Dexamethasone infusion and genital tingling/pruritus

Introduction

Dexamethasone is a corticosteroid drug and is used as an anti-inflammatory or immunosuppressive agent in the treatment of a variety of diseases. Systemic dexamethasone is available as oral tablets and oral solution or as a solution for intravenous, intramuscular, intra-articular or subcutaneous injection. Dexamethasone has been marketed internationally since 1958 (1).

Dexamethasone is a synthetic adrenal cortex hormone with predominant glucocorticoid and virtually no mineralocorticoid activity. Systemic dexamethasone for injection has a 6-times higher anti-inflammatory activity than prednisolone and 25-times higher than the natural glucocorticoid hydrocortisone. The effects of dexamethasone persist longer than the plasma concentrations. Because of its long biological half-life (36-54 hours), dexamethasone is especially suited for situations in which a continuous glucocorticoid action is desirable. Systemic dexamethasone for injection contains dexamethasone sodium phosphate. After administration it is hydrolysed to dexamethasone quickly (2).

Reports

Between January 22th of 2014 and September 9th of 2020, the Netherlands Pharmacovigilance Centre Lareb received 3 reports of genital tingling and pruritus associated with intravenously administered dexamethasone. The reports are listed in Table 1.

Table 1. Reports of genital tingling/pruritus associated with dexamethasone in the Lareb database

No., ID, primary Source, sex, age	Drug, Dosage, Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1, NL-LRB-00359265, Pharmacist, female, 15-20 Years	Dexamethasone inj fluid 20mg/ml, 4mg/day IV, nausea	Metamizol, Ondansetron, Macrogol, Metoclopramide, Temazepam, Ethinylestradiol/levonorgestrel, Sodium phosphate enema	Vaginal itching	Immediately	Dose not changed	Recovered
2, NL-LRB-00352891, Physician, male, 70-80 Years	Dexamethasone inj fluid 4mg/ml, 2 ml in total, prevention chemotherapy-induced nausea	Paroxetine, Cotrimoxazole, Metoclopramide, Granisetron, Bendamustine	Tingling sensation (irritation/ titilation of anal/ genital region)	Immediately	Not applicable	Recovered
3, NL-LRB-166718, Pharmacist, female, 20-30 Years	Dexamethasone inj fluid 4mg/ml, 8mg in total, prevention chemotherapy-induced nausea		Vaginal discomfort (vaginal tingling)	1 Minute	Not applicable	Recovered

Additional information on the cases:
1: appeared immediately after each bolus administration, 5 days in a row. Recovered mostly within 5 minutes, after flushing with sodium chloride 0,9%.
2: described by the patient as a stinging nettle-like feeling. Appeared immediately after each administration. Recovered after 2 minutes.
3: appeared after each administration, 3 times in total. Recovered after one minute.

Other sources of information

SmPC

The Dutch Summary of Product Characteristics (SmPC) of dexamethasone solution for injection does not mention pruritus, a burning sensation or paresthesia of the genital, perineal or anal region as an adverse reaction. It does mention allergic dermatitis and allergic reactions, like urticaria (2). However, the reported cases don't mention other allergic symptoms.

The US SmPC of dexamethasone sodium phosphate mentions as adverse reaction: “Burning or tingling, especially in the perineal area (after IV injection)”(3).

Literature

Perineal and genital irritation as a possible adverse event of dexamethasone has been described since the late eighties (4). Taleb et al performed a randomized, double blind, placebo-controlled study to investigate the antiemetic effect of high doses corticosteroids in patients treated by chemotherapy. They found that 32% of the female patients receiving a high-dose dexamethasone experienced vulvar pruritus and none of the patients in the placebo group. Also, this adverse event occurred with each subsequent administration of dexamethasone. Notable, this genital reaction appeared almost exclusively in females. Only one out of 59 male patients receiving dexamethasone (and none after receiving placebo) experienced anal irritation which persisted after switching to placebo (4). In subsequent years, more reports describe the same adverse event appearing after intravenous administration of dexamethasone. The symptoms were described as itching, burning, tingling, irritation or pain in the genital or perineal area. It appears immediately during or shortly after intravenous administration of dexamethasone (5-8). The symptoms resolve within several minutes (6-8). More females than males were affected (6, 8).

Databases

On September 10th, the Eudravigilance database of the European Medicines Agency contained 11 reports of 12 symptoms in the genital or perineal area associated with intravenously administered dexamethasone. Table 2 shows the number of the reported cases for the specific MedDRA terms. Table 2 also shows the number of the reported cases in the WHO database of the Uppsala Monitoring Centre.

Because the ATC code for systemic dexamethasone (H02AB02) includes dexamethasone for both oral and parenteral administration routes, Table 2 contains an extra column for the number of reports in which intravenous administration route is specified.

Table 2: Reports in Lareb, Eudravigilance (EV) and WHO VigiBase® databases regarding genital/anal pruritus/burning sensation/paresthesia/pain and dexamethasone (9, 10)

	Drug, ATC*	**MedDRA Preferred Term**	**N (N females[#])**	**N specified IV***
Lareb	Dexamethasone, H02AB02	Vulvovaginal pruritus	1	1
		Paraesthesia[$]	1	1
		Vulvovaginal discomfort	1	1
Eudravigilance	Dexamethasone, H02AB02	Genital burning sensation	3 (2)	3
		Anorectal discomfort	3 (1)	1
		Genital discomfort	2 (2)	2
		Vulvovaginal pruritus	2 (2)	2
		Vulvovaginal burning sensation	2 (2)	1
		Pruritus genital	2 (2)	1
		Vulvovaginal pain	1 (1)	1
		Genital pain	1 (1)	1
WHO	Dexamethasone, H02AB02	Pruritus genital	130 (110)	34
		Perineal pain	94 (86)	25
		Anal pruritus	88 (53)	55
		Vulvovaginal pruritus	89 (82)	20
		Anorectal discomfort	64 (43)	31
		Proctalgia	46 (26)	9
		Vulvovaginal discomfort	24 (23)	7
		Vulvovaginal burning sensation	12 (11)	4
		Genital burning sensation	11 (8)	9
		Vulvovaginal pain	8 (8)	6
		Genital pain	4 (2)	3
		Genital paraesthesia	3 (3)	-
		Genital discomfort	2 (2)	2
		Anal paresthesia	1 (1)	1

[#] in the other casus the patient sex was reported as male or unknown

* ATC H02AB02 consists of dexamethasone oral tablets, oral suspension and injection fluid. N specified IV are the number of cases in which an intravenous administration route is specified for all cases.
$ Cases in which the genital/anal region was specified.

Mechanism

It is thought that perineal symptoms are caused by the corticosteroid phosphate ester of dexamethasone sodium phosphate. The same reaction is also described with hydrocortisone-21-phosphate sodium and prednisolone phosphate, but not with other non-corticosteroid phosphate drugs (8). Furthermore, the incidence and severity of the symptoms seems to increase as the organic phosphate content of the injection increases (5). The short duration of the symptoms might represent the time required to hydrolyze the ester bond to dexamethasone and phosphate ions (5, 8).

In several reports it is described that this unpleasant adverse event might be reduced or abolished by administering dexamethasone diluted and by a slow infusion rate (5, 6, 8). Gu et al speculated that the perineal symptoms are related to actions on neurotransmitter mechanisms. They stated that the neurotransmitter may be phosphate itself or be stimulated by phosphate. Dexamethasone dilution and a slow infusion rate may result in a slower release of neurotransmitters, which may not reach threshold levels (11). There are no possible explanations for the higher incidence of this adverse event in females (8).

Discussion and conclusion

Lareb received three reports of genital tingling and pruritus associated with intravenously administered dexamethasone. Supporting cases for this association were also found in literature and in Eudravigilance and WHO databases.

The genital symptoms are somewhat heterogeneous described, as itching, burning, tingling, irritation or pain. But they all have in common that it is an extremely unpleasant adverse event which is brief and self-limiting. Although itching or tingling sensations can be part of a hypersensitivity reaction, the Lareb-cases lack other allergic symptoms like hives, (angio)edema, erythema or dyspnea. Because of the unpleasant feeling of this adverse event, the importance to recognize that it is not part of a hypersensitivity reaction and that it may be prevented by administering a diluted solution slowly, attention for this potential adverse drug reaction is warranted.

References

1. Informatorium Medicamentorum via KNMP Kennisbank [updated 2020.
2. Dutch SmPC Dexamethason CF 20 mg/ml, oplosssing voor injectie. [updated 06-2020. Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h55091_smpc.pdf.
3. US SmPC Dexamethasone Sodium Phosphate, USP, Fresenius Kabi [updated 05-2014. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/40572s002lbledt.pdf.
4. Taleb N GN, Ghosn M, Brihi E, Sacre P. Vulvar pruritus after high-dose dexamethasone. Eur J Cancer Clin Oncol. 1988;24(3):495.
5. Neff SP SF, Warmington A. Excruciating perineal pain after intravenous dexamethasone. Anaesth Intensive Care. 2002;30(3):370-1.
6. Perron G DP, Germain J, Bechard P. Perineal pruritus after i.v. dexamethasone administration. Can J Anaesth. 2003;50(7):749-50.
7. Kuczkowski KM. Perineal pruritus and dexamethasone. Anaesthesia. 2004;59(3):308.
8. Dylla L AN, Manzo F, Cushman JT. Dexamethasone-Related Perineal Burning in the Prehospital Setting: A Case Series. Prehosp Emerg Care. 2018;22(5):655-8.
9. Eudravigilance database [Internet]. [cited 10-09-2020]. Available from: http://bi.eudra.org (access restricted).
10. WHO database Vigilyze [Internet]. [cited 09-09-2020]. Available from: https://vigilyze.who-umc.org (access restricted).
11. Gu CY WY, Zhou MT, Li F, Tang QF. The effect of dilution and prolonged injection time on dexamethasone-induced perineal pruritus. Pharmazie. 2012;67(12):1015-7.

This signal has been raised on January 6, 2021. 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