

Influenza like reactions after vaginal administration of estriol – an update

Introduction

Estriol is a natural estrogen, which has been approved for the Dutch market since 1982. It is available as Synapause® cream and as Synapause® ovule. The registered indications for use are *hormone suppletion therapy for urogenital atrophy in postmenopausal women with estrogen deficiency*, as therapy in *postmenopausal women who undergo vaginal surgery* and as *diagnostic aid in case of a doubtful cervical smear* [1-3]. In clinical practice, vaginal estriol is also used in the *prevention of urinary tract infections in postmenopausal women* [3].

Estriol is well absorbed after vaginal administration, the peak serum levels occur after 1-2 hours. The elimination half life time is 6-9 hours after vaginal administration [1-3].

In Quarterly Report 2008-2, the Netherlands Pharmacovigilance Centre Lareb described Influenza like illness associated with vaginal administration of estriol [4]. This report gives an update of reports and literature about this association.

Reports

Quarterly Report 2008-2 described 13 reports of influenza like illness or pyrexia associated with the vaginal application of estriol [4]. This update shows 49 reports (table 1), received until the 1st of November 2015 Lareb, of influenza like illness or pyrexia associated with the vaginal application of estradiol [5]. The time to onset varied from directly after administration until 3 days after administration. The outcome was reported in 44 cases, a positive dechallenge was reported in 36 cases. If outcome was known, the symptoms disappeared in several hours or at least within a day. In 20 women estriol was introduced again and the women experienced a similar reaction (positive rechallenge).

Table 1. reports of influenza like illness or pyrexia associated with vaginal estriol [5]

Patient sex, age report number	Drug indication for use	Concomitant medication	Suspected adverse drug reactions	Time to onset Action with drug Outcome
A F, 51-60 22115	Synapause E3 ovule 0,5 mg (estriol) daily Urinary problems	Not reported	Malaise (chills, elevated temperature, sweating decreased, pain bone muscle, skin, nausea)	5 Hours Positive de- and rechallenge (Symptoms last 5 hours)
B F, 61-70 Pharmacist 24357	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Atorvastatin Bisacodyl Medazepam Doxepin Paroxetine	Fever (38-39°C) Malaise (chills, thirst, influenza like symptoms)	1 Day Positive de- and rechallenge (4x; Symptoms disappear after 1 day)
C F, 51-60 General Practitioner 28586	Synapause E3 ovule 0,5 mg (estriol) daily Not reported		Influenza like symptoms (chills, headache, myalgia)	6 Hours Positive de- and rechallenge (Symptoms disappear after several hours)
D F, 51-60 General Practitioner 29234	Synapause E3 vaginal cream 1mg/g (estriol) daily Postmenopausal atrophic vaginitis	Ibuprofen Naproxen	Chills Fever (39,5 °C)	8 Hours Positive de- and rechallenge No focus was found
E F, 51-60 Pharmacist 32992	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Simvastatin	Fever (40 °C)	1 Day Positive de- and rechallenge (Symptoms disappear within a day; Blood test for infections was negative)

F F, 71 years and older Pharmacist 33638	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Simvastatin Alprazolam Tolbutamide Calcium	Breast pain Fever Pain Burning sensation mucosal	1 Day Dose not changed Not recovered/not resolved
G F, 61-70 Pharmacist 37726	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Bisoprolol Acetaminophen Magnesium Mebeverine Ranitidine Acetylsalicylic acid Povidone Pravastatin Ciprofloxacin	Fever Chills Palpitations Blood pressure fluctuation	1 Day Positive dechallenge (Fever lasted 1-2 hours)
H F, 51-60 Consumer 45783	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Not reported	Nausea Fever Influenza like symptoms	Several hours Positive de- and rechallenge (Symptoms lasted 1 day)
I F, 51-60 General Practitioner 52915	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Not reported	Fever Substitution parallel	Several hours Positive dechallenge (Symptoms disappeared after 12 hours)
J F, 51-60 General Practitioner 52916	Synapause E3 ovule 0,5 mg (estriol) daily Atrophic vaginitis	Not reported	Influenza like symptoms (fever, nausea, heacache, myalgia) Substitution	Several hours Positive dechallenge (Symptoms disappeared after 12 hours; CRP increased)
K F, 61-70 General Practitioner 61927	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Not reported	Fever (39°C) Nausea	Several hours Positive de- and rechallenge
L F, 51-60 Pharmacist 63581	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Not reported	Influenza like symptoms (Chills, myalgia)	Several hours Positive dechallenge
M F, 51-60 General Practitioner 71856	Synapause E3 ovule 0,5 mg (estriol) Atrophy of vulva	Alendronic acid Calcium/Vitamin D3	Influenza like symptoms (fever 38,3 °C, chills, myalgia, nausea)	Several hours Positive de- and rechallenge (Acetaminophen ineffective)
N F, 41-50 Consumer 79268	Synapause E3 ovule 0,5 mg (estriol) daily Menopausal symptoms	Insulin Gabapentin	Influenza like symptoms Headache Increased skin sensitivity	7 Hours Positive de- and rechallenge
O F, 61-70 Pharmacist 85404	Synapause E3 ovule 0,5 mg (estriol) Not reported	Not reported	Sleep excessive Influenza like symptoms (fever chills)	6 Hours Positive de- and rechallenge
P F, 51-60 General Practitioner 87008	Synapause E3 ovule 0,5 mg (estriol) 3 times a week Menopausal symptoms	Not reported	Influenza like symptoms (fever 38 °C, myalgia)	8 Hours Positive de- and rechallenge

Q F, 61-70 General Practitioner 109587	Synapause E3 ovule 0,5 mg (estriol) Postmenopausal bleeding	Not reported	Arthralgia Fever (40 °C)	1 Hour Positive de- and rechallenge (4x, 1 negative rechallenge)
R F, 61-70 Consumer 119636	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Hydroxychloroquine Acetaminophen/Codeine	Influenza like symptoms (fever 39 °C, myalgia) Tachycardia	Within a day Positive dechallenge (Symptoms improved in the evening)
S F, 51-60 Consumer 126409	Synapause E3 ovule 0,5 mg (estriol) Atrophy of vulva	Clobetasol Calcium	Influenza like symptoms (myalgia, fever)	3 Hours Positive dechallenge
T F, 51-60 Pharmacist 128570	Synapause E3 ovule 0,5 mg (estriol) Not reported	Not reported	Influenza like symptoms (myalgia, headache)	Several hours Dose not changed Outcome unknown
U F, 51-60 Pharmacist 132730	Synapause E3 ovule 0,5 mg (estriol) daily Menopausal symptoms	Not reported	Fever (39 °C)	1 Day Positive de- and rechallenge
V F, 51-60 Pharmacist 137131	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Not reported	Influenza like symptoms	10 Hours Positive dechallenge
W F, 71 years and older Consumer 140342	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal discomfort	Bisoprolol Dipyridamole Losartan Acetylsalicylic acid Ezetimibe Amlodipine Beclometasone	Fever Influenza like symptoms	5 Hours The action for estriol ovule is unknown The patient had not recovered at the moment of notification
X F, 51-60 Consumer 140847	Synapause E3 ovule 0,5 mg (estriol) Vaginal dryness	Rosuvastatin Diazepam Paroxetine Omeprazole Bisoprolol Fluticasone	Influenza like symptoms (fever)	9 Hours Positive de- and rechallenge
Y F, 61-70 Hospital Pharmacist 141309	Synapause E3 ovule 0,5 mg (estriol) 2 times a week Postoperative therapy	Not reported	Burning sensation Vaginal discharge Fever Chills Vomiting	1 Hour Positive dechallenge (CRP increased; Ileus complaints)
Z F, 61-70 Consumer 141416	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal discharge	Not reported	Influenza like symptoms (fever) Abdominal pain	10 hours Dose reduced Recovered. (Latency abdominal pain 3 days)
AA F, 41-50 General Practitioner 141825	Synapause E3 ovule 0,5 mg (estriol) daily Atrophic vulvovaginitis	Fluvoxamine	Fever Vomiting	1 Day Positive de- and rechallenge
BB F, 51-60 General Practitioner 143428	Synapause E3 ovule 0,5 mg (estriol) Vaginitis atrophic	Not reported	Fever (39 °C) Chills Malaise	5 Hours Positive de- and rechallenge

CC F, 61-70 Pharmacist 146828	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Not reported	Chills Influenza like symptoms	3 Days Drug withdrawn Outcome unknown
DD F, 61-70 Pharmacist 146957	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal discomfort	Hydrochlorothiazide Simvastatin	Chills Influenza like symptoms (fever, myalgia)	4 Hours Positive de- and rechallenge
EE F, 51-60 Pharmacist 149332	Synapause E3 ovule 0,5 mg (estriol) daily Not reported	Lactulose	Influenza like symptoms Myalgia Dizziness	4 Hours Positive de- and rechallenge (Symptoms disappear after 12 hours)
FF F, 61-70 Consumer 150023	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Pantoprazole Sotalol	Influenza like symptoms (fever) Abdominal pain lower Headache Pruritus	12 Hours Drug withdrawn The patient had not recovered at the moment of notification
GG F, 61-70 Consumer 155439	Synapause E3 ovule 0,5 mg (estriol) Vaginal dryness	Not reported	Chills Fever malaise	1 Day Positive dechallenge
HH F, 61-70 Consumer 157713	Synapause E3 ovule 0,5 mg (estriol) daily Dysplasia of vagina	Omeprazole	Headache Abdominal pain Nausea Fever Vaginal discharge (green)	15 Hours Dose not changed Recovered/resolved with sequel (green discharge)
II F, 51-60 Pharmacist 157916	Synapause E3 ovule 0,5 mg (estriol) daily Endometrial disorder	Not reported	Influenza like symptoms (fever, cold chills)	Directly Dose is not changed Patient outcome is unknown
JJ F, 51-60 Consumer 164661	Synapause E3 ovule 0,5 mg (estriol) daily Drug use for unknown indication	Not reported	Influenza like symptoms	12 Hours Positive dechallenge
KK F, 51-60 Consumer 165663	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal discomfort	Not reported	Malaise Influenza like symptoms (chills, cold, headache)	Several hours Drug withdrawn Patient outcome unknown
LL F, 51-60 Consumer 168503	Synapause E3 ovule 0,5 mg (estriol) 2 times a week Vaginal dryness	Not reported	Influenza like symptoms (cold chills, fever)	5 Hours Positive dechallenge
MM F, 51-60 Consumer 171556	Synapause E3 ovule 0,5 mg (estriol) daily Menopausal symptoms	Not reported	Influenza like symptoms (fever, vomiting, diarrhoea, myalgia, chills, headache)	9 Hours Positive de- and rechallenge
NN F, 51-60 Consumer 174798	Synapause E3 ovule 0,5 mg (estriol) daily Menopausal symptoms	Acetaminophen	Influenza like symptoms	12 Hours Dose not changed The patient had not recovered at the moment of notification
OO F, 61-70 Consumer 175248	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal discomfort	Not reported	Influenza like symptoms (fever, sweating) Cardiac disorder Nausea	Several hours Drug withdrawn The patient had not recovered at the moment of notification

PP F, 51-60 Pharmacist 184133	Synapause E3 ovule 0,5 mg (estriol) daily Postmenopausal atrophic vaginitis	Nitrofurantoin	Influenza like symptoms (fever) Back pain	Directly Positive de- and rechallenge (Symptoms disappeared within a day)
QQ F, 51-60 Consumer 186259	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Diazepam Esomeprazole	Influenza like symptoms (fever 39,3 °C, cold chills, dizziness, headache)	8 Hours Positive dechallenge (Symptoms disappeared within 12 hours)
RR F, 71 and older Specialist doctor 192783	Synapause E3 vaginal cream 1mg/g (estriol) daily Vaginal dryness	Not reported	Fever	1 Day Positive de- and rechallenge (Symptoms disappeared after 1 or 2 days)
SS F, 51-60 Consumer 192870	Synapause E3 ovule 0,5 mg (estriol) daily Burning feeling vagina	Not reported	Influenza like symptoms (backpain, myalgia, sensitive skin, hair pain, cold hand and feet, cold chills, abdominal pain, nausea, dizziness, fever 37,8 °C)	12 hours Dose not changed Recovered (Recovered after 5 days)
TT F, 51-60 Pharmacist 195845	Synapause E3 ovule 0,5 mg (estriol) 2 times a week Not reported	Not reported	Abdominal discomfort Influenza like symptoms (sweating, headache)	1 Day Positive dechallenge
UU F, 51-60 Consumer 199405	Synapause E3 ovule 0,5 mg (estriol) daily Burning feeling vagina Uterine disorder NOS	Not reported	Fever Pruritus	1 Hour Positive dechallenge
VV F, 51-60 Consumer 203343	Synapause E3 ovule 0,5 mg (estriol) daily Vaginal dryness	Not reported	Influenza like symptoms	12 Hours Action taken and patient outcome unknown
WW F, 51-60 Consumer 203923	Synapause E3 ovule 0,5 mg (estriol) daily Drug use for unknown indication	Not reported	Administration site pain Influenza like symptoms (malaise, fever)	6 Hours Positive dechallenge

Patient HH and SS recovered while the dose for vaginal estriol was not changed. Patient E was examined and infectious causes were not found. In patient J a positive C-reactive protein (CRP) was found, and in case Y the patient had ileus complaints and CRP also was increased. Patient M mentioned acetaminophen was ineffective.

Other sources of information

SmPC

Influenza like illness or pyrexia in relation to the use of vaginal application of estriol is neither mentioned in the SmPC of Synapause E3 ovules® [1] nor in the SmPC of Synapause vaginal cream® [2].

Literature

A Pubmed search on "influenza like"[All Fields] or "fever"[MeSH Terms] in association with the

use of “estrogens” [Pharmacological Action] did not yield a relevant hit. In the American SmPC Minivelle®, a transdermal application of estriadiol, influenza-like illness is mentioned with an incidence up to 8% [6,7]. The Netherlands Pharmacovigilance Centre Lareb has previously published an article about this association [7].

Databases

Table 2. Reporting odds ratios of estriol and influenza like illness and of estriol and pyrexia in the database of the Netherlands Pharmacovigilance Centre Lareb [5], the WHO- and Eudravigilance (EMA) database [8,9].

Drug and ADR	Number of reports	ROR (95% CI)
Estriol and Influenza like illness	Lareb: 32	26.8 (18.4 – 39.2)
	Eudravigilance: 33	25.6 (17.9 – 36.6)
	WHO: 41	9.4 (6.9 – 12.9)
Estriol and Pyrexia	Lareb: 18	1.4 (0.9 – 2.2)
	Eudravigilance: 22	1.7 (1.0 – 2.4)
	WHO: 67	1.9 (1.5 – 2.4)

Prescription in the Netherlands

Table 3. Number of patients using Estriol (oral, vaginal, transdermal, topical) in the Netherlands between 2010 and 2014 [10]

Drug	2010	2011	2012	2013	2014
Estriol	92,731	93,238	92,189	88,909	87,010

Mechanism

Unfortunately, the exact mechanism for these reactions is still unknown. Estrogens have effects on the temperature regulation in the hypothalamus [11]. During menopause, women experience hot flushes due to a decrease of estrogen levels [12,13]. The mechanisms involved in temperature regulation are not entirely clear. In postmenopausal woman the body temperature is in balance again and hot flushes disappear [14,15]. Possibly a temporary increase in estrogen levels can disbalance body temperature regulation in postmenopausal women.

Another hypothesis is the local metabolism of estrogens into metabolites that act as haptens. It is known that the 4-hydroxylation of estrogens is mainly catalysed by CYP1B1 [16]. This CYP enzyme is expressed in estrogen target tissues, including mammary, ovary and uterus [16]. The 4-hydroxylation metabolites of estrogens produced locally by catalisation of this CYP enzyme are known to generate free radicals [16]. Like rifampicine induced influenza like illness [17], these haptens could cause influenza like illness by becoming antigenic, stimulate antibody formation and these hapten–antibody complexes bind complements [17].

Discussion and conclusion

The received cases of influenza-like illness and pyrexia which were reported after vaginal application of estriol suggest a causal relation. Especially since three quarter of the patients experienced a positive dechallenge and almost half the reporters mentioned a positive rechallenge. Also, the reported events seem to be in line with the pharmacokinetic characteristics of the vaginal administration of estriol. Unfortunately no mechanism is known to explain these reactions. Possibly a temporary increase of estrogen levels results in body temperature changes and influenza like illness and pyrexia in postmenopausal women. The other hypothesis suggests these reactions to occur especially after vaginal administration of estrogens, because potential hapten-metabolites are produced locally in the uterus and ovary [16]. Lareb has only received 30 reports on oral estriol tablets (Synapause-E3 1 or 2 mg, tablets) in total (compared to > 200 for the vaginal administration route) and among these there is only one reports of symptoms that might be related to influenza-like illness (headache, chills, feeling hot and cold).

Compared with the Eudravigilance and WHO databases, the Netherlands Pharmacovigilance Centre Lareb received a large number of reports on this association [5,8,9]. The reports from the Netherlands Pharmacovigilance Centre Lareb account for most reports in the Eudravigilance database and for a large part of the WHO reports.

In USA no product with estriol is available [18,18,19], so availability in other countries could cause this discrepancy. Lareb has published about this reaction in the Dutch Drug Bulletin in 2010 [7], which could also have led to more cases being reported.

Due to the number and the strength of the cases, Lareb recommends that influenza-like illness and pyrexia which were seen after vaginal application of estriol should be listed in the SmPC of vaginal estriol as adverse drug reactions.

- Influenza like illness should be mentioned in the SmPC of vaginal estriol

References

1. Dutch SPC Synopause-E3® ovule. (version date: 2-8-2012, access date: 4-11-2015) <http://db.cbg-meb.nl/IB-teksten/h08978.pdf>.
2. Dutch SPC Synopause-E3® cream. (version date: 2-8-2012, access date: 4-11-2015) <http://db.cbg-meb.nl/IB-teksten/h08977.pdf>.
3. Informatarium Medicamentorum via KNMP Kennisbank . (version date: 2015, access date: 1-9-2015) kennisbank.knmp.nl.
4. Quarterly Report Influenza like reactions after vaginal administration of estriol. (version date: 2008, access date: 4-11-2015) <http://www.lareb.nl/Signalen/2008-2-LQR-Influenza-like-reactions-after-vaginal->.
5. Lareb Database. (version date: 2015, access date: 9-6-2015) <http://databank.lareb.nl/Bijwerkingen?lang=nl>.
6. American SPC: Minivelle® transdermal system. (version date: 2014, access date: 4-11-2015) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203752s004lbl.pdf.
7. Lareb. Estriol en griepachtige verschijnselen. Geneesmiddelenbulletin 2010;44(Let opl):67
8. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2015, access date: 9-6-2015) <https://vigilyze.who-umc.org/>.
9. Eudravigilance Database European Medicines Agency. (version date: 2015, access date: 14-9-2015) http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=.
10. College for Health Insurances. GIP database. (version date: 2015, access date: 1-9-2015) <http://www.gipdatabank.nl/databank.asp>.
11. Kelly MJ, Ronnekleiv OK. Membrane-initiated Actions of Estradiol that Regulate Reproduction, Energy Balance and Body Temperature. Front neuroendocrinology 2012;33(4):376-87.
12. Casper RF, Barbieri RL, Crowley WF, and Martin KA. Clinical manifestations and diagnosis of menopause. (version date: 5-8-2015, access date: http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-menopause?source=search_result&search=menopausal+symptoms&selectedTitle=1%7E150).
13. Santen RJ, Loprinzi CL, and Casper RF. Menopausal hot flashes. (version date: 27-5-2015, access date: http://www.uptodate.com/contents/menopausal-hot-flashes?source=see_link).
14. Brooks EM, Morgan AL, Pierzga JM, Wladkowski SL, O'Gorman JT, Derr JA, Kenney WL. Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in post menopausal women. J Appl Physiology 1997;83:477-84.
15. Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. Ach Womens Ment health 2007;10:247-57.
16. Yuki Tsuchiya, Miki Nakajima, Tsuyoshi Yokoi. Cytochrome P450-mediated metabolism of estrogens and its regulation in human. Cancer Letters 2005;227:115-224.
17. Sudipta Pandit, Sabyasachi Choudhury, Anirban Das, Samadarshi Datta, Sibes K.Das. Isoniazid-induced flu-like syndrome: a rare side effect. Lung India 2013;30(1):61-3.
18. American regulatory agency (FDA). (version date: 2015, access date: 1-11-2015) <http://www.fda.gov/default.htm>.
19. Dutch regulatory agency (CBG). (version date: 2015, access date: 1-9-2015) www.cbg-meb.nl.

This signal has been raised on January 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