A single blind, randomized, cross-over placebo controlled dose finding study to investigate the pharmacokinetic profile of 3 doses of sublingual testosterone solution and their effect on physiological and subjective arousal in healthy, sexually functional premenopausal women.

Published: 16-03-2010
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Primary objectives:To establish the lowest effective dose using physiological and subjective measures of sexual arousal.To evaluate and compare the pharmacokinetics of testosterone and its metabolites following administration of three (3) doses (0....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual function and fertility disorders
Study type	Observational invasive

Summary

ID

NL-OMON34880

Source
ToetsingOnline

Brief title
PK-PD testosterone

Condition

- Sexual function and fertility disorders

Synonym
Female Sexual Dysfunction; Hypoactive Sexual Desire Disorder; decreased libido

Research involving
Human

Sponsors and support

Primary sponsor: Emotional Brain BV
Source(s) of monetary or material Support: Emotional Brain BV (sponsor)

Intervention

Keyword: pharmacokinetics, physiological sexual arousal, subjective sexual arousal, testosterone

Outcome measures

Primary outcome

Primary pharmacodynamic endpoints

• Vaginal Pulse Amplitude (VPA): difference between pre- and post dose relative increases to erotic stimuli (as compared to neutral stimuli) between treatments (placebo vs. 0.25, 0.50 mg. & 0.75 mg; 0.50 mg. vs. 0.75 mg).

• SARSAQ questionnaire: difference between pre- and post dose increases to erotic stimuli (as compared to neutral stimuli) between treatments (placebo vs. 0.25, 0.50 mg. & 0.75 mg; 0.50 mg. vs. 0.75 mg).

Primary pharmacokinetic endpoints (total and free testosterone)

• Maximum concentration (Cmax): difference between treatments (0.25 vs. 0.50 mg. vs. 0.75 mg).

• Area under the curve (AUC0-240): difference between treatments (0.25 vs. 0.50 mg. vs. 0.75 mg).

• Time to Cmax (Tmax): difference between treatments (0.25 vs. 0.50 mg. vs.

0.75 mg).

Secondary outcome

Secondary pharmacodynamic endpoints

• VPA: difference between different post dose measurement times (150 min vs.

240 min. vs. 330 min) in primary pharmacodynamic endpoints.

• SARSAQ questionnaire: difference between different post dose measurement

times (150 min vs. 240 min. vs. 330 min) in primary pharmacodynamic endpoints.

• Clitoral Blood Volume (CBV): as VPA described in primary & secondary

endpoints.

Secondary pharmacokinetic endpoints

• Cmax of dihydrotestosterone, estradiol, 3-alpha androstanediol glucuronide &

3-alpha androstanediol: difference between treatments (0.25 vs. 0.50 mg. vs.

0.75 mg).

Study description

Background summary

An important aspect of sexual motivation is physiological sexual responding. Measured as an increase in vaginal vasocongestion and clitoral blood volume (Gerritsen et al.,2009) elicited by sexual stimuli, this responding is considered to be preparatory for copulatory behavior (Tuiten et al., 1996). In hypogonadotropic, hypogonadal females we found that substitution with testosterone undecanoate 40 mg orally per day during an 8-week period enhanced vaginal responsiveness (Tuiten et al., 1996). This effect was not found in another group of hypogonadotropic hypogonadal patients (unpublished data). In both studies subjects received testosterone each morning, but patients in the first experiment were tested in the afternoon and patients in the second experiment in the morning. The different outcomes on physiological responding between these experiments may be caused by a time dependent effect of

testosterone on vaginal arousal. Further, we examined whether administration of a single dose of 0.5 mg testosterone sublingually, as compared with placebo, increases vasocongestion during presentation of visual erotic stimuli (Tuiten et al., 2000). On treatment days we exposed eight sexually functional women with intervals of an hour and a half, to six erotic films depicting intercourse. After 0.5 mg testosterone administration, plasma levels of testosterone peaked in the first post dose plasma sample 15 minutes and then fell, reaching baseline levels after 2-3 hours. About three to four and a half hours after this testosterone peak, we found a striking increase in vaginal responsiveness when the subjects were exposed to the visual sexual stimuli. These findings demonstrate a time lag in the effect of sublingually administered testosterone on genital arousal in sexually functional women. This study was replicated 2 years later with the same results (Tuiten et al., 2002). In a study investigating the pharmacokinetics of aerosol delivery of 0.1, 0.2 and 0.3 mg testosterone it was shown that plasma levels of testosterone peaked at 3 minutes after drug delivery (Davison et al., 2005). The route of administration in this study differs from our sublingual method, but it gives reason to assume that the peak in plasma testosterone concentration as found in our own study, may have fallen well before the first post dose measurement point (15 minutes).

The results of the above mentioned studies demonstrate that testosterone is involved in female sexual motivation in a time dependent fashion, and that this pharmacodynamic effect on sexual motivation does not coincide with the timing of the pharmacokinetics of testosterone administration (as was already concluded by Tuiten et al., 2000).

This research proposal describes a pharmacokinetic-pharmacodynamic study of which the main goal is to establish the lowest effective dose of testosterone sublingual in premenopausal sexually healthy women using physiological and subjective measures of sexual arousal. Also, it is directed at evaluating and comparing the pharmacokinetics of testosterone and its metabolites following administration of three single doses of testosterone sublingual (0.25, 0.50 and 0.75 mg).

Study objective

Primary objectives:
To establish the lowest effective dose using physiological and subjective measures of sexual arousal.
To evaluate and compare the pharmacokinetics of testosterone and its metabolites following administration of three (3) doses (0.25, 0.50 & 0.75 mg) of testosterone sublingual.

Secondary objective:
To investigate the effect of three (3) different doses (0.25, 0.50 & 0.75 mg) of testosterone sublingual on the duration of increased physiological and

subjective measures of sexual arousal.

Study design

This is a single-center, single-blind, randomized, cross-over placebo controlled dose-finding study with three (3) doses of testosterone administered sublingually and placebo.
A total of 16 subjects receive each investigational drug dose once in random order, so that 4 subjects will start at the 0.25mg dose, 4 at the 0.5mg dose, 4 at the 0.75mg dose and 4 on placebo. Wash-out between treatments will be at least 48 hours. Baseline assessments will be performed each experimental day before each dosing. Pharmacokinetic and pharmacodynamic (physiological and subjective measures of sexual arousal) assessments will be performed at pre-determined time points. Subjects visit the site a total of 6 times: 1 day screening (V0), 4 experimental days and 1 follow up visit. During all visits the subject*s health will be monitored.

Study burden and risks

HIV, hepatitis and pregnancy are determined during screening (pregnancy at eacht visit). A positive result on each of these 3 may have a negative impact on the subjects. Subjects are warned of this risk beforehand. Blood drawing may give rise to hematomas. Testosterone administration as used in the present study may give rise to mild decreases in blood pressure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of written informed consent;
2. Female 21-40 years of age without sexual dysfunction;
3. Healthy according to normal results of medical history, physical examination, laboratory values and vital signs, unless the investigator considers an abnormality to be clinically relevant;
4. Subject must be heterosexually oriented;
5. Venous access sufficient to allow blood sampling as per protocol.

Exclusion criteria

1 Subjects who had used testosterone therapy within 6 months before study entry;
2 Use of oral contraception containing anti-androgens (e.g. Diane 35; Minerva);
3 Use of oral contraception containing 50 µg estrogen or more;
4 Pregnancy, or intention to become pregnant during this study (Note: a serum or urine pregnancy test will be performed in all women prior to the administration of study medications);
5 Lactating, or subjects who have given birth in the previous 6 months;
6 Subjects who are taking CYP3A4-inhibitors: ritonavir (HIV-proteaseremmer), ketoconazol en itraconazol claritromycine, erytromycine and saquinavir;
7 Subjects who are taking CYP3A4-inducers: carbamazepine, fenytoïne, fenobarbital, st Johns Wort, rifampicine;
8 A substance abuse disorder that in the opinion of the investigator is likely to affect the subject's ability to complete the study or precludes the subject*s participation in the study; mild or moderately alcohol drinking behavior is allowed, only 12 hours before the experimental days is alcohol drinking not allowed. Three weeks before the start of the experimental day is the taking of any recreational drug not allowed. Smoking is allowed.
9 Subjects with a peri menopausal hormonal status (FSH > 30).

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-06-2010
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	testosterone
Generic name:	testosterone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-03-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-05-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-019285-86-NL
CCMO	NL31864.040.10