PEPTONIC
medical

Datum 2014-06-03

Report of EudraCT 2013-002690-22
OXYPEP003 , A pharmacokinetic study of vaginally and intravenously administered oxytocin in postmenopausal women with vaginal atrophy

Aim of the study
The study, which took place at the Karolinska hospital/Huddinge 2013 under the supervision of professor Aino Fianu-Jonasson, was aimed investigating the pharmacokinetic properties of Vagitocin.

Design of the study
12 healthy women were included in the study. The duration of the study was 26 days. The first 15 days of the study the women were treated intravaginally with vagitocin, a gel containing 400 IU of oxytocin.

On day 1 and 15 the responsible clinician at the hospital gave the gel at 8 o'clock in the morning. Blood samples were collected from an indwelling cannula 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 560 minutes after administration of the gel.

The rest of the days Vagitocin was applied intravaginally, by the women themselves at bedtime (around 11 o'clock in the evening). Single blood samples were collected at the hospital at 8 o'clock in the morning on days 5, 8, 12, 16, 19, 23 and 26.

On day 22 the responsible clinician at the hospital gave an intravenous infusion of 10 IU of oxytocin. Blood samples were collected according to the schedule described above.

Plasma oxytocin levels were measured by radioimmunoassay.

Results of the study
Some women experienced headache in connection with intravenous injection of 10 IE of oxytocin. No side effects were noted in the women receiving 400 IE of oxytocin.

Basal plasma levels of oxytocin averaged 16 pg/ml before the treatment with Vagitocin was started. Basal levels were reached again at the end of the study.

Oxytocin levels on the average rose to 175 pg/ml after 1 hour and thereafter oxytocin levels fell gradually during the 8 hours observation time after administration of 400 IU of Vagitocin. Basal levels were almost resumed after 8 hours.

The basal levels, as reflected by values obtained at 8 o'clock in the morning, were slightly elevated in women who applied Vagitocin in the evening, but remained at the same level during the 15 days long treatment period showing that there was no accumulation of oxytocin.

The maximal levels of oxytocin were more than 600 pg/ml 15 minutes after intravenous administration of 10 IE of oxytocin. The levels should have been at least two times higher immediately after the injection.

PEPTONIC medical AB (publ)
Org number: 556776-3064
VAT number: SE556776306401
Säte: Uppsala

Address: Gustavslundsvägen 143
SE-167 51 BROMMA, Sweden
Telephone: +46 (0)8 530 20 110

The area under the curve for oxytocin values obtained day 1, 15 and 22 was calculated. The values obtained for days 1 and 15 were identical, suggesting that the absorption of oxytocin at the two experimental occasions was the same.

Based on a preliminary comparison with the calculated area under the curve for 10 IU of oxytocin, the percentage of oxytocin absorbed after intravaginal application of Vagitocin was around 4 % of the given dose (400 IU). A preliminary inspection of the data also revealed that the half-life of oxytocin was around 20-30 minutes after application of Vagitocin, which is in accordance with previous studies.

Further pharmacomimetric analyses will be performed on the material in order to characterize the pharmacokinetics of Vagitocin using computer based models and programs. These studies will be performed in collaboration with associate professor Elisabet Nielsen, department of pharmacology at Uppsala University.

Kerstin Uvnäs Moberg

June 3rd 2014

PEPTONIC
medical

Datum 2014-06-03

Study to Evaluate the Pharmacokinetic Parameters of Vagitocin Gel after Intravaginal Administration

STUDY SYNOPSIS	
STUDY TITLE:	A pharmacokinetic study of vaginally and intravenously administered oxytocin in postmenopausal women with vaginal atrophy
Objective:	The objective of this study is to evaluate the uptake of oxytocin following intravaginal administration of Vagitocin 400IU over a period of 15 days and also to compare oxytocin bioavailability after vaginal and intravenous administration.
Design:	This is a single-center, open-label, two-period study
Study Population and Main Criteria for Inclusion:	12 healthy postmenopausal female volunteers, 40 to 70 years old, who were judged to be healthy on the basis of a pre-study physical examination.
Study Treatments and Dosing Regimen:	Each eligible subject will be administered intravaginally with Vagitocin 400IU [PeP-Tonic Medical AB] once daily for 15 days (Period I) and a single intravenous dose of oxytocin 10 IU Syntocinon® (Period II). There will be a minimum of 7 days washout between the two dosing periods.
Sample collection:	On Day 1, Day 15 (Period I) and Day 22 (Period II) of the study serial blood samples will be collected at the following times relative to dosing: -1.0, -0.5, 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0 and 8.0 hours. Single blood samples also will be collected on Days 5, 8 and 12 as well as on Days 16 and 19 (Period I) and on Days 23 and 26 (Period II). Patients will self-administer the Vagitocin product in the evening during days 2-14. Vagitocin will be administered in the morning of days 1 and 15 at the clinic. Plasma samples will be stored at -70°C ± 15°C until analysis.
Key Eligibility Criteria:	Inclusion Criteria 1. Postmenopausal women with vaginal atrophy 2. Subjects who are willing to participate in the study as indicated by signing the informed consent

	3. Subjects who are healthy post-menopausal women between the ages of 40 and 70 years, inclusive 4. Subjects who have body mass index (BMI) less than or equal to 32 kg/m^2 but greater than or equal to 19 kg/m^2 5. Subjects who are judged by the Investigator to be healthy on the basis of medical evaluation. <u>Exclusion Criteria</u> 1. Hospitalized subjects 2. Subject who have symptoms of any significant acute illnesses at the screening visit 3. Subjects who have a history of significant allergies (including food, asthma, or drug allergies including allergies to any ingredient of the trial product) 4. Subjects who have a known history of sensitivity to oxytocin or related derivatives 5. Subjects with FSH level < 40 pmol/mL 6. Subjects who have a known history of narcotic addiction, drug abuse or alcoholism 7. Subjects who simultaneously participate in another clinical study 8. Subjects who use any sex steroids including phytoestrogens, hormonal intrauterine device or herbal medicinal products with known estrogenic effects within 3 months prior to baseline 9. Subjects who have uncontrolled hypertension and/or hypercholesterolemia?

Safety Parameters:	Screening: Demographic data, medical and medication histories, physical examination, gynecological examination, PAP smear will be performed at screening.
Analytical method:	Plasma concentrations of oxytocin will be determined using validated (RIA) analytical method.
Outcome Measures:	Primary Endpoints - To determine the oxytocin plasma levels after intravaginal and intravenous administration and also pharmacokinetic parameters - To evaluate bioavailability of intravaginally administered oxytocin compared to intravenous administration
Statistical Analyses:	Mean and SD.