Desoximetasone and hyperglycaemia

Introduction

Desoximetasone is a high potency (class III) fluorinated corticosteroid for local administration that has anti-inflammatory, anti-pruritic and vasoconstrictive actions. It is used in non-infectious skin conditions like plaque psoriasis, lichen and annular granuloma in which less potent corticosteroids are ineffective. In The Netherlands there are two desoximetasone containing products available, actually a skin emulsion Topicorte® (available on the Dutch market since 1970) and a hydrophobic cream Ibaril® (available on the Dutch market since 1983) [1,2].
Systemic adverse drug reactions due to absorption from topical application are rare. Predisposing factors for systemic availability are application of large doses to a large surface area or use under occlusion, prolonged use, use to altered skin barrier and use in children. The Summary of Product Characteristics (SmPC) mentions adrenal suppression as major systemic adverse drug reaction of topical use desoximetasone. [1,2]
Hyperglycaemia is a condition in which blood glucose levels are increased, which is the case in diabetes mellitus. An excess of glucocorticosteroids is also associated with hyperglycaemia, like in Cushing's disease or as an adverse drug reaction of systemic administrated corticosteroids. [3]

Reports

The Netherlands Pharmacovigilance Centre Lareb received two reports of hyperglycaemia as adverse drug reactions of topical administration of desoximetasone.

Case 1 (129798), report-date 05-10-2011
This report from a pharmacist concerns a male aged 41-50 years, with hyperglycaemia following topical administration of desoximetasone for psoriasis with a latency of two days after start. The patient used both Topicorte® and Ibaril® concomitantly on a large, but not further specified, body surface area. The dose for desoximetasone was not changed. Since the patient had type 1 diabetes mellitus, the dose of insulin was increased after which blood glucose levels returned to normal range. Before, the patient was stable on his medication, except for his dermal medications. On previous use of desoximetasone, the patient also developed hyperglycaemia. During a temporarily stop period of desoximetasone for skin tests, the patient had stable and normal blood glucose levels. Concomitant medications were non-specified insulin, pravastatin, lisinopril and hydrochlorothiazide.

Case 2 (215512), report-date 20-06-2016
This report from a diabetes nurse concerns a female aged 80 years and older, with increased blood glucose level following topical administration of desoximetasone (Ibaril®) for generalised pruritus (from scalp to toes) with a latency of one day after start. The extent of the changes in blood glucose were not reported. Since the patient had diabetes, the dose of insulin was increased after which blood glucose levels returned to normal range. The skin barrier of the patient was intact, except for some small scratch marks. The medical history indicates that the patient had a not further specified renal impairment and cardiovascular disease. Concomitant medications were insulin glargine, insulin aspart, isosorbide mononitrate, pantoprazole, ferrous fumarate and clopidogrel.

Both patients were known diabetics and desoximetasone had been used on a large body surface area, although the exact amount administered was not specified in both cases. Both had a remarkably short latency of days for developing hyperglycaemia. Unfortunately, test values of blood glucose and the amount of dose increase of insulin are unknown for both patients. In case 1, a positive dechallenge and rechallenge can be concluded from the timing of events as specified in the narrative.

Other sources of information

SmPC
Hyperglycaemia is not mentioned as an adverse drug reaction in the 4.8 section of the SmPC of desoximetasone containing products. The SmPC does mention adrenal suppression as a systemic adverse drug reaction due to cutaneous absorption of desoximetasone. [1,2] The SmPC of Ibaril® also mentions that in excessive or long-term use, adrenal insufficiency and signs of hypercorticism including Cushing's disease can develop. [1] The patient label of Topicorte® mentions various symptoms of Cushing's disease, including increased blood glucose levels, as a sign of overdose after long-term use. [2]
Most of the SmPC's of other high potency dermal corticosteroids (class III and IV) do mention hyperglycaemia as adverse drug reaction: betamethasone, fluticasone, mometasone and clobetasol. In appendix 1 labelled adverse drug reactions considering hyperglycaemia in various dermal corticosteroid products has been given [4-7].
The FDA label of desoximetasone (Topicort®) does mention hyperglycaemia and glycosuria in some patients as a consequence of systemic absorption of topical corticosteroids. [8]

Literature
In literature and handbooks effects on blood glucose of glucocorticosteroids in general has been widely described, as well as deregulation of glycaemic control in diabetics. [9-11]
The percutaneous absorption of high-potency topical glucocorticosteroids has been documented, but HPA axis suppression, leading to clinically significant adrenal insufficiency or Cushing's syndrome is infrequent. [9] Systemic adverse drug reactions can occur during long-term treatment of large quantities of in situations of increased penetration like occlusion or disturbed skin barrier. [3] It has been described that application of 15-20 gram clobetasol (class IV) can cause systemic pharmacological activity in healthy persons in one to two days. This has also been described for betamethasone valerate (class IV) in patients with eczema. [3]
Cook et al. describe that fasting hyperglycaemia and increase of insulin can be induced in one day after topical administration of glucocorticosteroids. This also accounts for insulin resistance and abnormal carbohydrate tolerance and fluctuations in circulating leukocytes that paralleled the changes in carbohydrate metabolism. [12]
Kitahara et al. describe a case-report of topical desoximetasone induced hyperglycaemia, hypertension and liver damage in Japan. [13]

Databases
In other databases, of the WHO and Eudravigilance, no other reports of hyperglycaemia related to the use of topical desoximetasone are available.

Prescription data
Table 2. Number of patients using desoximetasone and other class III dermal corticosteroids in The Netherlands [16].

	2010	2011	2012	2013	2014
D07AC03 Desoximetasone	76,585	77,030	78,594	77,982	77,229
D07AC01 Betamethasone	260,780	258,730	251,250	251,070	267,420
D07AC06 Diflucortolone	3,001	2,806	2,440	2,126	1,967
D07AC13 Mometasone	128,390	130,330	130,220	131,830	141,290
D07AC17 Fluticasone	116,510	115,900	144,530	113,730	111,150

Mechanism
Corticosteroids bind to specific receptor proteins in target tissues to modulate gene expression and protein synthesis. In addition, corticosteroids have some non-genomic mechanisms.
Corticosteroids affect carbohydrate and protein metabolism in order to protect glucose-dependent tissues from starvation. They stimulate the liver to form glucose from amino acids and glycerol and to store glucose as glycogen, by induction of enzymes involved in gluconeogenesis and protein metabolism. In peripheral tissues glucose utilization is reduced by translocation of glucose transporters and protein breakdown and lipolysis are increased to provide amino acids and glycerol for gluconeogenesis.
Because the effects on glucose metabolism, glucocorticosteroids can worsen glycaemic control in diabetics or precipitate the onset of hyperglycaemia in susceptible patients [10, 11].

Discussion and conclusion

Hyperglycaemia is a well-known adverse drug reaction of systemically available corticosteroids. Absorption of topical administered high potent corticosteroids through the skin can lead to sufficient levels for inducing systemic adverse drug reactions [3,12]. The two reported cases suggest that hyperglycaemia can develop quickly after use on large body surface areas. Patients with diabetes might be at increased risk for glycaemic dysregulation, but in non-diabetic patients an increase of blood glucose level might not be noticed.

Since hyperglycaemic effects of desoximetasone are mentioned in literature and in other sources, and because these effects are mentioned in SmPC's of other high potent corticosteroids, we address that hyperglycaemia can also be an ADR of desoximetasone containing products.

References

1. Dutch SmPC Ibaril® (version date: 10-5-2016; access date: 20-6-2016) http://db.cbg-meb.nl/IB-teksten/h08164.pdf
2. Dutch SmPC Topicorte® (version date: 10-10-2015; access date: 20-6-2016) http://db.cbg-meb.nl/IB-teksten/h05829.pdf
3. KNMP Informatorium Medicamentorum. Corticosteroiden voor systemisch gebruik. (access date: 20-6-2016) https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/G151.html#G2021
4. Dutch SmPC Betnelan® (version date: 22-10-2014; access date 22-4-2016) http://db.cbg-meb.nl/IB-teksten/h04519.pdf
5. Dutch SmPC Cutivate® (version date: 9-1-2014; access date 22-4-2016) http://db.cbg-meb.nl/IB-teksten/h16647.pdf
6. Dutch SmPC Elocon® (version date: 5-10-2015; access date 22-4-2016) http://db.cbg-meb.nl/IB-teksten/h14173.pdf
7. Dutch SmPC Dermovate® (version date: 22-10-2014; access date 22-4-2016) http://db.cbg-meb.nl/IB-teksten/h06933.pdf
8. FDA label Topicort® (version date: April 1999; access date 20-6-2016) http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17856slr024,18309slr013_topicort_lbl.pdf
9. Aronson JK (ed). Meyler's Side effects of Drugs. 15th edition. Elsevier; 2006 p. 917
10. Schimmer BP, Funder JW. ACTH, adrenal steroids and pharmacology of the adrenal cortex. In: Goodman and Gillman The pharmacological basis of therapeutics, 12 th Ed (2011). Chapter 42, p. 1209-1235
11. Saag KG, Furst DE. Major side effects of systemic glucocorticoids. Up to Date (version date: 9-2-2016; access date 22-4-2016)
12. Cook LJ, Freinkel RK, Zugerman C, Levin DL, Radtke R. Iatrogenic hyperadrenocorticism during topical steroid therapy: assessment of systemic effects by metabolic criteria. J Am Acad Dermatol. 1982 Jun;6(6):1054-60
13. Kitahara A, Saga K, Koide S, Isobe T, Oki Y, Nakamura H. Iatrogenic hyperadrenocorticism and steatohepatitis caused by unapproved medicine. Intern Med. 2008;47(13):1231-6. Epub 2008 Jul 1
14. Database of The Netherlands Pharmacovigilance Database Lareb. (version date: 2016, access date: 20-6-2016) www.lareb.nl
15. WHO database Vigilyze. (version date: 2-6-2016, access date: 20-6-2016)
16. GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date: 21-4-2015, access date: 20-6-2016) https://www.gipdatabank.nl/databank.asp?tabel=01-basis&geg=gebr&item=D07AC

Appendix 1
Summary of labelled adverse drug reactions in dermal corticosteroid products considering hyperglycaemia.

Class	Active substance	RVG	SmPC labelling of ADR
I	hydrocortisone acetate 1%	RVG 51010	4.4/4.8 -
II	clobetasone 0,05%	RVG 07519	4.8 Cushing, hyperglycaemia/ glycosuria (frequency unknown)
II	flumetasone 0,02%	RVG 04475	4.4/4.8 -
II	hydrocortisone butyrate 0,1%	RVG 05911	4.4/4.8 -
II	triamcinolon acetonide 0,1%	RVG 50801	4.4/4.8 - Section 5.1 mentions the inhibition of uptake and use of glucose and amino acids in peripheral tissue and stimulating of glycogenesis and gluconeogenesis in the liver.
III	betamethasone 0,05%	RVG 04519	4.8 hyperglycemia/glycosuria (frequency unknown)
III	desoximetasone 0,25%	RVG 08164 RVG 05829	4.4/4.8 -
III	fluticasone (cream 0,05%, ointment 0,005%)	RVG 16647	4.8 hyperglycemia/glycosuria (frequency unknown)
III	mometasone 0,1%	RVG 14173	4.4 Cushing's syndrome, hyperglycaemia and glycosuria can occur in some patients due systemic absorption of local administered corticosteroids.
III	*Diflucortolone valerate 0,1%*	-	*Product not available in The Netherlands since 2016.*
IV	betamethasone dipropionate 0,05% in propyleneglycol	RVG 09522	4.4/4.8 -
IV	clobetasol 0,05%	RVG 06933	4.8 Cushing, hyperglycaemia/glycosuria (frequency unknown)

This signal has been raised on September 2016. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl