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

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To compare the pharmacokinetics of sublingual testosterone cyclodextrin followed by buspirone as an encapsulated tablet with administration of testosterone and buspirone as one tablet designed to release the components in a specific time-frame.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual dysfunctions, disturbances and gender identity disorders
Study type	Interventional

Summary

ID

NL-OMON37493

Source
ToetsingOnline

Brief title
PK-Lybridos Formulation 1 and 2

Condition

- Sexual dysfunctions, disturbances and gender identity disorders

Synonym
problems with sexal functioning, Sexual dysfunction

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Buspirone, Combination tablet, Testosterone

Outcome measures

Primary outcome

• Cmax of total testosterone (F2 >= 75% of Cmax F1);

• Cmax of free testosterone (F2 >= 75% of Cmax F1);

• Cmax of buspirone (F2 >= 75% of Cmax F1);

• AUC0-1590 of total testosterone (F2 >= 75% of AUC0-1590 F1);

• AUC0-1590 of free testosterone (F2 >= 75% of AUC0-1590 F1);

• AUC0-infinity of buspirone (F2 >= 75% of AUC0-infinity F1);

Secondary outcome

To investigate the time frame in which the mint flavored testosterone coating

is dissolved.

Study description

Background summary

Lybridos (0.5 mg testosterone + 10 mg buspirone) is under development by

Emotional Brain BV as an on-demand treatment for (the subset of) women with hypoactive sexual desire disorder (HSDD) characterized by maladaptive activity of sexual inhibitory systems. Lybridos is intended for use on a per need (i.e., not continuous) basis before proposed sexual activity. The cause of maladaptive activity of sexual inhibitory systems is not well elucidated, but both physiological and psychological factors are believed to be involved. Thus a combined treatment targeting the motivational sensitivity for sexual stimuli (testosterone) and enhancing a potential genital sexual response by decreasing possible inhibitory factors (buspirone) may increase genital arousal, as well as the frequency and quality of sexual encounters.

Our previous studies have shown that women with HSDD can be subdivided on the base of their pre-attentional bias for sexual stimuli (1,2). Although these women may be diagnosed with Female Sexual Dysfunction (FSD) according to the Diagnostic and Statistical Manual of Mental disorders, fourth edition (text revision) (DSM IV-TR), they appear to process sexual stimuli differently. When women with low sensitivity for sexual cues receive testosterone, alterations in pre-attentional bias for sexual stimuli occur, which could be an important condition for the induction of sexual motivation and sexual desire. Several studies have demonstrated that for women suffering from HSDD whose low initial sensitivity to sexual cues was boosted by sublingual testosterone, the combination of testosterone and a PDE-5 inhibitor (Lybrido) induced higher levels of vaginal blood flow when exposed to sexual stimuli (1,2), coupled with subjective reports of more intense genital sensations and sexual lust (1). It was also shown that neither testosterone nor a PDE-5 inhibitor produced these effects in women with HSDD when administered separately (1,2). In these same studies, subjects who did show an increased pre-attentional bias for sexual stimuli before testosterone administration, showed a decrease in pre-attentional bias after testosterone administration. Since these women showed no increase in vaginal blood flow or subjective reports of genital sensations in any of the drug conditions, and because most of them had a history of negative sexual experiences, it was hypothesized that this group suffered from maladaptive activity of sexual inhibitory systems. Acute 5HT1a agonism decreases serotonergic activity (3,4), an important mediator of inhibitory mechanisms (5). It was postulated that these individuals might benefit from the inhibition of these inhibitory mechanisms through acute 5HT1a agonism, especially in conjunction with testosterone-induced intensified sexual stimulation. In a study investigating the efficacy of the combination of testosterone and a PDE-5 inhibitor and of the combination of testosterone and a 5HT1a agonist it was indeed shown that women with HSDD who did not respond to the combination of testosterone and a PDE-5 inhibitor, responded positively to the combination of testosterone and a 5HT1a agonist (Lybridos), as measured by event logs and week diaries pertaining to their sexual activities at home (Tuiten et al., 2011 in preparation).

Sublingually administered testosterone (0.5mg) has been shown to have a delay in effect of about 4 hours on subjective and peripheral sexual arousal (6,7) in

sexually functional women, but not in women with HSDD (1,2). If this central effect of testosterone administration is coupled with the use of buspirone, an increase in subjective and peripheral sexual arousal may be observed in women with HSDD. However, the peak effect of buspirone must coincide with the peak effect of the 4 hour delay effect of testosterone. So for buspirone (Tmax approx. 60 minutes), one would have to administer the sublingual testosterone first, and after 2-3 hours the buspirone.

In the above reviewed clinical studies, 0.5 mg testosterone was administered sublingually as a solution, followed 2.5 hours later by a 10 mg buspirone tablet, thus creating overlapping peaks in effect of testosterone and buspirone. Because compliance to this method of administration requires accurate and thorough instructions, Emotional Brain has recently developed a combination tablet that will deliver testosterone (0.5 mg) sublingually and, 2.5 hours later, 10 mg buspirone hydrochloride. This will allow women with HSDD to take just one single preparation 3-6 hours before anticipated sexual activity.
This new developed drug product is a menthol flavored white tablet of 9 mm in diameter employing two routes of administration; sublingual and oral. First, 90 seconds sublingual administration which is then followed by the swallowing of the intact remainder of the tablet. The quickly dissolving outer coating will deliver testosterone (0.5 mg) sublingually, and the time-delayed release core will deliver buspirone (10 mg) 2.5 hours later. The outer coating comprises testosterone and a menthol flavor, so when the menthol flavor is gone (estimated to be around 30 sec), the testosterone is fully dissolved and maximally available for absorption via the mucosal membranes. The buspirone hydrochloride tablets as used in previous studies is an immediate release compound. Thus, the present time-delayed-release core containing the buspirone has been designed to release the buspirone all at once, 2 * hours after oral administration (buspirone dump should fall in the specified window of 2-3 hours). This method of release is accomplished through the use of a polymer coating of ethylcellulose which slowly permeates water in a pH independent manner. The buspirone core swells due to the water absorption and this increase in size leads to the rupture of the polymer coating, dumping all of the buspirone at once, after approximately 2 * hours. This combination tablet has thus been designed to mimic the pharmacokinetic (and thus also the pharmacodynamic) properties of the separate administration of the testosterone solution and the buspirone tablet 2 * hours later.

The present study is part of the ongoing drug development program for Lybridos. This research proposal describes a pharmacokinetic study of which the main goal is to compare the pharmacokinetics of testosterone and buspirone following administration of a sublingual solution of testosterone with an encapsulated tablet, versus the newly developed combination product.
The purpose of this study is not to determine bioequivalence, but to explore the pharmacokinetic profiles of both administration methods.

Study objective

To compare the pharmacokinetics of sublingual testosterone cyclodextrin followed by buspirone as an encapsulated tablet with administration of testosterone and buspirone as one tablet designed to release the components in a specific time-frame.

Study design

Randomized, crossover, controlled pharmacokinetic study with 2 pharmaceutical formulations containing testosterone and buspirone; wash-out between treatments will be at least 7 days. Blood sampling for pharmacokinetic measurements will be performed at predetermined time points.

Intervention

Two interventions will be performed on all participants:

1. Testosterone (0.5 mg) cyclodextrin administered sublingually as a solution, followed 2.5 hours later by an encapsulated tablet containing 10 mg buspirone HCl.

2. A fixed-combination tablet consisting of an inner-core component of 10 mg buspirone HCl, and a polymeric coating of 0.5 mg testosterone; this formula is designed to release the inner-core buspirone at about 2.5 hours after tablet intake. After this time delay of 2.5 hours, the buspirone is released immediately, rather than being released in a sustained mode. The coated buspirone core tablet is film-coated with an additional, immediately dissolving, polymeric, testosterone coating that releases 0.5 mg testosterone sublingually within 90 seconds. The tablets need to be in the mouth sublingually for 90 seconds after which the tablet is swallowed as a whole, without chewing or disrupting the dosage form.

Study burden and risks

The main adverse reactions to exogenous androgens given chronically in physiological to slightly supraphysiological concentrations are androgenic side effects, primarily hirsutism and acne. We consider it to be highly unlikely that testosterone administration in the doses and frequency to be used in this study will give rise to any serious health risks. In our previous studies, no serious health risks/adverse reactions were observed. Within 15 minutes of testosterone (0.5 mg, sublingually) intake plasma testosterone concentration increased 10-fold, and returned to baseline levels within 150 minutes.(Tuiten et al., 2000, van Rooij et al., in preparation). Testosterone is administered over two admission periods with a 7 day wash-out between the admission periods. The dosing regime regarding testosterone is therefore considered to be safe.

The combined use of sublingual testosterone and buspirone is considered safe because buspirone efficacy is not influenced when testosterone is given concomitantly. Moreover, the dose of buspirone in one dose of Lybridos is at most two thirds of the starting daily dose and less than a half (2/5) of the lightest weekly dose of buspirone prescribed for use as an anxiolytic drug. A previous home study (EB70) showed that Lybridos is well tolerated on long term, see the Investigator*s Brochure for Lybridos for additional information.

Data on the effect of buspirone and testosterone on oral contraceptives is lacking. For this reason, participants on oral contraceptives will be instructed to use a second anti-conception method (double barrier). All participants will be instructed not to become pregnant during the study.

Clinically relevant abnormalities in ECG and chemistry may be noticed, in which case a medical specialist may be asked for advice, upon decision of the research team. If the specialist confirms that medical treatment is necessary, the participant*s GP physician will be informed. This procedure is mandatory and explained to the subject in the Informed Consent form.

Contacts

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Selecteer

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Scientific
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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 18-35 years of age (inclusive)
3. Healthy based on medical history, physical examination, laboratory values and vital signs
4. Body mass index (BMI) >= 18 kg/m2 and <= 30 kg/m2
5. Venous access sufficient to allow blood sampling as per protocol

Exclusion criteria

Cardiovascular conditions
1. Any underlying cardiovascular condition, including unstable angina pectoris
2. Systolic blood pressure >= 140 mmHg and/or diastolic blood pressure >= 90 mmHg.
3. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure <50 mmHg;Gynecological and obstetric conditions
4. Use of oral contraceptive containing anti-androgens (e.g. Crypteron acetate) or (anti) androgenic progesteron (drospirone, dienogest, chlormadinone acetate and norgestrel)
5. Use of oral contraceptive containing 50 µg estrogen or more
6. Pregnancy or intention to become pregnant during this study (Note: An urine pregnancy test will be performed in all women prior to the administration of study medications.)
7. Lactating or delivery in the previous 6 months
8. Unexplained gynecological complaints, such as clinically relevant abnormal uterine bleeding patterns
9. Subjects with a perimenopausal hormonal status (follicle-stimulating hormone>30);Other medical conditions
10. Liver- and/or renal insufficiency
11. Current clinically relevant endocrine disease
12. Current clinically relevant neurological disease which, in the opinion of investigator, would compromise the validity of study results, or which could form a contraindication for buspirone and/or testosterone use
13. (A history of) hormone-dependant malignancy;Psychological/psychiatric factors
14. 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 moderate alcohol consumption is allowed but must be stopped 24 hours before the admission period. Recreational drug use is not allowed beginning 3 weeks before the start of the admission period until follow up. Smokers are not allowed to participate.;Concomitant medication
15. Subjects who are taking CYP3A4-inhibitors (eg, ritonavir, ketoconazol, itraconazol

claritromycine, erytromycine and saquinavir)
16. Subjects who are taking CYP3A4-inducers (eg, fenytoïne, fenobarbital, st Johns Wort, rifampicine)
17. Use of serotonergic drugs (eg, trazodon, fluvoxamine)
18. Use of testosterone therapy within 6 months before study entry
19. Use of any other medication that interferes with study medication (eg, monoamine oxidase (MAO) inhibitors (includes classic MAO inhibitors and linezolid), calcium channel blockers (eg, diltiazem and verapamil), use of corticosteroids);Drug/food interaction
20. Consumption of grapefruit or grapefruit-containing foods throughout the duration of the study;General
21. Illiteracy, unwillingness, or inability to follow study procedures
22. Any other clinically significant abnormality or condition which, in the opinion of investigator, might interfere with the participant*s ability to provide informed consent or comply with study instructions, compromise the validity of study results, or be a contraindication for buspirone and/or testosterone use.
23. Participation in any other clinical drug study in the previous 3 months.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-07-2012
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	buspar

Generic name:	buspirone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Lybridos fixed-combination tablet
Generic name:	Lybridos fixed-combination tablet
Product type:	Medicine
Brand name:	testosterone
Generic name:	testosterone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2011-003700-20-NL
CCMO	NL37775.056.12