budesonide (BUD) to approximately 99% for FP and MFNS [15]. Increased lipophilicity correlates with greater deposition of corticosteroid in the targeted respiratory tract tissue, greater binding affinity for and prolonged occupation of the corticosteroid receptor, and, consequently, less unbound drug to interact with systemic glucocorticoid receptors and potentially result in adverse events.

Table 1. Estimated Absolute Bioavailability of Intranasal Corticosteroids [1,9,12,14]

Corticosteroid	Systemic Bioavailability
Dexamethasone (oral)	76%
Flunisolide	49%
Triamcinolone acetonide	46%
Beclomethasone dipropionate	44%
Budesonide	34%
Fluticasone propionate ^a	<1%
Fluticasone furoate	0.5%
Mometasone furoate ^a	<0.1%
Ciclesonide aqueous	Below lower limits of assay quantification

^aA pharmacokinetic study of mometasone furoate (MFNS) and fluticasone propionate (FP) administered at 2400 µg/day—utilizing a dose 3 times higher than the maximum ciclesonide dose administered in a study by Nave et al. and 12 times the recommended dose of MFNS and FP—yielded barely detectable serum levels of each agent and estimated bioavailability of 0.42% and 0.46% for FP and MFNS, respectively [10,13,14].

Lipophilicity also correlates with slower release from the respiratory tissue [2]. The rank order of lipophilicity of some currently available INCs (from highest to lowest) is as follows: MFNS, FP, beclomethasone dipropionate (BDP), BUD, TAA, and flunisolide [8].

Local Adverse Effects

The most common AEs associated with INCs are epistaxis, throat irritation, and nasal dryness, burning, and stinging [1,2]. The incidence in most cases (except epistaxis) is similar to that of placebo, and most are mild, self-limiting, and resolve without discontinuing therapy [1,2]. Table 2 summarizes local AEs and incidence vs placebo observed in clinical trials of INCs in patients with acute rhinosinusitis, chronic rhinosinusitis (with or without nasal polyps), or allergic rhinitis.

Epistaxis is a concern among some patients and primary care providers. However, in most clinical trials of INCs, the incidence of epistaxis is similar to or modestly above that of placebo (Table 2) [1,16-44], and most episodes are mild and transient [17,26,28,29,36,45]. Epistaxis is common in the general population: the incidence of nasal bleeding not related to medication ranged from 7.6% in a 12-month study of 3500 mature women (50-64 years of age) [46] to 15.8% (minor recurrent nosebleeds) in a survey of 4538 US households [47]. A recent audit of INC use in a rhinitis clinic in the United Kingdom indicated a real-world incidence of epistaxis of 9% among 126 patients using INCs for 3 months [48].

Epistaxis may be related to drying and thinning of the nasal mucosa [48,49]. However, the incidence of epistaxis reported with placebo in some clinical trials is similar to that of active INC treatment, suggesting that direct physical trauma from the nasal applicator tip pressing against the septum or the anterior end of the inferior turbinate may contribute to occurrence [45,49]. Therefore, instruction in the proper use of INC sprays (eg, directing the spray laterally, away from the septum, to reduce direct septal deposition and physical trauma) may decrease the incidence of epistaxis (Table 3) [49-51].

Severe local AEs, such as nasal mucosal atrophy or ulceration and septal perforation, have rarely been associated with INCs [48,52-54] and can be prevented with an appropriate administration technique (Table 3) that helps avoid dryness, crusting, and bleeding from the septum [48,51]. Histologic data generated from long-term studies of several INCs (MFNS, FP, TAA, and BDP) in patients with perennial allergic rhinitis demonstrate no evidence of atrophy or deleterious pathologic changes in the nasal mucosa after 6 months to 5 years of use [52,53,55-58]. A query from the Adverse Event Reporting System of the US Food and Drug Administration (FDA) for spontaneous reports of nasal septal perforation associated with INCs between 1969 and 2006 yielded only a handful of cases, all between 1997 and 2006 [59]. However, this finding is not representative of a meaningful incidence rate, as it does not take into account the actual frequency of INC use. In contrast to several reports of damage to nasal epithelia associated with intranasal products containing benzalkonium chloride as a preservative, a review of the published literature from 1980 to 2003 based on *in vivo* data concluded that even prolonged use

Table 2. Summary of Commonly Reported Local Adverse Effects in Clinical Trials of Intranasal Corticosteroids, by Condition Treated

Adverse Effect	Active Treatment Group						
	MFNS	FP	C	FF	BUD	BDP	TAA
<i>Acute RS Trials</i>							
Epistaxis	MFNS: 3%-6% PL: 1%-6% [1,16,17]	FP: 6.5% PL: 2.1% [1,18]	NA	NA	NA	NA	NA
Nasal burning/ irritation	MFNS: <1%2% PL: 0%-2% [1,16]	NA	NA	NA	NA	NA	NA
Pharyngitis	MFNS: 2% PL: 3% [1,16]	NA	NA	NA	NA	NA	NA
<i>Chronic RS/Nasal Polyposis</i>							
Epistaxis	MFNS: 4-13.7% PL: 4.2-5% [19,20]	FP: 1-19% PL: 0-4% [21-23]	NA	NA	NA	BDP (QD): 46.2% BDP (BID): 43.8% No PL arm [1,24]	NA
Nasal burning/ irritation	MFNS: 0-2% PL: 0-2% [19]	FP: 0% PL: 1.8% [23]	NA	NA	NA	BDP (QD): 3.85% BDP (BID): 3.13-9.38% No PL arm [1,24]	NA
Pharyngitis	MFNS: 0-2.6% PL: 1-5.6% [19,20]	NA	NA	NA	BUD: 3.37% PL: 4.7% [1,25]	BDP (QD): 3.85% BDP (BID): 0% No PL arm [1,24]	NA
Sneezing	NA	FP: 3.7% PL: 1.8% [23]	NA	NA	NA	NA	NA
<i>Allergic Rhinitis Trials</i>							
Epistaxis	MFNS: 12-12.7% BDP: 9.4% PL: 8% [1,26,27]	FP: 2-19% Montelukast: 1% PL: 4-8% [1,22,28-30]	C: 4.3-10% PL: 2.5-7.2% [31-33]	FF: 4-20% PL: 4-8% [34,35]	NA	BDP: 20% PL: 27% [1,36]	TAA: 2.7-7% PL: 1% FP: 4.8 [37,38]
Nasal burning/ irritation	MFNS: 8% PL: 6% [1,26]	FP: 1-4% PL: 0% [1,28,29]	C: <1-6.1% PL: 1-5.5% [31-34]	NA	NA	BDP: 2-8% PL: 2-14% [1,36,39]	NA
Sneezing	MFNS: 0-4.2% BDP: 1.2% PL: 2% [1,26,27]	NA	NA	NA	NA	BDP: 0% PL: 10% [1,36]	NA
Coughing	NA	NA	C: 2.1-4.3% PL: 2.1-2.3% [31,32]	NA	BUD: 5.1% PL: 0% [1,40]	BDP: 0% PL: 4% [1,36]	TAA: 0.7% FP: 2.0% [38]
Pharyngitis	MFNS: 0-7.2% BDP: 5.9% PL: 2% [1,26,27,41]	FP: 3% Montelukast: 2% [30]	C: 3-13.2% PL: 3.7-18% [31-33]	FF: 5-6% PL: 5% [35,42]	NA	BDP: 9-10% MFNS: 6% PL: 5-9% [1,39,41]	TAA: 0.7-15% Active comparators: 2.7-9% [37,38,43]

Abbreviations: BDP, beclomethasone dipropionate; BUD, budesonide; C, ciclesonide; FF, fluticasone furoate; FP, fluticasone propionate; INC, intranasal corticosteroids; MFNS, mometasone furoate; NA, not analyzed; PL, placebo; RS, rhinosinusitis; TAA, triamcinolone acetate.

Table 3. Recommended Technique for Using Topical Intranasal Corticosteroid Sprays [51]

1. Hold head in a neutral, upright position
2. Clear nose of any thick or excessive mucus, if present, by gently blowing the nose
3. Insert spray nozzle into the nostril
4. Direct the spray laterally or to the side, away from the middle of the nose (septum) and toward the outer portion of the eye or the top of the ear on that side. (If possible, use the right hand to spray the left nostril and left hand to spray the right nostril, to direct the spray away from the septum)
5. Activate the device as recommended by the manufacturer, and use the number of sprays recommended by the doctor
6. Gently breathe in or sniff during the spraying
7. Breathe out through the nose

(Adapted from Benninger MS et al. *Techniques of intranasal steroid use. Otolaryngol Head Neck Surg.* 2004;130:5-24.)

of topical nasal preparations (including INCs) that contain benzalkonium chloride causes no significant damage to nasal mucosa [60].

Systemic Adverse Effects

Table 4 [61-85] summarizes the impact of INCs on systemic functions in the context of clinical trials involving patients with acute rhinosinusitis, chronic rhinosinusitis, allergic rhinitis, and asthma.

Effects on the HPA Axis

The primary action of corticosteroids on the HPA axis is a negative feedback effect caused by suppression of corticotrophin-releasing hormone and adrenocorticotrophic hormone (ACTH) levels, resulting in lower cortisol secretion [49]. HPA axis suppression, used as a marker of systemic bioactivity of INCs, is assessed by the extent of suppression of cortisol secretion, indicating the presence of systemically bioavailable INCs [8]. However, low-dose and high-dose cosyntropin (synthetic ACTH) stimulation tests and corticotrophin-releasing hormone stimulation tests are necessary to determine whether a clinically significant effect exists [8,49]. A large number of short- and long-term studies in adults and children have found no significant impact on HPA axis function with the newer INC agents [5,7,17,26-28,31,34,39,42,63,67-71,77-80,82].

MFNS: The effects of MFNS on the HPA axis have been investigated in 6 randomized controlled parallel-group or crossover trials in adults and children at doses ranging from 100 µg once daily to 400 µg twice daily for periods ranging from 21 days to 52 weeks (Table 4) [17,26,27,68,69,77]. Overall, no relevant differences from baseline or placebo were observed in any markers of adrenal suppression measured

in any of the studies, indicating no evidence of HPA axis suppression by MFNS in adults or children.

FP: The effects of FP on the HPA axis have been investigated in 7 randomized controlled trials in adults and children at dosages of 88 µg to 800 µg daily [5,28,78,79,80-82]. The results of these studies indicated no significant effect of FP on the HPA axis (Table 4). In 2 studies investigating the concurrent use of intranasal FP with orally inhaled FP for the treatment of comorbid rhinitis and asthma, the combination did not increase the risk of HPA axis abnormalities compared with orally inhaled FP alone [5].

FF: Five randomized controlled trials examining the effect of FF on the HPA axis in adults and children yielded no clinically meaningful differences in markers of adrenal suppression compared with placebo, including 24-hour cortisol excretion and the ratio from baseline in weighted mean serum cortisol (Table 4) [34,42,63,70,71]. Doses ranged from 55 µg to 110 µg once daily, and study durations ranged from 6 weeks to 12 months.

Ciclesonide: In a 1-year randomized trial in 663 patients ≥12 years with perennial allergic rhinitis who received once-daily ciclesonide 200 µg or placebo, no differences were observed between groups in either 24-hour urinary free cortisol or morning plasma cortisol levels, indicating a lack of HPA axis suppression [31]. The addition of once-daily intranasal ciclesonide 200 µg to twice-daily inhaled BDP 320 µg did not change mean plasma cortisol levels in a study of 150 adult patients, suggesting that concurrent use of intranasal ciclesonide with ICS for treatment of comorbid rhinitis and asthma does not increase the risk of HPA axis abnormalities [7].

BUD: In a double-blind randomized study in children aged 2 to 3 years (N=78) treated with BUD or placebo for 6 weeks, no significant differences were observed between groups in mean change in plasma cortisol level after cosyntropin stimulation from baseline to study end [40]. The results of an open, longitudinal study of 24 patients (aged 17 to 67 years) treated with nasal BUD for up to 5.5 years indicated no impact on the HPA axis, based on an ACTH stimulation test [61].

TAA: Based on the results of a cosyntropin stimulation test in a randomized placebo-controlled trial, TAA had no measurable effect on adrenocortical function in 80 pediatric patients (aged 6 to 12 years) after 6 weeks [62]. Other controlled trials in pediatric patients support this observation [86,87]. Similarly, in a double-blind placebo-controlled study in 64 adult patients, TAA 220 µg or 440 µg daily for 6 weeks had no significant effect on adrenocortical function with either dose compared with placebo, as measured using the cosyntropin stimulation test [66].

BDP: The results of 2 studies in adult patients revealed that BDP did not affect adrenal function. Findings were based on morning serum cortisol levels after 12 weeks of treatment in one study [24] and on cosyntropin stimulation after 36 days of treatment in the other [39].

Effects on Statural Growth in Children

Systemic corticosteroids are known to exert a suppressive effect on growth through several mechanisms, including decreased release of growth hormone, inhibition of insulinlike

Table 4. Summary of Commonly Reported Local Adverse Effects in Clinical Trials of Intranasal Corticosteroids, by Condition Treated

Condition	Study	N	Patient	INC	Treatment	Safety
<i>Acute RS</i>						
	Nayak et al, 2002 [17]	967	Children and adults (8-78 y)	MFNS 200 or 400 µg BID	21 d	No HPA-axis suppression (cosyntropin stimulation)
<i>Chronic RS</i>						
	Giger et al, 2003 [24]	112	Adult (19-66 y)	BDP 400 µg QD or 200 µg BID	12	Minimal decrease in morning serum cortisol levels
<i>Allergic rhinitis</i>						
	Grossman et al, 1993 [28]	250	Children (4-11 y)	FP 100 or 200 µg QD	14 d	No effect on morning cortisol levels
	Pipkotn et al, 1988 [61]	24	Adolescent and adult (17-67 y)	BUD 200-400 µg BID	Up to 5.5 y	No decreases in cortisol (ACTH challenge)
	Nayak et al, 1998 [62]	80	Children (6-12 y)	TAA 220 or 400 µg QD	42 d	No effect on cortisol (cosyntropin stimulation)
	Patel et al, 2008 [63]	112	Adolescent and adult (12-65 y)	FF 110 µg QD	42 d	No effect on 24-h urinary cortisol levels
	Moller et al, 2003 [64]	78	Children (5-15 y)	BUD 200 µg BID	12 mo	No effect on morning plasma cortisol or 24-h urinary cortisol No effect on statural growth or bone age No ophthalmologic aberrations
	Weinstein et al, 2009 [65]	436	Children (2-5 y)	TAA 110 µg QD	6 mo	No change from baseline in serum cortisol (cosyntropin stimulation) Stature-for-age percentile distribution remained stable
	Howland et al, 1996 [66]	64	Adults (male; 18-65 y)	TAA 220 µg QD or TAA 440 µg QD	6 wk	No evidence of altered HPA-axis response to cosyntropin with either TAA dose compared with PL
	Brannan et al, 1997 [67]	96	Children (3-12 y)	MFNS 50, 100, or 200 µg QD	7 or 14 d	No effect on cortisol concentrations, 24-h urinary free-cortisol concentrations, or cortisol response to cosyntropin stimulation
	Kim et al, 2004 [40]	78	Children (2-5 y)	BUD 64 µg QD	42 d	No decrease in cortisol (cosyntropin stimulation)
	Wilson et al, 1998 [68]	20	Adults (mean, 35.7 y)	MFNS 200 µg QD BUD 200 µg QD TAA 220 µg QD	5 d on each treatment (crossover study)	No significant difference between PL and any active treatment in fractionated or 24-h measurements of plasma or urinary cortisol levels No significant difference between PL and any active treatment in osteocalcin levels (bone turnover marker)
	Lee et al, 2003 [69]	27	Adults (mean, 37 y)	MFNS 200 µg QD TAA 220 µg QD	3 wk on each treatment (crossover study)	No significant difference between baseline and either active treatment, or between active treatments, in overnight urinary cortisol corrected for creatinine or in morning plasma cortisol No significant difference between baseline and either active treatment or between active treatments in osteocalcin levels

Table 4. Continued

Condition	Study	N	Patient	INC	Treatment	Safety
	Chervinsky et al, 2007 [31]	663	Adolescent and adult (12-73 y)	CIC 200 µg QD	Up to 1 y	No effect on morning plasma cortisol or 24-h urinary cortisol No difference vs PL in IOP, visual acuity or lens opacification
	Rosenblut et al, 2007 [34]	806	Adolescent and adult (12-77 y)	FF 110 µg QD	12 mo	No clinically meaningful differences vs PL in 24-h urinary cortisol excretion or ophthalmic parameters
	Maspero et al, 2008 [70]	558	Children (2-11 y)	FF 110 µg or 55 µg QD	12 wk	No clinically meaningful differences vs PL in 24-h urinary cortisol excretion or ophthalmic parameters (IOP, cararact)
	Tripathy et al, 2009 [71]	112	Children (2-11 y)	FF 110 µg QD	6 wk	No significant difference between PL and FF in change from baseline in 24-h plasma or urinary cortisol levels following 6 wk of treatment
	Martinati et al, 1993 [72]	39	Children	BDP 200 or 400 µg QD	2 mo	No significant changes from baseline in markers of bone metabolism
	Agertoft and Pedersen, 1999 [73]	22	Children (7-12 y)	MFNS 100 or 200 µg QD or BUD 400 µg QD	2 wk	No short-term effects on growth rate (knemometry)
	Skoner et al, 2000 [36]	100	Children (6-9 y)	BDP 168 µg BID	1 y	No effect on morning cortisol levels or response to cosyntropin; a growth-suppressive response was observed with BDP
	Schenkel et al, 2000 [26]	98	Children (3-9 y)	MFNS 100 µg QD	1 y	No effect on cortisol (cosyntropin stimulation) or growth rate (knemometry)
	Allen et al, 2002 [79]	150	Children (3.5-9 y)	FP 200 µg QD	1 y	No growth changes
	Gradman et al, 2007 [74]	58	Children	FF 110 µg QD	2 wk	No short-term effects on growth rate (knemometry)
	Ozturk et al, 1998 [75]	26	Adults (18-66 y) [p848,col2, par3, 4]	BUD 200 µg BID BDP 200 µg BID	3-19 mo	No increase in IOP, no cataracts, no changes in visual acuity
	Simons et al, 1993 [76]	95	Children and adult (6-25 y)	BDP or BUD (median dose: 750 µg/d)	Median: 5 y (range 1-15 y)	No posterior subcapsular cataracts
	Cutler et al, 2006 [77]	56	Children (2-6 y)	MFNS 100 µg QD	42 d	No significant changes vs PL or baseline in serum cortisol or 24-h urinary-free cortisol
	Fluticasone Propionate Collab Ped Working Group 1994 [78]	249	Children (4-11 y)	FP 100 or 200 µg QD	4 wk	No significant changes vs PL or baseline in morning serum cortisol or 24-h urinary cortisol
	Galant et al, 2003 [79]	65	Children (2-3 y)	FP 200 µg QD	6 wk	FP equivalent to PL in mean change from baseline in 12-h creatinine-corrected urinary-free cortisol concentration
	Vargas et al, 1998 [80]	105	Adults (18-65 y)	FP 200 µg QD or FP 400 µg BID	4 wk	No evidence of altered HPA-axis response to cosyntropin with either FP dose compared with PL

Table 4. Continued

Condition	Study	N	Patient	INC	Treatment	Safety
	Howland 1996 [81]	81	Adults (male, 18-40 y)	FP 200 µg QD	1 y	Mean and peak morning plasma cortisol and AUC similar to PL at screening, 24 wk and 52 wk No evidence of altered HPA-axis response to cosyntropin compared with PL No changes in bone density or markers of bone turnover within or between FP and PL groups at 52 wk No occurrence of posterior subcapsular cataract or glaucoma in either group at 52 wk
	Ngamphaiboon et al, 1997 [82]	106	Children (5-11 y)	FP 100 µg QD	4 wk	No evidence of effects on adrenal function based on similar mean morning plasma cortisol concentrations between FP and PL before and after treatment
	Teper and Ratner, 2008 [83]	251	Children (6-11 y)	MFNS 100 µg QD BDP 168 µg QD	52 wk	No clinically relevant HPA-axis suppression (cosyntropin stimulation) No significant changes in IOP No posterior subcapsular cataracts
	Murphy et al, 2006 [84]	229	Children (4-8 y)	BUD 64 µg QD	52 wk	No significant difference in growth rate vs PL
<i>Unclassified rhinitis</i>						
	Bross-Soriano et al, 2004 [85]	360	Adult (18-60 y)	BDP 200 µg BID MFNS 200 µg QD	1 y	Observed variations in IOP in all treatment groups remained within normal limits

Abbreviations: ACTH, adrenocorticotropic hormone; AUC, area under the curve; BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FP, fluticasone propionate; HPA, hypothalamus-pituitary-adrenal; INC, intranasal corticosteroid; IOP, intraocular pressure; MFNS, mometasone furoate; PL, placebo; RS, rhinosinusitis; TAA, triamcinolone acetonide.

Table adapted from Table 4 in Demoly P. Safety of intranasal corticosteroids in acute rhinosinusitis. *Am J Otolaryngol Head Neck Med Surg*. 2008; 29:403-413, with additional data.

growth factor 1 activity, downregulation of growth hormone receptor expression, and suppression of collagen synthesis and adrenal androgen production [8]. Overall, studies have shown that most INCs administered at recommended doses are not associated with impairment of growth or final adult height [3]. Specifically, studies have shown no effect on growth with MFNS, FP, BUD, ciclesonide, or TAA given at recommended doses for up to 1 year [26,29,73,84,86,88,89]. FF was noninferior to placebo in its lack of effect on short-term lower-leg growth in children assessed in a 2-week crossover study [74].

Growth suppression has been reported with long-term use of some INCs when recommended doses were exceeded [36]. In a double-blind parallel-group study, 100 prepubertal children (age 6 to 9 years) with perennial allergic rhinitis were treated with BDP 168 µg or placebo twice daily for 1 year [36]. Overall growth rate was significantly slower in the BDP group: mean changes in standing height after 1 year were 5 cm in the

BDP group vs 5.9 cm in the placebo group. There were no significant differences between groups in HPA axis assessments [36]. However, some research has found triamcinolone to be associated with reduced bone density when administered long-term via inhalation [90].

Effects on Bone Density

Systemic corticosteroids exert their negative effect on bone metabolism by altering both calcium homeostasis (osteoblastic and osteoclastic activity) and sex hormone production [8]. Based on the lack of significant changes in biochemical markers of bone turnover in several studies of MFNS, FP, BUD, and BDP and the lack of a significant effect on bone mineral density in a 1-year study of FP 200 µg daily, these INC agents do not appear to be associated with reductions in bone mineral density or osteoporosis [66,68,69,72,81,91].

Ocular Effects

A handful of cases reported in the literature have suggested a possible association between INCs and either increased intraocular pressure (IOP) [92] or cataract formation [93]. However, several recent long-term studies have demonstrated no evidence of ocular changes with INCs [34,70,75,81,83,85,94-96]. In a 12-month active control trial in 251 children aged 6 to 11 years, no significant changes in IOP were observed with MFNS 100 µg daily (n=166); 1 patient receiving BDP 168 µg (n=85) had increased IOP at 52 weeks [83]. Results of a 12-month, randomized placebo-controlled trial of FF 110 µg per day in patients aged ≥12 years indicated very few ocular changes as assessed by fundoscopic and slit lamp examinations, and mean changes in IOP were similar in the FF and placebo groups at 12, 24, and 52 weeks [34].

The incidence of cataract formation in adult patients (<70 years) using INC sprays was investigated in a retrospective observational study of 286 078 patients classified as users of only INC, users of only oral corticosteroids, or nonusers of either [97]. The study showed no increased risk of cataract formation in users of INCs compared with nonusers.

Use in Pregnancy

Based on their extremely limited systemic absorption due to their pharmacokinetics, all second-generation INCs are generally considered relatively safe to use in pregnancy [98], and no data indicate an association between INCs and congenital malformations [99]. In the one published prospective human study of INC use during pregnancy, 8 weeks of intranasal FP did not have any deleterious effects on fetal growth or pregnancy outcome [100]. A meta-analysis of the use of ICS during pregnancy, as well as a systematic review by the National Asthma Education and Prevention Program showed no increase in risk of major malformations, preterm delivery, low birth weight, or pregnancy-induced hypertension with inhaled corticosteroids [101,102]. The FDA Pregnancy Category B rating given to BUD (all other INCs are Category C) was based on a review of 3 Swedish registries covering over 2000 births from 1995 to 2001 that indicated no increased risk for overall congenital malformation from the use of intranasal BUD during early pregnancy [103-105]. In the FDA Pregnancy Category ratings A, B, C, D, and X, Category A indicates drugs that present the least risk to the developing fetus and Category X drugs present the greatest risk. Approximately two-thirds of approved drugs are rated Category C because data in pregnant women are lacking and animal studies have either not been performed or revealed AEs [106]. The FDA is currently remodeling the pregnancy rating system, recognizing that the 5-letter system can lead to an inaccurate view of risks and is not reflective of newer studies and medical knowledge [107].

Conclusions

The safety profiles of INCs have been well established over 30 years of use. Safety has been particularly well demonstrated for newer agents (MFNS, FP, FF, and ciclesonide) in many

clinical trials and in extreme conditions (eg, higher than recommended doses, long-term treatment, specific populations). Concerns among some health care providers, caregivers, and patients about systemic AEs with these agents are not supported by evidence. Rather, robust clinical evidence demonstrates the safety and efficacy of the newer INCs for management of allergic rhinitis, rhinosinusitis, and nasal polyps.

Conflicts of Interest

Joaquín Sastre reports the following: having served as a consultant to Phadia, Schering-Plough, Merck, GSK, and FAES FARMA; having been paid lecture fees by Novartis, GSK, Stallergenes, MSD, and UCB; and having received grant support from Phadia, GSK, and ALK-Abelló.

Ralph Mosges reports the following: serving as a consultant for AFI/Diamed, Alcon Pharma, ALK-Scherax, Allergen Therapeutics/Bencard, Almirall, ASTA Medica/Meda, Sanofi-Aventis, Bayer, BGT Uberlingen, Daimler AG, Essex-Pharma, Ferrero, Fresenius, HAL, Hoechst AG, Intersan, Johnson & Johnson/Janssen Research, Karl Storz Tuttlingen, Klosterfrau Köln, Lofarma, MSD Munich, Novartis/Leti, Optima, Pfaff AG Kaiserslautern, Philips B.V. Eindhoven, Pierre Fabre Freiburg, Promonta Hamburg, Roxall, Schering-Plough, Schwabe, Schwarz-Pharma Monheim, Servier/IRIS Paris, Stada, Stallergènes, Anthony, UCB, Ursapharm Saarbrücken, and Zyma München; grant/research support from AFI/Diamed, Alcon Pharma, Almirall, ASTA Medica/Meda, Sanofi-Aventis, Essex-Pharma, HAL, Hoechst AG, Intersan, Johnson & Johnson/Janssen Research, Karl Storz Tuttlingen, Klosterfrau Köln, Lofarma, Optima, Pierre Fabre Freiburg, Promonta Hamburg, Roxall, Schering-Plough, Servier/IRIS Paris, Stallergènes, Anthony, UCB, Ursapharm Saarbrücken, and Zyma München; serving on the speaker's bureau for AFI/Diamed, ALK-Scherax, Allergen Therapeutics/Bencard, Almirall, ASTA Medica/Meda, ASTRA AB, Asche, Sanofi-Aventis, Bayer, Bionorica, Dr. Beckmann, Essex-Pharma, Fresenius, Grünenthal, GlaxoSmithKline, Hoechst AG, Intersan, Johnson & Johnson/Janssen Research, Novartis/Leti, Schering-Plough, Schwabe, Schwarz-Pharma Monheim, Servier/IRIS Paris, Stada, Stallergènes, Anthony, UCB, Yamanouchi, and Zyma München.

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