Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Inhaled and intranasal fluticasone propionate and haematoma

Introduction

Fluticasone propionate is a locally acting potent corticosteroid and is registered in the Netherlands since November 1990. It is marketed as nasal drops and nasal spray (Flixonase®) for the indications *vasomotor and allergic rhinitis, nasal polyps,* and as inhalation corticosteroid (ICS) (Flixotide®) in both an inhalation dosisaerosol and a powder inhalation form for indications *asthma and chronic obstructive pulmonary disease (COPD).* Fluticason ICS is marketed also in combination with salmeterol, a long acting β_2-agonist, (Seretide®) for *asthma and COPD*.
Common local adverse drug reactions (ADR) include hoarseness, oropharyngeal fungal infections and paradoxal bronchoconstriction [1-3]. Systemic ADRs include suppression of the adrenal function, glaucoma, cataract, reduction of bone density and growth retardation in children [4]. Especially higher doses are related to the occurrence of systemic ADRs, yet large inter-personal differences exist.
Haematoma, ecchymosis or purpura, due to an increased vascular vulnerability and thus an increased tendency to bruise, are well known adverse drug reactions (ADR) in systemic corticosteroids and ICSs [5]. In contrary to the SPCs of the fluticasone propionate preparations, these ADRs are mentioned in the SPCs of nasally acting corticosteroid preparations or ICSs containing budesonide or beclomethasone [6,7].

Reports

On September 3, 2007 the database of the Netherlands Pharmacovigilance Centre Lareb contained 12 reports of haematoma following use of fluticasone propionate containing medication. Of these reports nine concerned the occurrence of haematoma related to the use of salmeterol/fluticasone propionate inhalation preparation, three the use of fluticasone propionate nasal spray or nasal drops and one to fluticasone propionate ICS. One patient used both the fluticasone propionate ICS and the fluticasone propionate /salmeterol preparation.
In an additional six reports the symptoms were reported as purpura. All six cases were related to the use of inhaled fluticasone propionate.
No cases were reported using terms ecchymosis or increased tendency to bruise.
Report characteristics are presented in table 1.
Patients E, M, N, O and Q used potentially confounding medications like oral prednisone or non-steroidal anti-inflammatory drugs (NSAIDs). The symptoms experienced by patient N can also be explained by an immunologic mediated reaction.

Table 1. reports of haematoma and purpura associated with the use of inhaled fluticasone propionate

patient, sex, age	drug indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
A F, 53	salmeterol/fluticasone propionate inhalation powder 50/250 ug bd not mentioned fluticasone propionate nasal spray	pantoprazole, macrogol	haematoma	9 years withdrawal partial recovery	coagulation disorders excluded

patient, sex, age	drug indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
	50 ug bd Nasal polyps				
B F, 31	fluticasone propionate inhalation powder 500ug bd not mentioned	-	haematoma, feeling cold	years no changes no recovery	
C M, 71	fluticasone propionate inhalation powder cara fluticasone propionate nasal spray CARA	terbutaline, codein, triamterene/-hydrochlorothiazide, allopurinol	haematoma	not reported, dose not changed unknown	
D F, 49	salmeterol/fluticasone propionate inhalation powder 50/250 ug bd not mentioned	macrogol, pantoprazole	haematoma	not reported no changes no recovery	coagulation disorders excluded, less extensive haematomas during prior use of beclo-methasone
E F, 65	fluticasone propionate nasal spray 50 ug od allergic rhinitis	famotidine, alendronate	haematoma, dizziness	not reported unknown unknown	
F F, 70	salmeterol/fluticasone propionate aerosol 50/250 ug bd not mentioned	ipratropium	haematoma, myalgia	“shortly after start” ongoing use no recovery	
G M, 62	salmeterol/fluticasone propionate inhalation powder 50/250 ug bd asthma	flecainide	haematoma, flushing	2 years no changes partial recovery	
H F, 47	salmeterol/fluticasone propionate inhalation powder 50/500 ug bd COPD	salbuterol, tiotropium, acetylcystein	haematoma, drug withdrawal syndrome, cramps, menometrorrargia	2 years drug withdrawn no recovery	
I F, 14	salmeterol/fluticasone propionate aerosol 50/250 ug bd fluticasone propionate asthma	budesonide nasal spray, montelukast, salbutamol	haematoma	8 days no changes recovered	
J F, 50	salmeterol/fluticasone propionate disc inhalation powder 50/250 ug od COPD	beclometasone	haematoma	2 days withdrawal of both salmeterol/fluticasone propionate and beclomethasone no recovery at time of report	
K F, 78	salmeterol/fluticasone propionate aerosol 50/250 ug bd dyspnea, COPD	tiotropium	haematoma	39 days no changes unknown	prior use of prednisone

patient, sex, age	drug indication for use	concomitant medication	ADR	time to onset, action taken with drug, outcome	remarks
L F,51	salmeterol/fluticasone propionate Inhalation powder 50/500 ug COPD	microgynon	haematoma, swelling, dysuria, pruritus, lymph-adenopathy	14 days drug withdrawn unknown	
M M, 72	fluticasone propionate inhalation powder 400 ug qd copd	oral prednisone 5mg, acetyl salicylic acid, theophyllin, furosemide, acetylcystein, salbutamol, ipratropium, ciprofloxacin, ranitidine, lansoprazole, triamcinolone injected	purpura	1 year No changes recovery	use of possible confounding co-medication
N M, 11	fluticasone propionate aerosol 50 ug bd fluticasone propionate nasal spray 2x50 ug bd	salbutamol, montelukast	purpura	unknown no changes no recovery	purpura noticed after the start of montelukast
O M,71	fluticasone propionate inhalation powder 500 ug bd	diclofenac, acetylsalicylic acid omeprazole, salbutamol, temazepam, bisacodyl, hydroquinine, ultracite	purpura, leg pain, coldness local	months fluticasone propionate withdrawn before evolvement of symptoms	
P F, 8	fluticasone propionate powder inhaltation 250 ug bd	clotrimazole, salbutamol salmeterol	purpura, tiredness	unknown dose not changed no recovery two months after symptoms evolved	
Q F,69	fluticasone propionate inhalation powder 500 ug bd fluticasone propionate nasal spray 50 ug bd	ipratropium, tetinoide, acetylsalicylic acid, ranitidine, salbutamol, hydrocortisone	purpura	days dose reduction partial recovery	use of possible confounding co-medication
R F, 66	fluticasone propionate inhalation powder 500 ug bd	salmeterol, ipratropium, acetylcystein	purpura	years dose reduction unknown	

Other sources of information

SPC

Haematoma, easy bruising or ecchymosis are not described in the SPCs of fluticasone propionate nasal spray, nasal drops or fluticasone propionate containing inhalation products. Haematoma or bruising is described in budesonide and beclomethason inhalation products [6,7].

Literature

No long-term studies directly aimed at determining a relation between use of inhaled fluticasone propionate and dermal side effects have been performed. Yet a higher incidence of easy skin bruising while using inhaled corticosteroids has been clearly demonstrated in shorter term questionnaire and observation based studies. An observational questionnaire based study (n=206) performed by Mak *et al*. shows a significantly higher incidence of skin bruising in a dose-dependant way in 202 ICS using respiratory patients compared to a control group of 204 non corticosteroid using patients (relative risk 2.2, 95%CI 1.6-2.9) [8].
Roy *et al*. demonstrated an increased incidence of skin bruising and a significantly lower adrenal function in subjects with marks of easy skin bruising in a study in which 100 ICS (budesonide or beclomethasone) using asthmatic subjects were compared to 100 non-ICS using ophthalmic patients [9]. Skin bruising is mentioned explicitly in the American clinical guideline on asthma treatment of the National Institute of Health [10] and *Allen et al*. express in their review article certain astonishment on the absence of skin bruising in the product information of fluticasone propionate [11].
Information on the incidence of fluticasone propionate related skin bruising compared to bruising related to other ICS's is contradictory. In a double blind crossover study (n=69) Malo *et al*. stated that compared to beclomethasone, fluticasone propionate in a dose with the same potency leads to a lower incidence in occurrence of skin bruising [12].
Yet there are strong indications for a higher systemic activity of fluticasone propionate compared to other ICS's. In a meta-analysis of 27 studies Lipworth *et al.* demonstrated a significantly steeper dose-response curve of fluticasone propionate and systemic bioactivity, expressed in urine cortisol levels and 8AM cortisol plasma concentrations, compared to beclomethasone, triamcinolone and budesonide for urine cortisol and to budesonide and triamcinolone for plasma cortisol [4]. Moreover in a case series of adrenal crises occurring in patients using an ICS, fluticasone propionate, not commonly prescribed in the United Kingdom at the time of publication, was involved in 30 of in total 33 cases of adrenal crisis [13].

Databases

Both the nine reports of haematoma with use of fluticasone propionate/salmeterol (ROR 16.0, 95%CI: 8.1-31.9) and the three reports on fluticasone propionate nasal spray (ROR 4.9, 95%CI: 1.5 - 15) are disproportionally represented in the Lareb database.

In the WHO Uppsala Monitoring Centre database in total 44 cases of haematoma or purpura exist related to intranasally administered or inhaled fluticasone propionate which is not disproportional.

Mechanism

Haematomas occur in treatment with corticosteroids due to easy bruising. This is a well known ADR of corticosteroid treatment. It is caused by an increased vulnerability of blood vessels because of a decreased collagen turnover due to an inhibition of fibrocyte function [4]. A relation between use of ICS and occurrence of easy bruising has clearly been demonstrated, just like a relationship between bruising and adrenal suppression [9]. Although a direct relationship to other collagen-related side effect is not clearly demonstrated in literature, haematoma's or other marks of easy skin bruising can because of their clear visibility be used as a biomarker of systemic activity of inhaled corticosteroids both in clinical practice and research [11].

Discussion

Based on a systemic review and meta-analysis performed by Lipworth there are pharmacokinetic arguments that suggest that the highly potent ICS fluticasone propionate may be more strongly involved in skin bruising and in related systemic ADRs, compared to other ICSs. Fluticasone propionate is resorbed in the respiratory tract without being metabolized by a first pass mechanism. Its higher lipophilicity leads to an increased potential for absorption in the respiratory tract and retention in fatty tissues gives rise to longer elimination half–life times and so longer duration of systemic activity and a possibility of accumulation [14].

Eighteen cases were reported to the Netherlands Pharmacovigilance Centre of fluticasone propionate related haematomas or purpura. These symptoms were reported both in users and non-users of the fluticasone propionate/salmeterol combination preparation, so confounding by concomitant use of salmeterol due to an unknown ADR is unlikely. Concomitant use of medications leading to higher corticosteroid plasma levels like oral prednisone for exacerbations of asthma or COPD or to a decreased thrombocyte aggregation due to use of medication like acetylsalicylic acid for cardiovascular co morbidity and other NSAIDs for analgesia potentially confounds three reports. Yet there remain a substantial number of reports of haematomas or purpura related to the use of inhaled or intranasally administered fluticasone propionate without the use of suspect co-medication to demonstrate a relation of use of these medications and occurrence of haematomas or purpura. Beside negative cosmetic aspects, haematomas or purpura can be used as a marker of systemic corticosteroid activity [11]. Because of this undesirable effect, haematomas due to an increased bruising may trigger the clinician to re-evaluate the dose of fluticasone propionate or to use an alternative inhaled corticosteroid or other medication.

Conclusion

Haematoma due to easy skin bruising is a well known ADR of systemic acting corticosteroids and ICSs. Haematoma and purpura have been reported eighteen times to the Netherlands Pharmacovigilance Centre Lareb. Ecchymosis and an

increased tendency to bruise is mentioned in the SPCs of other comparable ICSs but not in the SPC of fluticasone propionate. Action towards mentioning in the SPCs of the fluticasone propionate preparations of haematoma or an increased tendency to bruise could be considered.

References

1. Dutch SPC Flixonase®. (version date 23-9-2004) http://www.cbg-meb.nl/IB-teksten/h14424.pdf.
2. Dutch SPC Flixotide®. (version date 5-2-2002) http://www.cbg-meb.nl/IB-teksten/h16211-h16212-h16213-h16214-h16215-h16216-h16217-h16218.pdf.
3. Dutch SPC Seretide®. (version date 25-9-2006) http://www.cbg-meb.nl/IB-teksten/h23529-h23530-h23531.pdf.
4. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999;159(9):941-55.
5. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, Kovac SH, Spettell CM, Saag KG. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006;55(3):420-6.
6. Dutch SPC Pulmicort®. (version date 20-10-2003) http://www.cbg-meb.nl/IB-teksten/h100634.pdf.
7. Dutch SPC QVAR®. (version date 17-10-2005) http://www.cbg-meb.nl/IB-teksten/h21937-h21938-h21939-h21940-h29141-h29142-h29143-h29144.pdf.
8. Mak VH, Melchor R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. Eur Respir.J 1992;5(9):1068-74.
9. Roy A, Leblanc C, Paquette L, Ghezzo H, Cote J, Cartier A, Malo JL. Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. Eur Respir.J 1996;9(2):226-31.
10. National Institute of Health. Guidelines for the Management and Treatment of Asthma (EPR-3). (access date 7) http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.
11. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol. 2003;112(3 Suppl):S1-40.
12. Malo JL, Cartier A, Ghezzo H, Mark S, Brown J, Laviolette M, Boulet LP. Skin bruising, adrenal function and markers of bone metabolism in asthmatics using inhaled beclomethasone and fluticasone propionate. Eur Respir.J 1999;13(5):993-8.
13. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis.Child 2002;87(6):457-61.
14. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 2000;23(1):11-33.