**Hydrocortisone and Adrenal insufficiency after switch between (compounded) products**

## Introduction

Hydrocortisone has glucocorticoid as well as mineralocorticoid properties. Hydrocortisone is similar to endogenous cortisol, which is the most important circulating adrenal hormone of the human body. Patients with adrenal insufficiency don't produce enough corticosteroids and need suppletion with hydrocortisone and/or fludrocortisone. The hydrocortisone intake is mostly spread over three doses (ratio 2:1:1) per day to simulate the natural day rhythm. The average daily maintenance dose is 17,5-25 mg. In stress situations it is necessary to increase the normal corticosteroid dosage in order to prevent a life-threatening adrenal crisis (Addison crisis). Dosage increase is based on a specific glucocorticoid stress schedule [1].

Lareb received signs from clincal practice that switching between different hydrocortisone tablet/capsules had led to dosing problems. Also the patient organization Dutch pituitary patient foundation (Hypofyse Stichting) contacted Lareb about these issues. This was the reason for Lareb to start analysing the reports concerning hydrocortisone.

For oral administration two different hydrocortisone products are registered in the Netherlands. These are the Plenadren® tablets (5 and 20 mg) with modified release (MGA) and the hydrocortisone tablets (20 mg) from the manufacturer Tiofarma. The hydrocortisone tablets of Tiofarma contain a functional score to split the tablet in two equal parts.
There are also several different compounded products (tablets as well as capsules) available in a wide arrange of dosages (see table 1) and produced on a larger scale (*in Dutch 'doorgeleverde bereiding'*). There is also an upcoming registration for Acecort compounded products for various strengths.

Table 1. Compounded oral hydrocortisone products in the Netherlands

| **Tablets** | **Capsules** |
|---|---|
| CEB: 1 mg; 2 mg; 2,5 mg and 5 mg | CEB: 2,5 mg en 5 mg |
| DCB: 1 mg; 2 mg; 5 mg and 10 mg | DCB: - |
| DMB: 1 mg; 2 mg; 5 mg; 10 mg<br>(1 mg; 2 mg and 5 mg also coated available) | DMB: - |
| PHL: 1 mg; 2 mg; 3 mg and 5 mg | PHL: 1 mg; 2 mg; 3 mg; 5 mg and 10 mg |
| PLC: 1 mg; 2 mg and 5 mg | PLC: 5 mg and 10 mg |
| ACE: 1 mg; 10 mg<br>ACECORT: 3 mg; 5 mg and 10 mg | ACE: 5 mg and 10 mg |
| | DAB: 1 mg; 2 mg; 3 mg; 5 mg and 10 mg |
| | SVM: 2,5 mg; 3 mg; 5 mg and 10 mg |

CEB = Centrale Bereidingsapotheek Nederland, DCB = Apotheek De Collegiale Bereiding, DMB = Apotheek De Magistrale Bereider,
PHL = Pharmaline, GMP Bereidingsapotheek, PLC = Pharmalot Compounding BV, ACE = ACE Pharmaceuticals BV,
DAB = De Ad Hoc Bereider, GMP Bereidingsapotheek, SVM = Savemaak C.V. [2]

Incorrect dosing of hydrocortisone in patients with adrenal insufficiency may lead to adrenal crisis. This is an acute adrenal insufficiency; it is most common in patients with primary adrenal insufficiency, but may also occur in those with secondary or tertiary adrenal insufficiency. It is a life-threatening emergency that requires immediate treatment [3]. In that perspective, differences in bioavailability may cause problems if a patient switches between products [4].

## Reports

Between September 22th of 2014 and February 4th of 2020, the Netherlands Pharmacovigilance Centre Lareb received 8 reports of substitution problems or product complaints (MedDRA® PT "Therapeutic response unexpected" or "SOC Product Issues") concerning hydrocortisone tablets or capsules.
Six of these reports were received in a time period of about only three months. (December 2019 – February 2020) The reports are listed in table 2.

Table 2. Reports of substitution problems or product complaints concerning hydrocortisone tablets or capsules

| ID, sex, age, primary source, receive date | Drug | Indication | Concomitant medication | Reported ADRs | Latency after start | Action taken | Outcome |
|---|---|---|---|---|---|---|---|
| A: NL-LRB-00376853, female, 30-40 Years, Consumer<br><br>04-02-2020 | Hydrocortison Tablet 5Mg<br>DMB | Androgenital syndrome | Fludrocortison Tablet 100 mg | Therapeutic response unexpected with drug substitution,<br><br>Neck discomfort, Fatigue, Irritability, Headache, Shoulder discomfort, Sensation of pressure in eye,<br><br>Muscle weakness, ACTH decreased, Addisonian crisis, Muscle discomfort | -<br><br>2 Days<br><br>Unknown | Drug Withdrawn | Recovered<br><br>(except for ACTH decreased: unknown) |
| B: NL-LRB-00375596, female, 60-70 Years, Physician<br><br>28-01-2020 | HYDROCORTISON TABLET 10MG<br>DMB | Adrenal cortex insufficiency | | Pharmaceutical product complaint,<br><br>Endocrine disorder NOS,<br><br>Feeling unwell, Palpitations, Nausea | -<br><br>Within 1 month<br><br>Unknown | Drug Withdrawn | Recovering |
| C: NL-LRB-00371049, female, 40-50 Years, Consumer<br><br>25-12-2019 | Hydrocortison Tiofarma Tablet 20Mg<br><br>(lot:18L14/C1) | Adrenal insufficiency | Budesonide Hydroxocob. Fentanyl Macrogol/Zouten Topiramaat, Omeprazol | Product quality complaint, Therapeutic response unexpected with drug substitution, Tablet split incorrectly, Adrenal crisis | 1 Day | Dose Increased | Not Recovered |
| D: NL-LRB-00370089, female, 30-40 Years, Consumer<br><br>19-12-2019 | Hydrocortison Tablet 5Mg<br>----------<br>Hydrocortison Tablet 10Mg<br><br>DMB: Batch number: 18K30/E | Addison's disease | Venlafaxine Levothyroxine | Taste bitter, Product quality complaint, Product availability issue,<br><br>Addisonian crisis, Product lot specific issue<br><br>Maternal exposure | 3 years and 7 months after start<br><br>3 years and 8,5 months after start | Not Applicable | Not Recovered<br><br>Recovered |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | during pregnancy | - | | |
| E: NL-LRB-00369242, female, 30-40 Years, Consumer<br><br>14-12-2019 | Acecort Tablet 3Mg ACE | Adrenal insufficiency | Levothyroxine Timolol Ooggel Estradiol/Norethisteron Desmopres. Lamotrigine Levetiracetam Somatropine Lamotrigine | Product complaint,<br><br>Lack of drug effect,<br><br>Addisonian crisis,<br><br>Therapeutic response unexpected with drug substitution | 5 Days | Drug Withdrawn | Recovered |
| F: NL-LRB-00369216, female, 70 years and older, Consumer<br><br>14-12-2019 | Hydrocortison Tablet 3Mg PHL<br><br>(batch number: C277-000285330) | Pituitary disorder | Levothyrox.<br><br>Desmopres.<br><br>Povidon Rosuvast. | Fatigue, Somnolence,<br><br>Therapeutic response unexpected with drug substitution, Product complaint,<br><br>Addisonian crisis | 1 Days<br><br>-<br><br>Unknown | Dose Increased | Not Recovered,<br><br>Unknown |
| G: NL-LRB-240652, female, 40-50 Years, Consumer<br><br>31-05-2017 | Hydrocortison Tablet 10Mg DMB | crisisl insufficiency | | Short of breath, Hoarseness, Dyspnoea, Therapeutic response unexpected with drug substitution, Reaction to drug excipient | 30 Minutes | Drug Withdrawn | Recovered<br><br>(except for short of breath: Not Recovered) |
| H: NL-LRB-181959, female, 50-60 Years, Consumer<br><br>22-09-2014 | Hydrocortison Tablet 5mg and 10 mg PHL | Addison's disease | Fludrocortison Tablet 62,5Ug | Lack of drug effect, Therapeutic response unexpected with drug substitution | 5 Days | Drug Withdrawn, | Recovered |

A: The complaints occurred after the patient switched of compounding product (from CEB to DMB). Because of the complaints the patient couldn't take care of her child and household. Twice she even had an Addisonian crisis. According to her endocrinologist the ACTH values were also lower when she used the brand DMB.

B: Report of an internist endocrinologist. The reporter indicated that she had several patients with different kinds of complaints, including several cases of an unexplained Addisonian crisis. According to her it seems like all of the patients used hydrocortisone of DMB.

C: Report of a patient about the registrated hydrocortison tablets 20 mg of the manufacturer Tiofarma. According to the patient it's difficult to split the tablets on the score, even with a tablet splitter. The tablets crumble. Because of this not enough hydrocortisone was administered The patient uses 10 mg and this strength was not available. The patient had been using this product since 11-12-2019. Batch number is lot:18L14/C1. It is unknown which product was used before.

D: Report of a patient using hydrocortisone 5 mg or 10 mg tablets of DMB. She reported that she had a beginning Addisonian crisis, possibly due to a batch specific issue of hydrocortisone tablets, since her doctor heard similar stories with several patients that period. Patient was pregnant for 22 weeks, had Hb of 6,5, but this could not cause her complaints.

In addition; The patient also reports about Tiofarma tablets of 20 mg, according to her splitting of the tablets is not accurate and it causes a bitter taste.

E: Report probably about complaints after substitution to Acecort. The patient indicated that twice an Addisonian crisis occurred. According to the patient this occurred because his body couldn't absorb the hydrocortisone out of the ACE product.

F: This patient first used tablets of DCB (since 2010) and switched to PHL. PHL has a coating (which DCB hadn't). According to the reporter possibly the hydrocortisone was not absorbed well because of this coating.

G: This patient reported about different compounding products (including DMB and possibly DAB). She reported that she had complaints on three different kinds of tablets of 5 mg and 10 mg. She had no complaints on the 1 mg tablets of DMB. According to the patient the complaints are probably due to the talc and/or povidone since the three different kinds of tablets on which she had complaints, all contained these excipients. The patient now uses tablets made in Belgium and containing lactose.

H: This patient didn't have complaints on DMB (8 months of use). Complaints occurred after the switch to PHL. According to the patient it seems like PHL contains less hydrocortisone or that the hydrocortisone is absorbed less.

## Discussion and conclusion

The reports Lareb received were about several hydrocortisone products. Four reports (A, B, D and G) were about compounded products of 5 and 10 mg of De Magistrale Bereider (DMB), two reports (F and H) were about (different strengths of) Pharmaline products (PHL), two reports were about the registered product of Tiofarma (C and a comment in report D) and one report (E) was about the compounded product Acecort 3mg.. In five reports (A, E, F, G and H) it was specifically indicated that complaints occurred after switching to another hydrocortisone product. Bioavailability studies between these compounded products have likely not been performed. In four reports it was indicated that the patient got (one or more) adrenal crises.

Lareb received one report (B) from an internist endocrinologist who indicated that she recently noticed that several (about eight) of her patients had unexplained and unexpected complaints on hydrocortisone products, mostly of DMB. Unfortunately, only one of these cases was officially reported by the internist endocrinologist to Lareb, even after several attempts by Lareb to receive the other reports as well. One of the patients of the above mentioned internist-endocrinologist reported to Lareb herself (report D).

In a short period Lareb received several reports about hydrocortisone products. In some cases there was a reduced effect after switching from one product to the other. In the case with hydrocortisone ofTiofarma an inaccurate dosing due to difficulties in splitting the tablet was described, leading to under-dosing and adrenal crises.

The consequences of a reduced effect of hydrocortisone products can be very serious for patients with adrenal insufficiency. In half of the amount of reports, the patient experienced one or more adrenal crises. Although, there is no clear pattern in the manufacturers of the compounded products it is remarkable that several reports were received in a short period of time. Therefore Lareb wishes to inform the Inspectorate for Healthcare and Youth (IGJ) end the Medicines Evaluation Board (MEB) about the received reports

Literature


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*This signal has been raised on April 22, 2020. It is possible that in the meantime other information became available*