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Comparison of the pharmacokinetic profiles of separately administered sublingual testosterone followed by a sildenafil citrate tablet, versus sublingual testosterone and sildenafil citrate combined in a fixed-dose combination tablet

Submission date
08/04/2015

Recruitment status
No longer recruiting

Registration date
16/04/2015

Overall study status
Completed

Last Edited
17/05/2023

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Hypoactive Sexual Desire Disorder is a problem affecting many women. These women have extremely low or no sexual desire and they are very distressed by this. If your low sexual desire is caused by a bad relationship with your partner, a high amount of stress, another illness that you have, or it is a side effect of medication that you are taking, you do not have Hypoactive Sexual Desire Disorder. There are several medications being tested to see if they help solve these problems in sexual desire. One of these medications has two active ingredients: testosterone and sildenafil. Testosterone and sildenafil have to be taken in two different ways because otherwise, the medication doesn't work. The testosterone is dissolved under the tongue and the sildenafil tablet is swallowed. In earlier studies, these two ingredients were administered separately (the old way). Now a tablet has been made that combines these two ingredients into one tablet (the new way). This study investigates if these two different ways of taking the medication, the old way and the new way, are the same. This is done by comparing the blood levels of testosterone and sildenafil in women who take the medication in the old way and in the new way.

Who can participate?
Healthy women between the ages of 18 and 35.

What does the study involve?
The women are first screened by a physician to see if they are eligible to participate in the study. If so, they are invited to the research centre for two overnight visits. During the first overnight visit they are given the medication in the old or new form. Just before taking the medication blood is drawn. After taking the medication, blood is drawn another 27 times over a period of 26

and a half hours. During the second overnight visit, the women are given the other medication form and blood is drawn in the same way as the first visit. The subjects blood is sent to a laboratory where it is tested for how much of each drug is in the blood at different points in time.

What are the possible benefits and risks of participating?
The participants are given 828 Euros for participation and a fixed fee of 38 Euros for travel expenses. A total amount of 246.2 ml of blood is drawn from each participant during the entire study. Participants may experience side effects from the medication. The most common side effects are headache, flushing, nausea, a runny nose and dizziness.

Where is the study run from?
University Medical Center Groningen (Netherlands).

When is the study starting and how long is it expected to run for?
December 2010 to July 2011.

Who is funding the study?
Emotional Brain B.V. (Netherlands).

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2011-000457-23

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
EB81, NL35616.044.11

Study information

Scientific Title
A randomized, cross-over controlled study to compare the pharmacokinetic profiles of sublingual administered testosterone solution followed by a sildenafil citrate tablet, versus sublingual testosterone and sildenafil citrate combined in one tablet in healthy premenopausal women

Study objectives
1. Primary objective: To compare the pharmacokinetics of testosterone and sildenafil citrate given as a sublingual solution of testosterone with an encapsulated tablet of sildenafil (formulation 1 = F1) versus a combination product, containing both testosterone and sildenafil in one tablet (formulation 2 = F2).
2. Secondary objective: To investigate the time frame in which the mint flavored testosterone coating is dissolved.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medisch Ethische Toetsingscommissie Twente (Enschede, The Netherlands). Medical Ethics Review Board Twente, 20/05/2011, ref: METC/11179.kop

Study design
Single-center, randomized, cross-over controlled study.

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Hypoactive sexual desire disorder

Interventions

1. Testosterone (0.5mg) and sildenafil (50mg) administered separately as a solution containing testosterone for sublingual administration followed 2 1/2 hours later by a tablet containing sildenafil for oral administration
2. Testosterone (0.5mg) and sildenafil (50mg) administered in a single fixed-dose combination tablet

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Lybrido

Primary outcome measure
Pharmacokinetic (PK) parameters for total testosterone, free testosterone and dihydrotestosterone as well as for sildenafil and Ndesmethyl-sildenafil:
1. Maximum concentration (Cmax)
2. Area under the plasma concentration curve (AUC0-infinity/ AUC0-1590)
3. Time to Cmax (Tmax)

The total testosterone and dihydrotestosterone were analyzed in plasma in a combination assay using High Performance Liquid Chromatography Tandem Mass Spectrometry (HPLCMS/MS). Free testosterone was determined in plasma through ultra filtration followed by LCMS/MS. Incurred sample reanalysis was performed in 5% of all samples. The existing method of analysis has been validated in a prior study.

The analytes Sildenafil and N-desmethyl-sildenafil in human plasma were determined by means of a HPLC-MS/MS. Incurred sample reanalysis was performed in 10% of all samples.

Samples were analysed using a mobile phase containing water, methanol and 0.1% acetic acid. The analytical column Hypersil GOLD (Thermo Scientific), dimension 50 x 2.1 mm, particle size 3 µm was used. An API-4000 triple quadrupole tandem mass spectrometer (Applied Biosystems) was used as the detector.

Secondary outcome measures
Safety assessments including:
1. Standard clinical chemistry, hematology and serology tests
2. Vital signs
3. Electrocardiogram (ECG)
4. Body temperature
5. Physical examination

Overall study start date
01/12/2010

Completion date
15/07/2011

Eligibility

Key inclusion criteria
Subject had to fulfill all of the following criteria to be enrolled into the study:
1. Provide written informed consent
2. Be female, between 18 and 35 years of age inclusive
3. Be healthy based on medical history, physical examination, laboratory values and vital signs
4. Have a body mass index (BMI) 18 kg/m2 and 30 kg/m2
5. Have sufficient venous access to allow blood draws

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
35 Years

Sex
Female

Target number of participants
12

Total final enrolment
12

Key exclusion criteria
Subjects could not be entered into the study if any of the following criteria were met:
1. Cardiovascular conditions:
1.1. Any underlying cardiovascular condition, including unstable angina pectoris
1.2. History of myocardial infarction, stroke, or life-threatening arrhythmia within 6 months prior to study entry
1.3. Uncontrolled atrial fibrillation/flutter at screening or other significant abnormality observed on electrocardiogram (ECG)
1.4. Systolic blood pressure 140 mmHg and/or diastolic blood pressure > 90 mmHg
1.5. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure <50 mmHg
2. Gynecological and obstetric conditions:
2.1. Use of oral contraceptive containing anti-androgens
2.2. Use of oral contraceptive containing 50 g estrogen or more
2.3. Pregnancy or intention to become pregnant during this study (Note: All women were to undergo a urine pregnancy test prior to study entry)
2.4. Lactating or delivery in the previous 6 months
2.5. Unexplained gynecological complaints, such as clinically relevant abnormal uterine bleeding patterns
2.6. Subjects with a perimenopausal hormonal status (follicle-stimulating hormone > 30)

3. Other medical conditions:
3.1. Liver and/or renal insufficiency
3.2. Current clinically relevant endocrine disease
3.3 Current clinically relevant neurological disease which, in the opinion of the investigator, would compromise the validity of study results, or which could constitute a contraindication for sildenafil and/or testosterone use
3.4. History of hormone-dependent malignancy
4. Psychological/psychiatric factors:
4.1. A substance abuse disorder that, in the opinion of the investigator, was likely to affect the subject's ability to complete the study or preclude the subject's participation in the study; mild or moderate alcohol consumption was allowed but had to be stopped 24 hours before the admission period until follow up. Smokers were not allowed to participate.
5. Concomitant medication:
5.1. Subjects who were taking CYP3A4-inhibitors (e.g., ritonavir, ketoconazole, itraconazol claritromycine, erytromycine and saquinavir)
5.2. Subjects who were taking CYP3A4-inducers (e.g., carbamazepine, fenytoinefenobarbital, St Johns Wort, rifampicine)
5.3. Use of nitrates or nitric oxide donor compounds
5.4. Use of any other medication that could interfere with study medication (e.g., monoamine oxidase (MAO) inhibitors (includes classic MAO inhibitors and linezolid), calcium channel blockers (e.g., diltiazem and verapamil), use of corticosteroids)
5.5. Use of testosterone therapy within 6 months before study entry
6. Drug/food interaction
6.1. Consumption of grapefruit or grapefruit-containing foods throughout the duration of the study
7. General:
7.1. Illiteracy, unwillingness, or inability to follow study procedures
7.2. Any other clinically significant abnormality or condition which, in the opinion of the investigator, might interfere with the subject's ability to provide informed consent or comply with study instructions, compromise the validity of study results, or be a contraindication of sildenafil and/or testosterone use
7.3. Participation in any other clinical drug study in the previous 3 months

Date of first enrolment
16/06/2011

Date of final enrolment
24/06/2011

Locations

Countries of recruitment
Netherlands

Study participating centre
QPS Groningen
University Medical Center Groningen, Biotech Center
Hanzeplein 1 - input 53
Groningen

Netherlands
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Sponsor information

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Sponsor type
Research organisation

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ROR
https://ror.org/03vy5fy74

Funder(s)

Funder type
Research organisation

Funder Name
Emotional Brain BV (The Netherlands)

Results and Publications

Publication and dissemination plan
We plan to publish these results in 2015. We have submitted to PLOS ONE and are awaiting a trial ID before it can move ahead to the next stage of review.

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/03/2016	17/05/2023	Yes	No