Review

Euromediterranean Biomedical Journal
for young doctors
(formerly: Capsula Eburnea)

PROFILE OF INTRANASAL CORTICOSTEROIDS IN ITALY: SAFETY, COST/EFFECTIVENESS, LOCAL AND SYSTEMIC ADVERSE EFFECTS.

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SUMMARY

Background: Allergic Rhinitis is a common and often debilitating disease that affect, nowadays, not only young people. For this reason an effective treatment is necessary to minimize the impact of allergic rhinitis in general population.
Objective: The aim of this review is to inquire intranasal corticosteroids.
Results: We have obtained several randomized, double-blind, placebo-controlled clinical trials, by a MEDLINE search. We analyzed the safety profile, the adverse effects described by the authors, the relation between cost/effectiveness. We have made a search for trade profile, dosage and chemical characteristics by on-line handbook.
Discussion: Several studies demonstrate that intranasal corticosteroids are more effectiveness in nasal symptoms control than other medications for Allergic Rhinitis. Intranasal corticosteroids are relatively safe, only few studies demonstrated systemic adverse effects. In conclusion, newest corticosteroids (Fluticasone Propionate, Mometasone Furoate, Fluticasone Furoate, Ciclesonide aqueous) are safer than older, probably because of their less bioavailability.

Introduction

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment. Allergic rhinitis is classified into "intermittent", "persistent", "mild" and "moderate-severe" (1).
Prevalence and incidence of allergic rhinitis change according to populations studied, different classification and assessment methods ("working definitions"). The prevalence of seasonal allergic rhinitis ranges from 1 to 40%. The prevalence of perennial rhinitis varies from 1 to 18% (1).
In Italy, in a multicentre study designed by De Marco, the "gold standard" was to assesses time trends in the prevalence of current asthma, asthma-like symptoms and allergic rhinitis in Italian adults from 1990 to 2010. Data collected by the European Community Respiratory Health Survey (ECRHS) (1991-1993; n = 6,031), the Italian Study on Asthma in Young Adults (ISAYA) (1998-2000; n = 18,873) and the Gene Environment

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***Received**: November10h, 2014 — **Revised**: November 30th, 2014 — **Accepted**: December 15th 2014*

Interactions in Respiratory Diseases (GEIRD) study (2007-2010; n = 10,494), reported a median prevalence of current allergic rhinitis that increased from 16.8% to 25.8% in twenty years (2).

The management of allergic rhinitis includes allergen avoidance, medication (pharmacological treatment), immunotherapy and education. Surgery may be used as an adjunctive intervention (3).

The updated Allergic Rhinitis and its Impact on Asthma document has produced guidelines in order to suggest pharmacotherapy considering severity, type of symptoms, and length (intermittent or persistent).

In case of *Mild intermittent* disease the options (not in any order of preference) are: oral or intranasal H1-antihistamine and/or decongestant or leukotriene receptor antagonist. Options change in case of *Mild persistent* disease or *moderate/severe intermittent* disease and are: oral or intranasal H1-antihistamines and/or decongestant or intranasal corticosteroids or leukotriene receptor antagonist (or cromone).

A *moderate-severe* persistent case is treated, in preferred order, with intranasal corticosteroid with H1-anthihistamine or leukotriene receptor antagonist and is reviewed after 2–4 weeks and medications stepped up if there is no improvement (1).

About nasal symptom's control, the large variability of the available medications is shown in table 1(5).

Allergic Rhinitis is a common and often debilitating disease that affect not only young people. For this reason an effective treatment is necessary to minimize the impact of AR in all population, and to prevent the onset of exacerbation of asthma (6).

As we know, oral H1 antihistamines are the first line therapy for mild-to-moderate AR. Furthermore, intranasal steroids are the first line therapy for patients with more severe symptoms (7). They act by suppression of inflammation at multiple points in the inflammatory cascade and reduce all rhinitis symptoms (8).

Material and Methods

The aim of this review is to inquire intranasal corticosteroids. In consideration of the varying molecules exist, we are interested in their safety profile, as local or systemic adverse effects, and in the relation between cost/effectiveness. We have obtained several randomized, double-blind, placebo-controlled clinical trials, by a MEDLINE search. We have made a search for trade profile, dosage and chemical characteristics by on-line handbook.

The well-known anti-inflammatory action of corticosteroids, has led many scientists to investigate their use also in allergic rhinitis. In order to reduce theadverse effects there was a tendency towards topical formulations.

The first intranasal delivery of Beclometasone Dipropionato for AR was in 1973 and BDP remains the most clinically used steroid formulation (9). Seven further licensed intranasal preparations are currently available: flunisolide (since 1976), budesonide since the early 1980s , fluticasone propionate (FP) and triamcinolone acetonide since the early1990s (10-13). Trials with ciclesonide were first published in 1999 and mometasone furoate since

Symptom	Nasal antihistamine	Nasal steroids	Nasal decongestant	Nasal ipatropium bromide	Nasal cromone
Rhinorrhea	↑↑	↑↑↑	/	↑↑	↑
Sneezing	↑↑	↑↑↑	/	/	↑
Nasal itching	↑↑	↑↑↑	/	/	↑
Nasal congestion	↑	↑↑↑	↑↑↑↑	/	↑
Ocular symptoms	/	↑↑	/	/	/
/ no effect, ↑ least, ↑↑↑↑ most effective					

Table 1: Effectiveness in symptom control of various nasal medications for AR – (modified from Van Cauwenberge PB et al, Allergy 2000)

1996 (14,15). Fluticasone furoate (FF) was launched in 2009. Each corticosteroid is defined by a specific pharmacokinetic and pharmacodynamic profile. Fluticasone furoate (FF) is an evolution of FP and there are reports of therapeutic advantages over FP (16).

Results and discussion

Onset of action

In an article published in 2006 Yawn analyzed, according to literature, the onset of action of four different molecules. The informations collected show a faster improvement of nasal symptom with Budesonide and Mometasone Furoate (7 hours), followed by Triamcinolone Acetonide (12 hours) and Fluticasone Propionate (36 hours) (17).

Pharmacokinetic differences

Airway absorption and bioavailability of nasal corticosteroids is influenced by differences in pharmacokinetic properties such as lipophilicity. So much greater is their lipophilicity, so less will be their systemic bioavailability. For this reason, the second-generation INC agents currently in use (MF, FP, FF) increased their lipophilicity with greater deposition in the targeted respiratory tract tissue (18). In Figure 1 is showed the differences existing between all INC. Results shown an estimated systemic biovailability respectively greater in case of oldest molecules like Flunisolide (49%), Triamcinolone acetonide (46%) and Bechlometasone dipropionate (44%), that decrease with Budesonide (34%), and the newest Fluticasone Propionate (<1%), Mometasone Furoate (0.5%) and Fluticasone Furoate (<0.1%). Ciclesonide aqueous was below lower limits of assay quantification (19-22). Five INC are available in a once-daily dosing regimen, a characteristic that has been shown to improve patient adherence. These include Budesonide, fluticasone propionate, mometasone furoate, triamcinolone acetonide and fluticasone furoate. Patients often need long-term treatment to properly control their symptoms and adherence to therapy is critical to the effective management of the allergic rhinitis (17).

Local adverse effects

Local adverse effects are principally: bitter aftertaste, atrophy, burning, epistaxis,

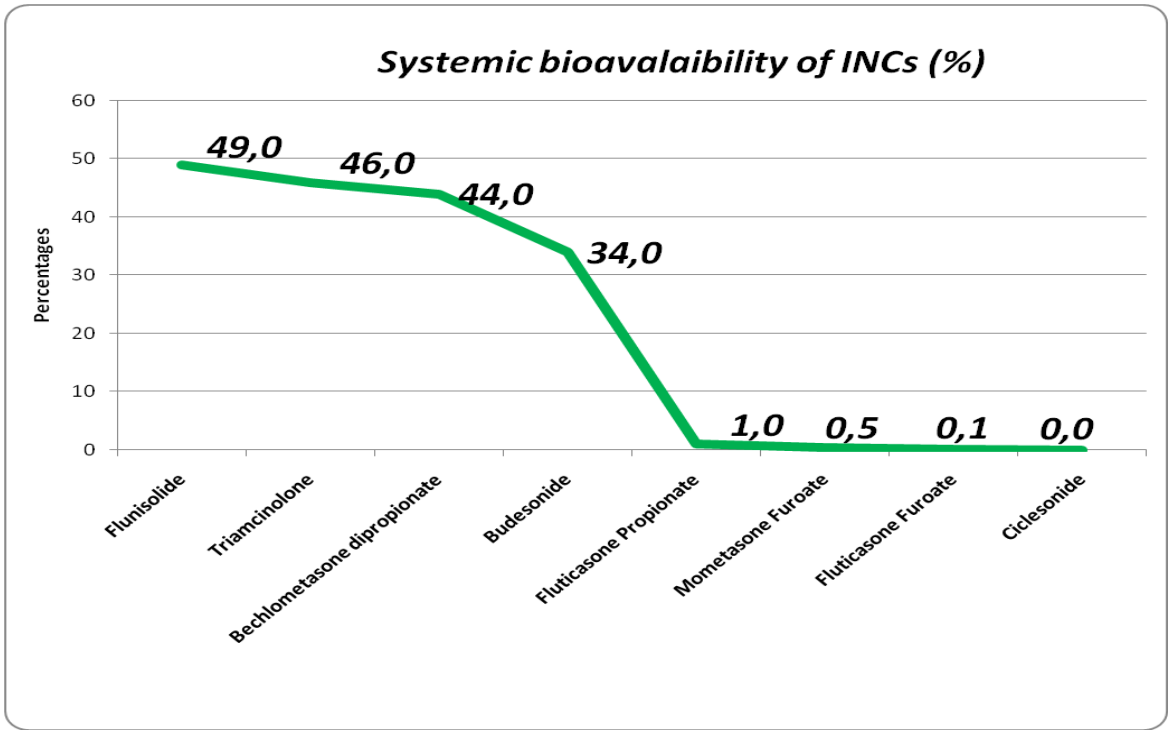

Figure 1: Estimated systemic bioavailability of intranasal corticosteroids (%) (modified from Sastre et al, J Investig Allergol Clin Immunol 2012)

headache, nasal dryness, rhinitis medicamentosa, throat irritation (18). All these conditions are not always strictly related to the molecule employed, because the way to use the INC is same important.

Epistaxis

Epistaxis is a very common condition in all population, depending on many factors, sometimes is self limited or a treatment could be necessary. Regarding to INC and

	Epistaxis		Nasal burning Irritation		Sneezing		Coughing		Pharyngitis	
	molecules	*placebo*	*molecules*	*placebo*	*molecules*	*placebo*	*molecules*	*placebo*	*molecules*	*placebo*
MFNS [19,27,28,48]	12-12.7%	8%	8%	6%	0-4.2%	2%	Not Analyzed	Not Analyzed	0-7.2%	2%
FP [19,29,30,31,51]	2-19%	4-8%	1-4%	4-8%	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	3%	
C [32,33,34,35]	4.3-10%	2.5-7.2%	4.3-10%	0%	Not Analyzed	Not Analyzed	2.1-4.3%	2.1-2.3%	3-13%	3.7-18%
FF [35-39,46-49]	4-20%	4-8%	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	5-6%	5%
BUD [19,47]	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	5.1%	0%	Not Analyzed	Not Analyzed
BDP [19,37,46]	20%	27%	2-8%	2-14%	0%	10%	0%	4%	9-10%	5-9%
TAA [38,39,50]	2.7-7%	1%	Not Analyzed	Not Analyzed	Not Analyzed	Not Analyzed	0.7%		0.7-15%	

Abbreviations: MFNS, mometasone furoate; FP, fluticasone propionate; C, ciclesonide; BUD, budesonide; BDP, beclomethasone dipropionate; TAA, triamcinolone acetonide

Table 2: Local adverse effect of chronic INC use: a comparison of different studies from literature (modified from Sastre et al, J Investig Allergol Clin Immunol 2012)

epistaxis, prolonged or improper use of intranasal steroids is commonly identified as a cause of nosebleeds. It could be related to drying and thinning of the nasal mucosa induced by drug, and to mechanical effect of nasal spray (23,24). The correct employment of nasal device is the main factor, as demonstrated in several studies, where the incidence of epistaxis reported with placebo is similar to that of active INC treatment. Advice regarding administration of INC is to avoid direct physical trauma from the nasal applicator to the septum, managing the tip laterally and using two different sites for the two actuations, in order to maximize the area of mucosal contact and avoid septal deposition (24,25,16). Clear nose of any thick or excessive mucus, if present, by gently blowing the nose. Other suggestions are using the right hand to spray the left nostril and left hand to spray the right nostril, to direct the spray away from the septum; gently breathe in or sniff during the spraying; breathe out through the nose (26). Trials analyzing the different incidences of epistaxis using INC, suggest a large variability depending on studies (Table 2).

Atrophy

The nasal mucosa is very thin, and multiples injuries could produce any kind of damages. One of these is the atrophy of mucosa caused by general, local condition or surgery. The worst consequence occurring is the septal perforation. Dryness, crusting, and bleeding are the steps before a mucosal damage. Concernig INC administration and atrophy, encouraging data demonstrate no evidences of worsening aspect of mucosa, after the employment of steroid nasal spray after a long period (from 6 months to 5 years) (40-43). A common and debated excipient used in several INC devices is benzalkonium chloride. Some studies suggest that it may elicit local adverse effect (44), but in contrast with this opinion a review of the published literature from 1980 to 2003, based on vivo data, concluded that even prolonged use of topical nasal preparation that contain Benzalkonium chloride causes no significant damage to nasal mucosa (45).

Nasal Burning/Irritation, Sneezing, Coughing, Pharyngitis

All these symptoms are commonly complained from patients employing INC. Some studies analyzed them and the correlation between INC's use or placebo treatment (Table 2). As the other adverse local effect, the results are almost the same between the two ones, in case of correct use of nasal applicator.

Systemic adverse effects

Growth

Corticosteroid have an inhibition effect on growth. The hormonal effects related to increase of steroids including decreased release of growth hormone, inhibition of insulinlike growth factor 1 activity, down-regulation of growth hormone receptor expression, and moreover suppression of collagen synthesis and adrenal androgen production (52). The worldwide known effect of steroid on growth, in case of INC depending first of all on the molecular pharmacokinetic and bioavailability. Furthermore, the adherence of recommended doses without exceed is essential. Indeed, growth suppression has been reported with long-term use of some INCs when recommended doses were exceeded. Only one study demonstrated a negative effect on growth after INC employment: the mean change in height was 5.0 cm/year in the BDP group compared with 5.9 cm/year in the placebo group (37). Except this study, the others published have shown no effect on growth with MFNS, FP, BUD, C, TAA. The only limit is that all the literature examine no longer than one year (27,31).

HPA Axis

The hypothalamic-pituitary-adrenal axis (HPA or HTPA axis), is a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland, and the adrenal glands. The paraventricular nucleus of the hypothalamus, which contains neuroendocrine neurons, synthesize and secrete vasopressin and corticotropin-releasing hormone (CRH). Administration of large doses of corticosteroids cause a negative feedback on CRH with a decrease of release of serum cortisol. Data collected

MOLECULES	Spray trade name	Type and mcg/ spray	Prices (€)	Excipients	Adult dose	Child dose	Therapy: cost per day (€)	
							Adult	Child
BECLOMETASONE DIPROPIONATO	**BECOTIDE®**	200 spray - 50 mcg	8.8	BKC	1-2 spray nos bid	1-2 spray nos bid (>6 years)	0.18-0.35	0.18
	INALONE®	100 spray - 50 mcg	15	BKC	1-2 spray nos bid	NA	0.6-1.2	/
	RINOCLENIL®	200 spray - 100 mcg	18.8	BKC	2 spray nos q d	1 spray nos bid (>6 years)	0.38	0.19
	TURBINAL®	200 spray - 50 mcg	12.3	BKC	1-4 spray/nos q d	1-2 spray nos q d	0.12-0.49	0.12-0.25
FLUNISOLIDE	**LUNIS®**	200 spray - 25 mcg	15.5	propylene glycol	2 spray nos bid to tid	1 spray nos tid (>5 years)	0.62-0.93	0.47
FLUNISOLIDE EMIIDRATO	**SYNTARIS®**	100 spray - 25 mcg	8.25	BKC, propylene glycol	2 spray nos bid to tid	1 spray nos tid (>5 years)	0.66-0.99	0.5
BUDESONIDE	**AIRCORT®**	200 spray - 50 mcg	15.5	NO BKC	2 spray nos bid	2 spray nos bid (>6 years)	0.62	0.62
		200 spray - 100mcg	20.5	NO BKC	1 spray nos q d	1 spray nos q d (>6 years)	0.20	0.20
	ELTAIR®	200 spray - 50 mcg	15.5	NO BKC	2 spray nos bid	2 spray nos bid (>6 years)	0.62	0.62
		200 spray - 100 mcg	20.5	NO BKC	2 spray nos q d	2 spray nos q d (>6 years)	0.41	0.41
	KESOL®	200 spray - 50 mcg	15.5	NO BKC	2 spray nos bid	2 spray nos bid (>6 years)	0.62	0.62
		200 spray - 100mcg	20	NO BKC	2 spray nos q d	2 spray nos q d (>6 years)	0.4	0.4
	RHINOCORT®	200 spray - 100mcg	25	NO BKC	2 spray nos q d	N A	0.5	/
FLUTICASONE PROPIONATO	**FLIXONASE®**	60 spray - 50 mcg	19.5	BKC	2-4 spray nos q d	1-2 spray nos q d (> 4 years)	1.3-2.6	0.65-1.3
		120 spray - 50 mcg	27.5	BKC	2-4 spray nos q d	1-2 spray nos q d (> 4 years)	0.92-1.83	0.46-0.92
	NASOFAN®	120 spray - 50 mcg	22.9	BKC	2-4 spray nos q d	1-2 spray nos q d (> 4 years)	0.76-1.53	0.38-0.76
MOMETASONE FUROATO	**NASONEX®**	60 spray - 50 mcg	16.8	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.56-1.12	0.56
		140 spray - 50 mcg	25.2	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.36-0.72	0.36
	RINELON®	60 spray - 50 mcg	17	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.57-1.13	0.57
		140 spray - 50 mcg	25.5	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.36-0.73	0.36
TRIAMCINOLONE	**NASACORT®**	120 spray - 55 mcg	22	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.37- 0.73	0.37
FLUTICASONE FUROATO	**AVAMYS®**	60 spray - 27.5 mcg	18.9	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.63-1.26	0.63
		120 spray - 27.5 mcg	26.5	BKC	1-2 spray nos q d	1 spray nos q d (>6 years)	0.44-0.88	0.44

Table 3: Summary of pharmacological characteristics of INC present in Italy. Data reported have to refer to allergic rhinitis condition. The same molecule is used by different companies, in several dosage and with different excipients. (Updated data from www.torrinomedica.it/ Last accessed: 15th Dec 2014) *(Abbreviations - nos: Nostril; bid: 2 times a day; q d: every day; tid: 3 times a day; NA: not applicable; BKC: benzalkonium chloride)*

by different studies demonstrate that dose -related suppression may occur after use of INC (53). Indeed, a statistically significant suppression (43%) of overnight urinary cortisol levels or changes in 12-hour overnight cortisol levels is reported with FP use. This effect on HPA Axis was without any reported symptom and appears to be dose related. Despite of these results, a large number of studies have found no significant impact on HPA axis function with the newer INC agents (27, 30, 34, 35, 49).

Bone density

Although one of the most famous effect of the chronic use of systemic corticosteroids is the decrease of bone formation because of suppressive effect on osteoblastogenesis in the bone marrow and promotion the apoptosis of osteoblasts and osteocytes (54); all the newer INC employed do not appear to be associated with lack of biochemical markers of bone turnover or of mineral density (55).

Ocular Effects

The intraocular pressure elevation and posterior sub capsular cataracts associated with nasal corthicosteroids have been debated.

Ocular safety was observed in several recent trials (35, 56, 57). Many of the subjects described in those studies were children or young adults. It is know that cataract risk increases with age and it is very rare in children, thus, a relative risk could have been missed in these evaluations (55). An important retrospective study conducted in the United Kingdom investigated 286˙078 patients classified as users of only INC, or oral corticosteroids or nonusers. The incidence of cataract in the group of users nasal corticosteroids was the same of non users. Approximately 70% of INC exposure was to BDP only (57).

Use in pregnancy

The INC should be used only when absolutely necessary. Newer INC are in general considered safe during pregnancy: the limit is the few number of studies. One of the most important study conducted, based on a review of 3 Swedish registries covering over 200 births from 1995 to 2001, show no risk for overall congenital malformation from the use of intranasal BUD during early pregnancy. The FDA given to BUD Pregnancy Category B, instead of the others that are all C (55, 59).

Indeed, recent meta-analysis show that INC not increase the risk of preterm birth, low birth weight and gestational hypertension. So, it's rational to continue, during pregnancy, the INC that previously controlled effectively symptoms. In case of start of INC treatment during pregnancy, Budesonide should be preferred (1).

Conclusion

Nowadays allergic rhinitis is coming a widespread disease, affecting not only children. For this reason, several studies inquire different aspects of AR, including its involvement as risk factor in other diseases (60). We focused our attention on medication of AR, INCs exactly, to verify the safety of their employment. Although further publications are required to confirm all data, overall during pregnancy, we can assert that the large use of INCs is related to its evident benefit and safeness.

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