

1.1. Influenza like reactions after vaginal administration of estriol

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[®] vagitory. 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*. [1,2]. 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 is 6-9 hours after vaginal administration.

Reports

Until the 1st of March 2008 Lareb received 13 reports of influenza like reactions or fever associated with the vaginal application of estriol. The time to onset varied from 5 hours until one day. The outcome was reported in 12 cases, a positive dechallenge was reported in these cases. The symptoms disappeared in a few hours or at least within a day. In 8 women estriol was introduced again and the women experienced a similar reaction. Patients D and E, were examined and infectious causes were not found.

Table 1. reports of influenza like reactions or fever associated with vaginal estriol

patient, sex, age, report nr	drug indication for use	concomitant medication	suspected adverse drug reaction	time to onset, outcome
A F, 59 22115	Synapause E3 ovule 0,5mg (estriol) daily, urinary problems	not reported	malaise (chills, elevated temperature, sweating decreased, pain bone muscle, skin, nausea)	5 hours, symptoms last 5 hours, positive de- and rechallenge
B F, 64 24357	Synapause E3 ovule 0,5mg (estriol), nr	atorvastatin, medazepam, bisacodyl, sinequan, paroxetin	fever 38-39 °C, chills, thirst, influenza like symptoms	1 day, symptoms disappear after 1 day, positive de- and rechallenge (4x)
C F, 53 28586	Synapause E3 ovule 0,5mg (estriol) daily, nr	furadantin	chills, influenza like reaction, headache, myalgia	6 hours, symptoms disappear after several hours, positive de- and rechallenge
D F, 60 29234	Synapause E3 vaginal cream 1mg/g (estriol) daily, vaginal atrophy	ibuprofen, naproxen	chills, fever 39,5°C	8 hour, positive de- and rechallenge, no focus was found
E F, 60 32992	Synapause E3 ovule 0,5mg (estriol), nr	simvastatin	fever 40 °C	1 day, symptoms disappear within a day positive de- and rechallenge, blood test for infections was negative
F	synapause	alprazolam,	breast pain, fever,	1 day, the patient

patient, sex, age, report nr	drug indication for use	concomitant medication	suspected adverse drug reaction	time to onset, outcome
F, 73 33638	E3 ovule 0,5mg (estriol) 2x/ week, nr	tolbutamide, calciumgluconate, simvastatin	burning mucosal	had not recovered at the moment of notification
G F, 70 37726	Synapause E3 ovule 0,5mg (estriol), nr	bisoprolol, paracetamol, magnesiumhydroxid mebeverin, ranitidin, acetylsalicylic acid, pravastatin, ciprofloxacin	fever, chill, palpitations, blood pressure fluctuation	1 day fever lasted 1-2 hours, recovered
H F, 58 45783	synapause E3 ovule 0,5mg (estriol), nr	not reported	nausea, fever, influenza like symptoms	several hours, symptoms lasted 1 day, positive rechallenge
I F, 58 52915	Synapause E3 ovule 0,5mg (estriol) nr	not reported	fever, substitution parallel	several hours, disappeared after 12 hours
J F, 59 52916	Synapause E3 ovule 0,5mg (estriol), nr	not reported	fever, nausea, headache, myalgia, substitution	several hours, disappeared after 12 hours
K F, 61 61927	synapause E3 ovule 0,5mg (estriol), nr	not reported	pyrexia 39 °C, nausea	several hours, positive de and rechallenge
L F, 56 63581	synapause E3 ovule 0,5mg (estriol) nr	not reported	infuenza like reaction, chills, myalgia	several hours, withdrawn and recovering
M F, 60 71856	synapause E3 ovule 0,5mg (estriol), vaginal atrophy	alendronate, calcium/ vitamin D3	influenza like reaction, fever 38,3 °C, chills, myalgia and nausea	several hours, positive dechallenge, paracetamol ineffective

nr = not reported

Other sources of information

SmPC

Influenza like reactions or fever in relation to the use of vaginal application of estriol is neither mentioned in the SmPC of Synapause E3 ovules® nor in the SmPC of Synapause vaginal cream®.

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 any relevant hits. However in the American SmPC of Vivelle® (estradiol) influenza and influenza like reactions are mentioned. Influenza and influenza like reactions were observed in 4-9% of the women treated with transdermal estradiol [4]. The product information of the Dutch equivalent of this product (Climara®) does not mention this adverse drug reaction [5].

Databases

Lareb received 13 reports of fever or influenza like reactions, but not all reports were coded as influenza-like reaction, but often as malaise or as individual symptoms. Therefore the calculated ROR for influenza like reactions cannot be calculated correctly. The ROR calculated for influenza like reactions in association to vaginal estriol, is 19.5 (95% CI: 7.8-48.4), the calculation is based on 5 reports.

The database of the WHO contains 457 ADRs associated with the use of estriol. A total of 8 reports concern influenza like reactions, 8 reports concern malaise and 33 reports concern fever [6]. Table 2 shows an overview of the reporting odds ratio's of these associations.

Table 2: Reporting odds ratio WHO-ADR database

ADR associated to estriol	number of reports	ROR (95% CI)
influenza like reaction	8	4.09 (2.03-8.23)
fever	33	1.63 (1.14-2.33)
malaise	8	2.54 (1.26-5.14)
Total	49	2.04 (1.52-2.74)

Mechanism

Estrogens have effects on the temperature regulation in the hypothalamus. During menopause, women experience hot flushes due to a decrease of estrogen levels. The mechanisms involved in temperature regulation are not entirely clear. In postmenopausal woman the body temperature is in balance again and hot flushes disappear [7,8]. Possibly a temporary increase in estrogen levels can disbalance body temperature regulation in postmenopausal women.

The reported events seem to occur when estrogen levels are decreasing (5-6 hours after administration) and disappear when estrogen levels are at postmenopausal levels again (within a day)

Prescription in the Netherlands

Estriol is prescribed to approximately 100.000 women annually. Most women are treated with vagitories or vaginal cream

Table 3: The number of patients using Estriol (Synopause-e3 ®)[9]

	2002	2003	2004	2005	2006
SYNAPAUSE-E3 CREME 1MG/G	46,195	46,260	45,187	43,589	47,974
SYNAPAUSE-E3 OVULE 0,5MG	37,375	38,808	39,300	40,382	47,683
SYNAPAUSE-E3 TABLET 1MG	4,707	4,368	3,578	3,404	3,889
SYNAPAUSE-E3 TABLET 2MG	15,557	14,574	11,485	10,424	9,775

Conclusion

The influenza-like reactions and fever which were seen after vaginal application of estriol could be adverse drug reactions. The reactions occur 5-6 hours after administration and disappear within a day. Possibly a temporary increase of estrogen levels results in body temperature changes in postmenopausal women.

References

1. Dutch SmPC Synopause E3 ovules ®. (version date 24-06-2005) <http://db.cbg-meb.nl/IB-teksten/h08978.pdf>
2. Dutch SmPC Synopause 1mg/g vaginal cream®. (version date 07-06-2007) <http://db.cbg-meb.nl/IB-teksten/h08977.pdf>
3. KNMP/Winap. Informatarium Medicamentorum 2008, via <http://kennisbank.knmp.nl> assessed 21-03-2008
4. US-SmPC Vivelle (estradiol transdermal) <http://www.pharma.us.novartis.com/product/pi/pdf/vivelle.pdf> assessed 21-03-2008
5. Dutch SmPC Climara (estradiol transdermal)
6. WHO-ADR database Uppsala Monitoring Centre assessed 21-03-2008
7. 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: 247-257
8. 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: 477-484
9. Gipdatabank. GIP/College voor zorgverzekeringen 2007 Geactualiseerd op: 30-11-2007 <http://www.gipdatabank.nl/> assessed 21-03-2008

This signal has been raised on June 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).