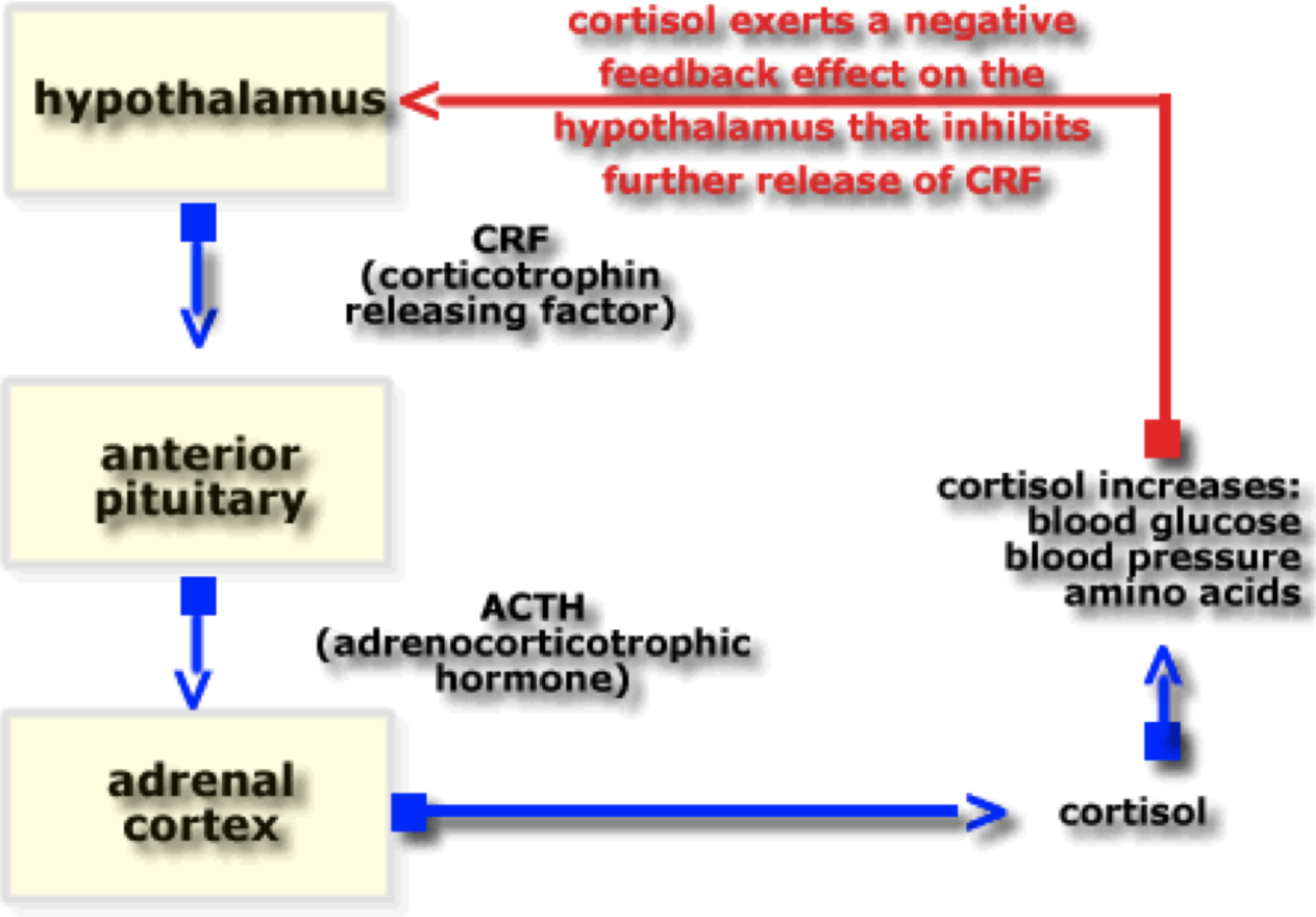
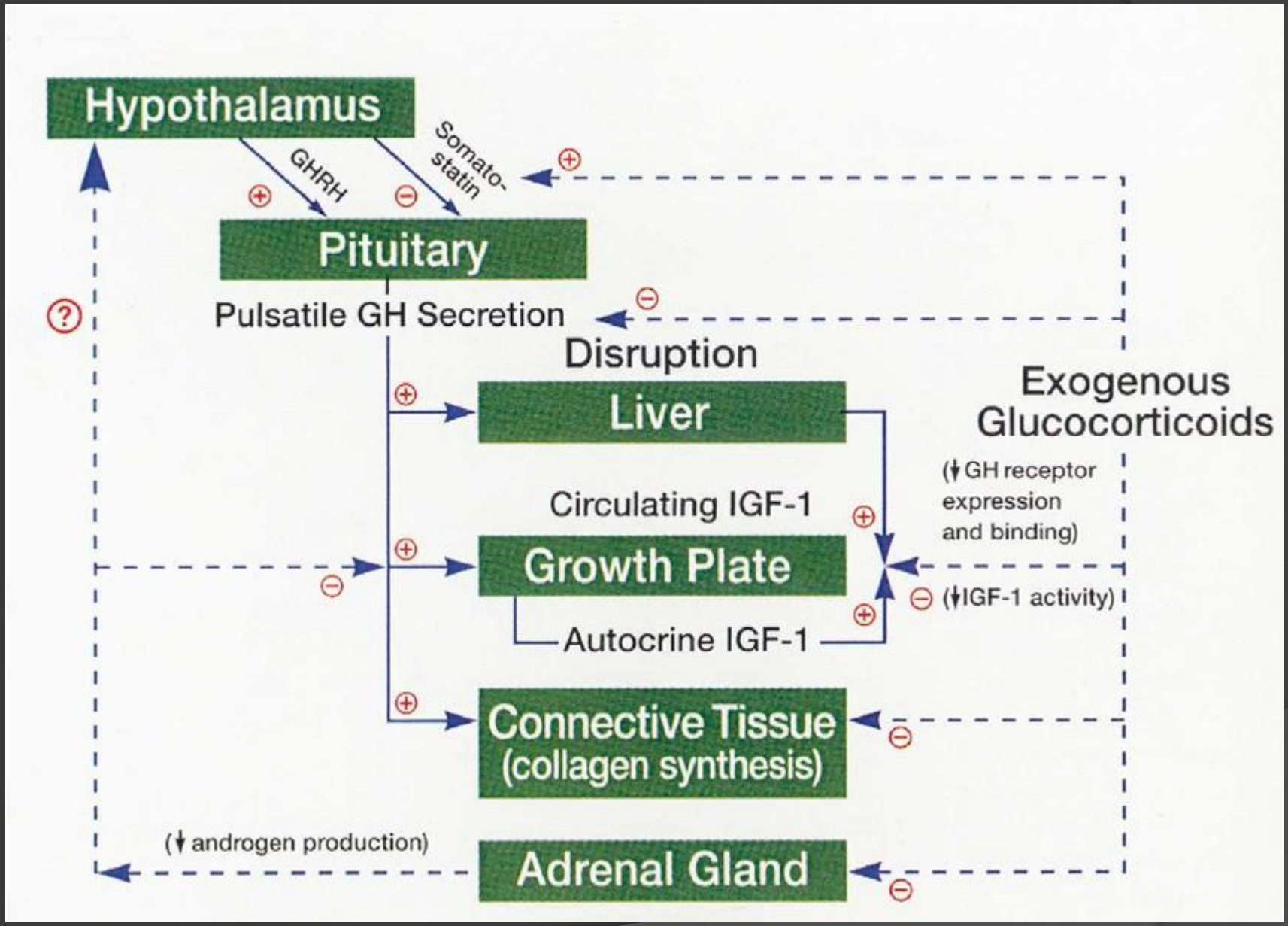
INCS.....

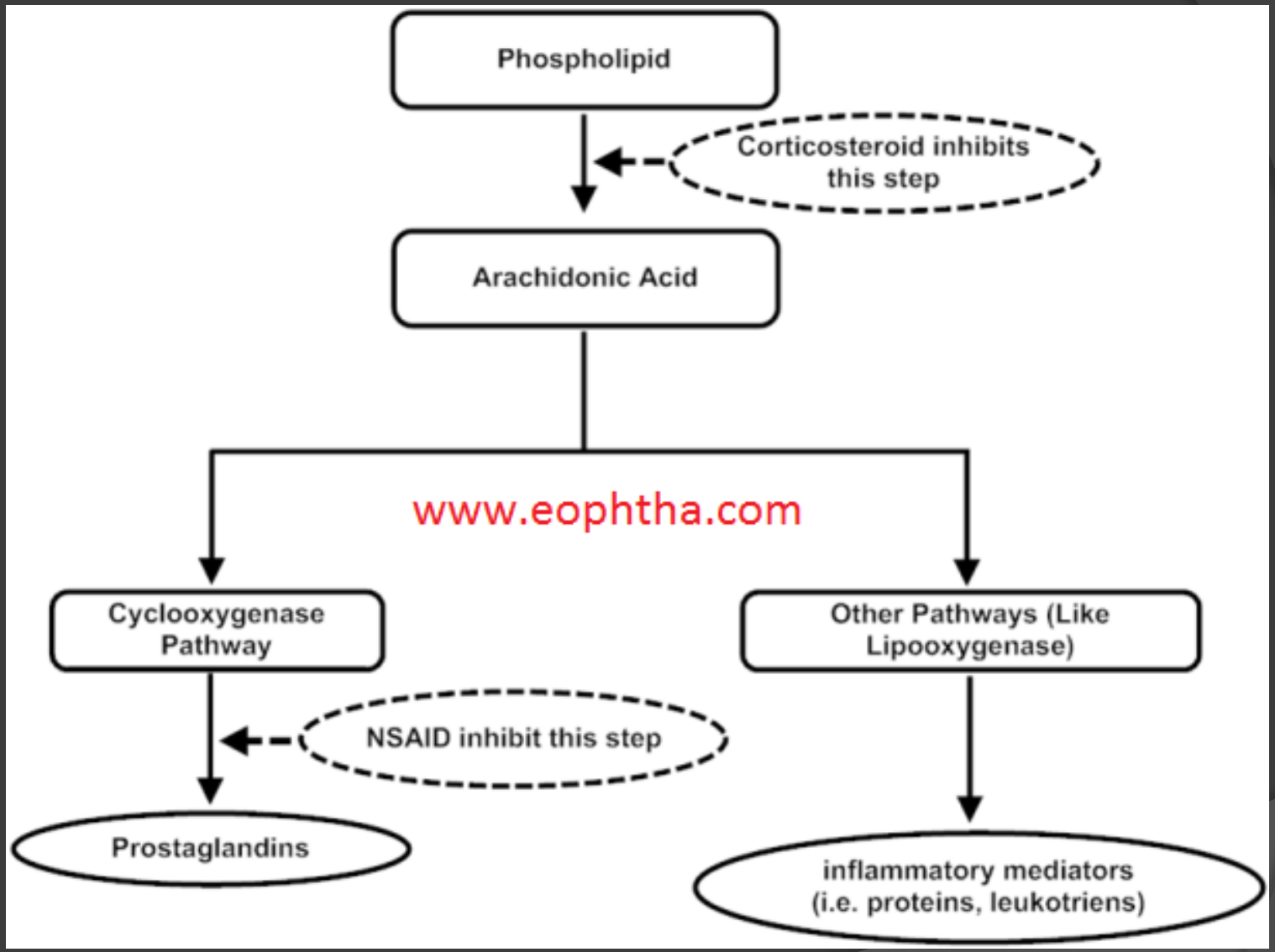
Doubts about safety

Dr. Labeb Sailan F1 24.4.2017

The Pituitary-Adrenal-Axis




Hypothalamus
GHRH
Somato-statin
Pituitary
Pulsatile GH Secretion
Disruption
Liver
Exogenous Glucocorticoids
(↓GH receptor expression and binding)
Circulating IGF-1
Growth Plate
(↓IGF-1 activity)
Autocrine IGF-1
Connective Tissue (collagen synthesis)
(↓androgen production)
Adrenal Gland


Phospholipid
Corticosteroid inhibits this step
Arachidonic Acid
www.eophtha.com
Cyclooxygenase Pathway
Other Pathways (Like Lipooxygenase)
NSAID inhibit this step
Prostaglandins
inflammatory mediators (i.e. proteins, leukotriens)

Adverse effects

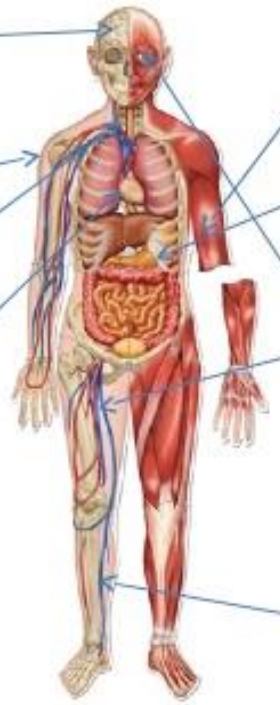
- Occur with prolonged use of high doses
- Cushing's disease

Psychiatric
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

Skin/soft tissue
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

Neurologic
- Neuropathy
- Pseudomotor cerebri

Cardiovascular
- Hypertension



MSK
- Osteoporosis
- Asceptic necrosis of bone
- Myopathy

Endocrine
- Diabetes mellitus
- Adrenal cortex suppression

Immunologic
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

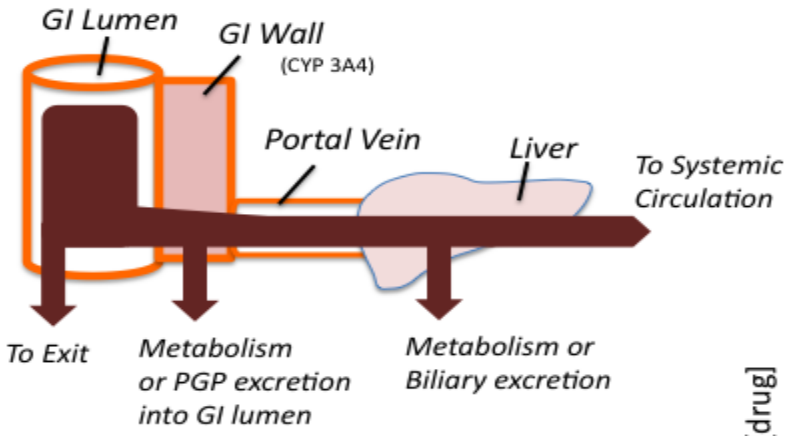
Opthalmic
- Cataract
- Narrow-angle glaucoma

Developmental
- Growth retardation

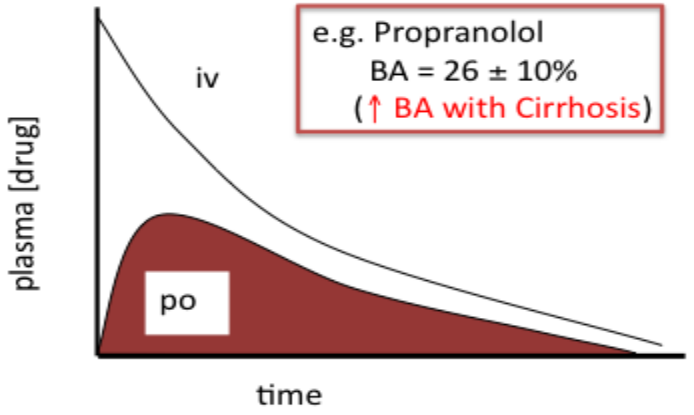
- First generation: beclomethasone (unknown bioavailability);
- Second generation: budesonide (10-34% bioavailability);
- Third generation: fluticasone propionate (< 2%), mometasone furoate (undetectable), and fluticasone furoate (< 1%).

Bioavailability

- the fraction absorbed into the systemic circulation is the drug's bioavailability



$$BA = \frac{AUC_{po}}{AUC_{iv}} \times 100$$



e.g. Propranolol
BA = 26 ± 10%
(↑ BA with Cirrhosis)

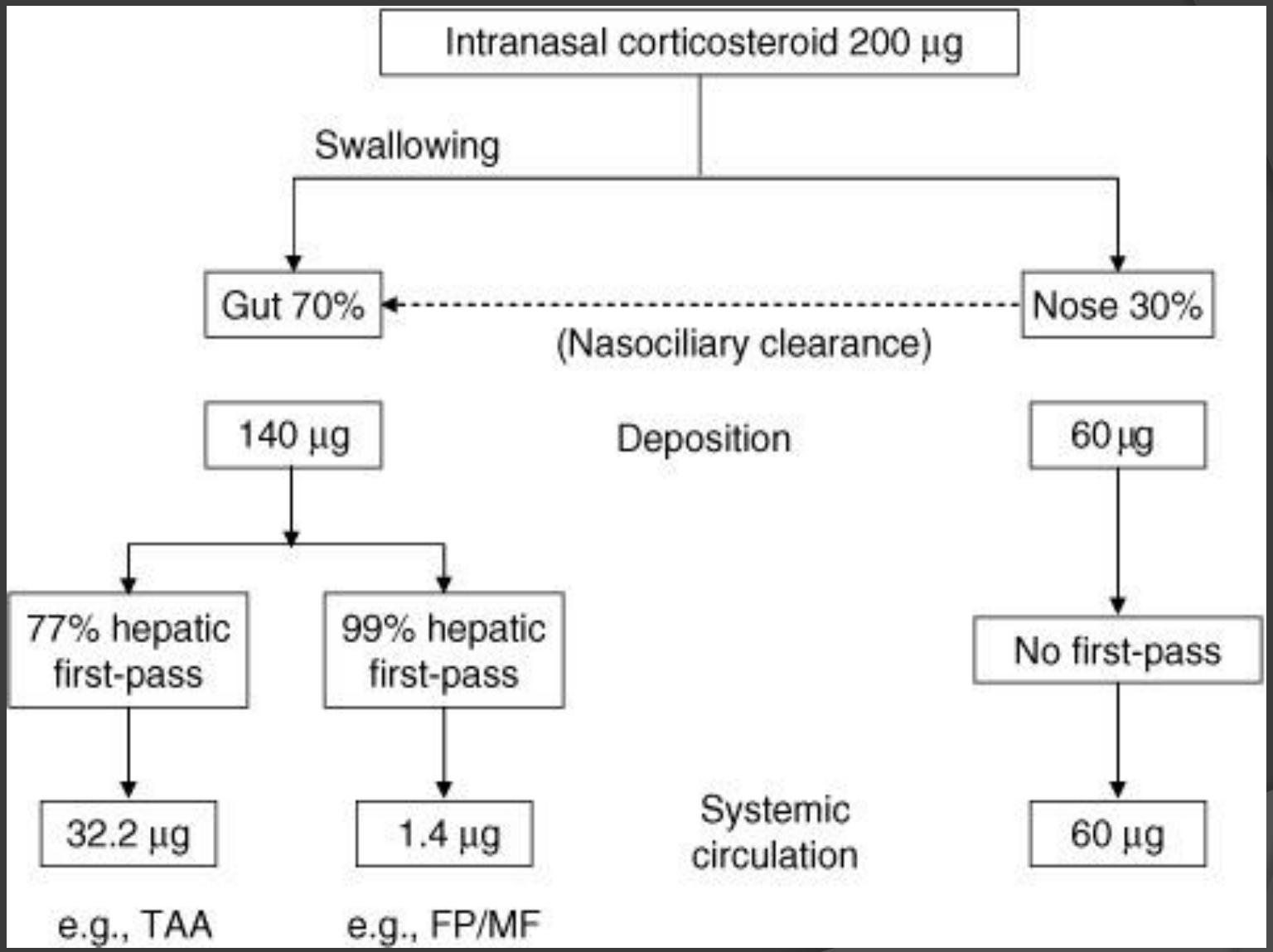

Intranasal corticosteroid 200 µg
Swallowing
Gut 70%
Nose 30%
(Nasociliary clearance)
140 µg
Deposition
60 µg
77% hepatic first-pass
99% hepatic first-pass
No first-pass
32.2 µg
1.4 µg
Systemic circulation
60 µg
e.g., TAA
e.g., FP/MF

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

Clinical and Experimental Immunology REVIEW ARTICLE doi:10.1111/j.1365-2249.2009.04010.x

Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis

Mechanisms of glucocorticosteroid

Molecular level

GC exerts its anti-inflammatory effects through at least two pathways, transactivation and transrepression [42]. Transactivation occurs when the receptor complex binds to the glucocorticosteroid-response elements (GRE) in the

Transactivation occurs when the receptor complex binds to the glucocorticosteroid-response elements (GRE) in the promoter regions of glucocorticosteroid-responsive genes, which encode anti-inflammatory genes such as annexin 1, IκB and CD163 [43]. Alternatively, the GR complex represses

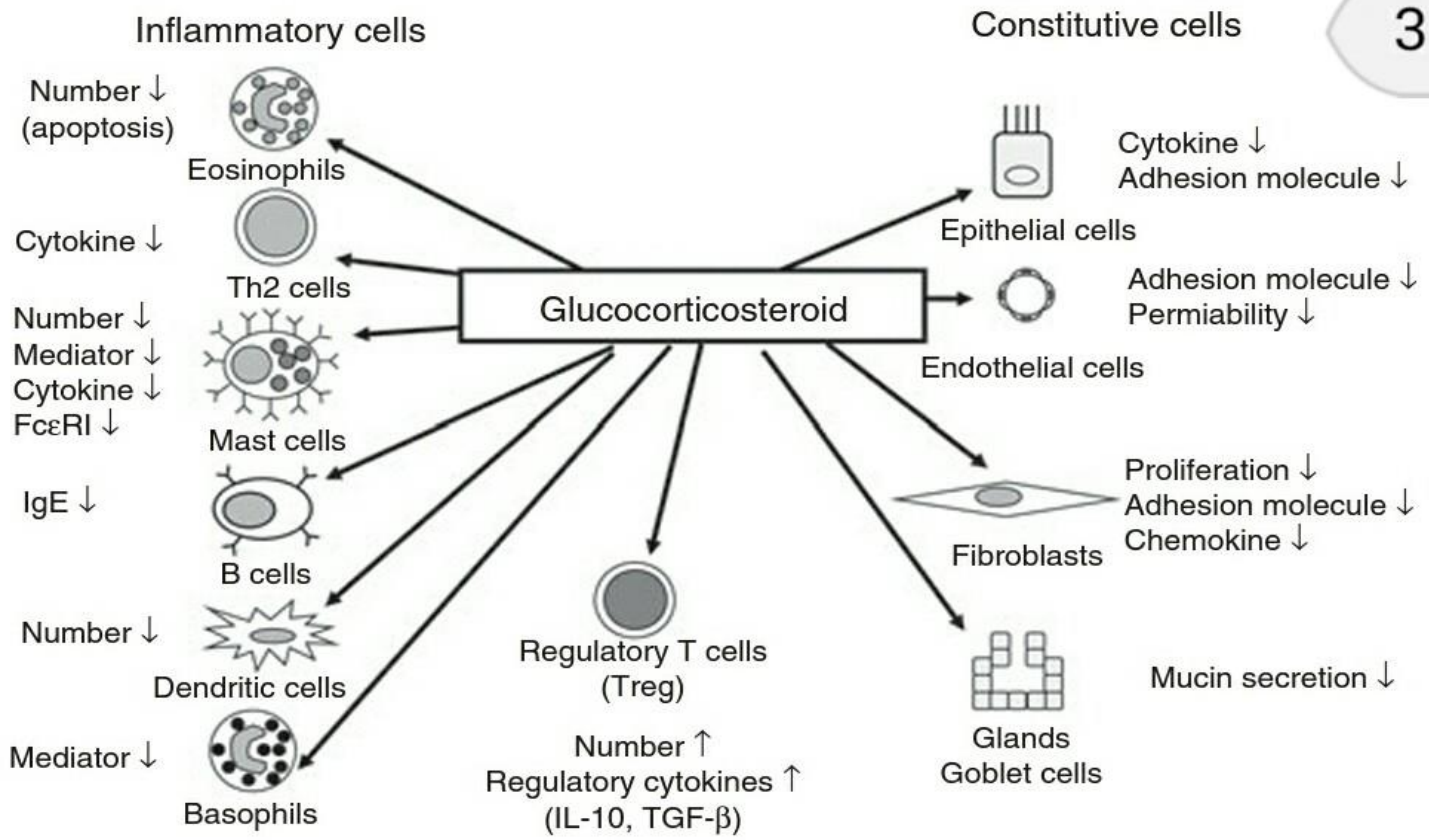
the transcription of proinflammatory genes by protein–protein interactions such as GR–nuclear factor kappa B (NFκB) and GR–activator protein 1 (AP-1) [44]. Evidence for a co-activator competition model of transrepression involving CBP/p300 was first provided for GR transrepression of AP-1 target genes [45].

Cellular level (Fig. 2)

GC inhibits the functions of infiltrating inflammatory cells and their recruitment into the nasal mucosa. GC inhibits the maturation, cytokine production, FcεRI expression and mediator release of mast cells [46,47]. GC inhibits histamine release from basophils [48,49], induces apoptosis of eosinophils [50] and reduces the recruitment of antigen-presenting cells such as Langerhans cells [51]. GC decreases the numbers of GATA-3^+ Th2 cells and the production of Th2

the transcription of proinflammatory genes by protein–protein interactions such as GR–nuclear factor kappa B (NFκB) and GR–activator protein 1 (AP-1) [44]. Evidence for a co-activator competition model of transrepression involving CBP/p300 was first provided for GR transrepression of AP-1 target genes [45].

Intranasal glucocorticosteroids



REVIEW

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.

Objective :

investigate the safety profile of INCS and provides an overview of relevant

pharmacokinetic differences between older and newer INCs.

Table 1. General characteristics of the formulations of intranasal steroids, age from which they can be used in allergic rhinitis, and corresponding dosages for children and adults.

Name	Formulation	Minimum age	Dose per spray mcg*/nostril	Maximum dose/children mcg/day	Dose/adults mcg/day	Maximum dosage for rhinitis and nasal polyps** mcg/day
Triamcinolone acetonide	Isotonic	4 years	55	110	220	220
Budesonide	Isotonic	6 years	32, 50, 64, 100	100	200	400
Ciclesonide	Hypotonic	6 years	50	100	200	400
Beclomethasone dipropionate	Isotonic	6 years	50	100	200	400
Mometasone furoate	Isotonic	2 years	50	100	200	400
Fluticasone propionate	Isotonic	2 years	50	100	200	400
Fluticasone furoate	Isotonic	4 years	27.5	52.5	105	210

* mcg micrograms. Source: Medication inserts, ** Standard dosages are not available for nose polyps at present; clinical trials usually use the medication's maximum dosage[3].

Local Adverse Effects

The most common AEs associated with INCs are:
Epistaxis
throat irritation
and nasal dryness
burning, and stinging

The incidence in most cases (except epistaxis) is similar to that of placebo, and most are mild, self-limiting, and resolve without discontinuing therapy

Demoly P. Safety of intranasal corticosteroids in acute rhinosinusitis. Am J Otolaryngol. 2008;29:403-13

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**

Blaiss MS. Safety considerations of intranasal corticosteroids for the treatment of allergic rhinitis. Allergy Asthma Proc. 2007;28:145-52.

Severe local AEs, such as nasal mucosal atrophy or ulceration and septal perforation, have rarely been associated with INCs and can be prevented with an appropriate administration technique that helps avoid dryness, crusting, and bleeding from the septum

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

Histologic data generated from long-term studies of several INCs 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**

Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. Ann Allergy Asthma Immunol. 2007;99:473-80.

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

	Active Treatment Group						
Adverse Effect	MFNS	FP	C	FF	BUD	BDP	TAA
Acute RS Trials							
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
Chronic RS/Nasal Polyposis							
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
Allergic Rhinitis Trials							
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]

Systemic Adverse Effects

Effects on the HPA Axis

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

MFNS

6 RCT 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

no evidence of HPA axis suppression by MFNS in adults or children

FP

7 RCT in adults and children at dosages of 88 µg to 800 µg daily

The results of these studies indicated no significant effect of FP on the HPA axis

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

Effects on Statural Growth in Children

Overall, studies have shown that most INCs administered at recommended doses are not associated with impairment of growth or final adult height

Growth suppression reported with long-term use of some INCs when recommended doses were exceeded

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
Unclassified rhinitis						
	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

e 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 level following 6 wk of treatment
	Martinati et al, 1993 [72]	39	Children	BDP 200 or 400 μg QD	2 mo	No significant changes from basel 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-

In a double-blind study, 100 prepubertal children with perennial allergic rhinitis were treated with BDP 168 µg or placebo twice daily for 1 year

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

Skoner DP, Rachelefsky GS, Meltzer EO, Chervinsky P, Morris RM, Seltzer JM, Storms WW, Wood RA. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics. 2000;105:e23.

Effects on Bone Density

Based on the lack of significant changes in biochemical markers in a 1-year study of FP 200 µg daily**, these INCS agents do not appear to be associated with reductions in bone mineral density or osteoporosis**

Howland WC 3rd, Dockhorn R, Gillman S, Gross GN, Hille D, Simpson B, Furst JA, Feiss G, Smith JA. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. J Allergy Clin Immunol. 1996;98:32-8

Ocular Effects

several recent long-term studies have demonstrated no evidence of ocular changes with INCs.

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 wks.

Rosenblut A, Bardin PG, Muller B, Faris MA, Wu WW, Caldwell MF, Fokkens WJ. Long-term safety of fl uticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. Allergy. 2007;62:1071-7

Pregnancy

all second-generation INCs are generally considered relatively safe to use in pregnancy

and no data indicate an association between INCs and congenital malformations

Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug . 2005;28:707-19

A meta-analysis of the use of ICS during pregnancy, as well as a systematic review showed no increase in risk of:

major malformations

preterm delivery

low birth weight

pregnancy-induced hypertension

with inhaled corticosteroids

FDA

The FDA Pregnancy Category B rating given to BUD (all other INCs are Category C)

This 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

FDA

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

Conclusion

Robust clinical evidence demonstrates the safety and efficacy of the newer INCs for management of AR,CRS& polyposis.

Intranasal corticosteroids do not affect intraocular pressure or lens opacity: a systematic review of controlled trials

ARTICLE *in* RHINOLOGY · AUGUST 2015

Impact Factor: 3.76 · DOI: 10.4193/Rhin15.020 · Source: PubMed

INCS use.

Methodology: A systematic review of literature from Medline and Embase databases (January 1974 to 21st of November 2013) was performed. Using the PRISMA guidelines, all controlled clinical trials of patients using INCS, that reported original measures of IOP, LO, glaucoma or cataract incidences were included. Studies with adjuvant administration of oral, inhaled and intravenous steroids were excluded.

control.

Conclusion: Data from studies with low levels of bias, do not demonstrate a clinically relevant impact of INCS on neither ocular pressure, glaucoma, lens opacity nor cataract formation.

Key words: Intranasal steroids, Intraocular pressure, Glaucoma, Cataract, Chronic upper airway disease

Annals of Allergy, Asthma & Immunology

Official Publication of ACAAI American College of Allergy, Asthma & Immunology

Safety of intranasal corticosteroids

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DOI: http://dx.doi.org/10.1016/j.anai.2016.06.009

Objective

To discuss INCS safety data for the use of INCSs in patients with asthma and allergic rhinitis.

Results

Data on concurrent use of INCSs and ICSs are limited, but these limited data reveal no evidence systemic effects on the hypothalamic-pituitary-adrenal axis.

Results

clinically significant. Early growth studies indicated that bec[illegible]ethasone dipropionate but not other INCSs have systemic effects on growth; however, newer, larger, and better

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Table 7. Dosage and Administration of the Intranasal Corticosteroids in Adult Patients [7-12]

Generic Name	Brand Name	Dose per Actuation (# doses per unit)	Usual daily dose (possible number of sprays/month)	Usual daily dose in micrograms
Beclomethasone Dipropionate (BDP)	Beconase	42 mcg (80 or 200)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Beconase AQ	42 mcg (200 or >)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase	42 mcg (80 or 200)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase Pocket	42 mcg (200 or >)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase AQ	84 mcg (120 or >)	1-2 sprays in each nostril qd (60-120)	168-336
Budesonide (BUD)	Rhinocort Rhinocort Aqua	32 mcg (200 or >) 32 mcg 200 or >	2 sprays in each nostril bid or 4 sprays in each nostril qd (240)	256
Flunisolide (FLU)	Nasalide	25 mcg (200 or >)	2 sprays in each nostril bid-tid (240-360)	200-300 Max=400
	Nasarel	25 mcg (200 or >)	2 sprays in each nostril bid-tid (240-360)	
Fluticasone Propionate (FP)	Flonase	50 mcg (120)	2 sprays in each nostril qd (120)	200
Mometasone Furoate (MF)	Nasonex	50 mcg (120)	2 sprays in each nostril qd (120)	200
Triamcinolone Acetonide (TAA)	Nasacort Nasacort AQ Tri-Nasal Spray	55 mcg (100 or >) 55 mcg (30 or 120) 50 mcg (120)	2 sprays in each nostril qd (120) 2 sprays in each nostril qd (120)	220 Max=440 200 Max=400

International Forum of Allergy & Rhinology *Explore this journal >*

View issue TOC
Volume 6, Issue 6
June 2016
Pages 568–572

ORIGINAL ARTICLE

Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery

Methods

This was retrospective case series. Adrenal function was assessed by using the high-dose cosyntropin stimulation test.

Results

A total of 48 patients were assessed, with a mean duration of budesonide irrigations of 22 months. Stimulated cortisol levels were abnormally low in 11 patients (23%). None reported to have symptoms of adrenal suppression. Three of 4 patients who

levels. Logistic regression analysis revealed that concomitant use of both nasal steroid sprays and pulmonary steroid inhalers was significantly associated with HPAA suppression ($p = 0.024$). Patients with low

Conclusion

Long-term use of budesonide nasal irrigations is generally safe, but asymptomatic HPAA suppression may occur in selected patients. Concomitant use of both nasal steroid spra and pulmonary steroid inhalers while using daily budesonide nasal irrigations is associated with an increased risk. Rhinologists should be alerted to the

- [ ] Management of rhinosinusitis during pregnancy: systematic review and expert panel recommendations.
(PMID:26800862)

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rhinorrhea.Eighty-eight manuscripts underwent full review after screening 3052 abstracts. No relevant level 1, 2, or 3 studies

were found. Expert panel recommendations for rhinosinusitis management during pregnancy included continuing nasal corticosteroid sprays for CRS maintenance, using pregnancy-safe

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