Psychoneuroendocrinology (2013) 38, 171—178

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Pharmacokinetics of testosterone and estradiol gel preparations in healthy young men

Christoph Eisenegger [a,*], Arnold von Eckardstein [b], Ernst Fehr [c], Sigrid von Eckardstein [d]

[a] *Behavioral and Clinical Neuroscience Institute, Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, United Kingdom*
[b] *Institute of Clinical Chemistry, University Hospital Zürich, Raemistr. 100, 8091 Zürich, Switzerland*
[c] *Department of Economics, Laboratory for Social and Neural Systems Research, University of Zurich, Blümlisalpstrasse 10, 8006 Zurich, Switzerland*
[d] *Department of Gynecology, Kantonsspital Luzern, 6000 Luzern 16, Switzerland*

Received 4 February 2012; received in revised form 25 May 2012; accepted 25 May 2012

KEYWORDS
Behavioral endocrinology;
Pharmacokinetics;
Testosterone;
Estradiol;
Gel

Summary The paucity of pharmacokinetic data on testosterone gel formulations and absence of such data on estradiol administration in healthy young men constitutes a fundamental gap of knowledge in behavioral endocrinological research. We addressed this issue in a double-blind and placebo controlled study in which we applied a topical gel containing either 150 mg of testosterone (N = 10), 2 mg of estradiol (N = 8) or a respective placebo (N = 10) to 28 healthy young men. We then assessed serum concentrations of estradiol and testosterone in one hour intervals up to seven hours after drug application, measured LH, SHBG and cortisol levels once at baseline and three, four as well as six hours after gel administration. Treatment with testosterone gel resulted in maximum total serum testosterone concentration three hours after administration and did not suppress LH, cortisol and SHBG levels at any time point. Administration of estradiol gel led to maximum estradiol serum concentration two hours after administration. There was no suppression of cortisol, SHBG and absolute LH levels. We report here, for the first time, pharmacokinetic data on both high dose testosterone and estradiol gel application in healthy young males. The proposed model will assist in the design of future studies that seek to establish causality between testosterone and estradiol gel administration and behavioral as well as neurophysiological effects.

1. Introduction

The medical use of sex hormone preparations has a long history and is clinically well established. Testosterone is administered as a treatment of the hypogonadal state in young and aging men (Wang et al., 2004), and is investigated

* Corresponding author. Tel.: +44 7402233698.
E-mail address: christoph.eisenegger@gmail.com (C. Eisenegger).

0306-4530/$ — see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2012.05.018

as a hormonal male contraceptive (Nieschlag, 2010). Estradiol administration plays a similar role in women, who use ''the pill'' worldwide on a daily basis as a contraceptive. The wide-spread use of sex hormones by the general public bears the obvious question whether there may be behavioral changes associated with their administration.

So far, a relatively large number of studies have investigated acute single-dose testosterone effects on emotion processing and social interaction and its neural correlates in healthy subjects, but these studies were performed in females exclusively (Eisenegger et al., 2011; Bos et al., 2012). Thus, an important question is whether behavioral effects following testosterone administration observed in females can be extended to males.

The well known fact that testosterone is aromatized to estradiol could raise the question whether behavioral effects of exogenously administered testosterone are in fact mostly estradiol effects. Despite this, there are surprisingly few experimental studies available that administered estradiol, and these were conducted in healthy females (Schleifer et al., 2002; Kaya et al., 2003). Thus, whether and how estradiol administration influences behavior of healthy males is unknown.

The study of the behavioral effects of exogenously applied sex hormones requires considering a number of methodological issues. First, the knowledge of the precise pharmacokinetics after an acute single dose is necessary to allow assessing the optimal time-point for behavioral testing. Second, these pharmacokinetic data should be collected in healthy subjects who have similar anthropometric characteristics [such as for example body mass index (Kornmann et al., 2009)] and educational background as those subjects who are typically studied in behavioral endocrinological experiments. Third, hormone application should be non-invasive. Injectable preparations might reduce the willingness of volunteers to participate in the study and thereby introduce a selection bias or induce psychological stress possibly interfering with the behavioral response. Finally, as there are sensitive negative feed-back loops within the male neuroendocrine system, exogenous application of high doses of testosterone might cause secondary effects, such as suppression of pituitary hormones, especially of luteinizing hormone (LH) (Wang et al., 1998), and/or adrenal hormones (cortisol) (Viau, 2002).

Therefore, a clean model for investigating behavioral effects of sex hormone administration in males consists of pharmacological preparations with a relatively short half-live at a dose that minimizes feedback effects. The two most important non-invasive ways of administering hormones is the oral and the trans-dermal route. Among these two, the trans-dermal route has the advantage that the increase in circulating hormones can be confirmed relatively easily, in each individual, using saliva sampling. Salivary concentrations correlate well with the ones obtained from serum measurements (Riad-Fahmy et al., 1982, 1987; Granger et al., 2004). However, as oral administration would confound salivary measures, the trans-dermal route is superior for large scale behavioral endocrinological studies.

In sum, a hormone preparation that fulfills the above criteria is the administration of a topical gel which can be applied to chest and upper arms of the body. However, to date, there are no studies available that addressed the pharmacokinetics of high dose testosterone and estradiol gels in healthy male subjects. We therefore performed a pharmacokinetic trial of a single dose of a gel containing 150 mg of testosterone (Androgel), 2 mg of estradiol (Divigel), or a placebo gel in healthy young males. We determined sex hormone concentrations, pituitary as well as adrenal hormones at different time-points following gel application. As many of these fundamental endocrine parameters can only be assessed in blood serum, we use blood draws to establish the pharmacokinetic profile of the two gels.

2. Methods

2.1. Subjects and study design

28 Healthy young males were enrolled and randomized for our double-blind, parallel-groups and placebo controlled experiment that had been approved by the local ethics committee of the Kanton Zürich, Switzerland and the federal board for medications ''Swissmedic'', Bern, Switzerland. Subjects had been recruited from press advertisement and the volunteers database of the Economics Department at the University of Zürich, Switzerland. General health status was evaluated by medical history, physical and genital examination. Abnormal findings as well as clinical signs of hypogonadism or use of any hormones within 8 weeks prior to study entry served as an exclusion criterion. Subjects provided written informed consent and were then included in the study.

2.2. Procedure

Prior to application of study medication, body weight and height were determined and a blood sample for measuring baseline hormones of the male pituitary—testicular axis [LH, testosterone, estradiol, sex-hormone-binding globuline (SHBG)] and cortisol was taken. All baseline examinations were performed between 0800 and 1000 h. Volunteers were then allocated to one of three treatment groups in a double-blind, randomized manner.

Blood samples for determination of estradiol and testosterone were taken in one hour intervals after drug application up to seven hours post administration. LH, SHBG and cortisol measurements were taken once at baseline and repeated after three and four hours, when maximum testosterone and estradiol levels were expected [see Chik et al., 2006]. The last measurement was taken towards the study end (after six hours).

2.3. Hormone preparations

Group A received a single dose of testosterone gel, containing 150 mg testosterone [Androgel®, Bayer (Schweiz) AG, Zürich, Switzerland]. Group B received one single dose of estradiol gel, containing 2 mg of estradiol (Divigel®, Orion Pharma AG, Zug, Switzerland). Group C received a placebo gel. All gels were applied to shoulders and upper arms by a single person of the study personnel, who was not further involved in the clinical part of the study.