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Sleep after intranasal progesterone vs. zolpidem and placebo in postmenopausal women – A randomized, double-blind cross over study

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ABSTRACT

Context: The loss of progesterone during menopause is linked to sleep complaints of the affected women. Previously we demonstrated sleep promoting effects of oral progesterone replacement in postmenopausal women. The oral administration of progesterone, however, is compromised by individual differences in bioavailability and metabolism of the steroid.
Objective: We compared the sleep-endocrine effects after intranasal progesterone (MPP22), zolpidem and placebo in healthy postmenopausal women.
Design: This was a randomized double-blind cross-over study.
Setting: German monocentric study
Participants: Participants were 12 healthy postmenopausal women.
Interventions: Subjects received in randomized order four treatments, 2 doses of intranasal progesterone (4.5 mg and 9 mg of MPP22), 10 mg of zolpidem and placebo.
Outcome measures: Main outcome were conventional and quantitative sleep-EEG variables. Secondary outcomes were the subjective sleep variables and the sleep related concentrations of cortisol, growth hormone (GH), melatonin and progesterone.
Results: Sleep promoting effects were found after the higher dosage of MPP22 and after zolpidem. Zolpidem prompted benzodiazepine-like effects on quantitative sleep EEG as expected, whereas no such changes were found after the two dosages of MP22. Nocturnal progesterone levels increased after 9.0 mg MPP22. No other changes of hormone secretion were found.
Conclusions: Our study shows sleep promoting effects after intranasal progesterone. The spectral signature of intranasal progesterone did not resemble the sleep-EEG alterations induced by GABA active compounds. Progesterone levels were elevated after 9.0 mg MPP22. No other endocrine effects were observed.

1. Introduction

The hypnotic effect of progesterone is documented by preclinical and human studies. In cats after administration of progesterone into the frontal cortex total sleep time increased (Heuser et al., 1967). Intraperitoneal progesterone administration induced at dose-dependent decrease of wakefulness in rats (Lancel et al., 1996). After oral administration of progesterone to young healthy male subjects non-REM sleep and spectral power of the higher frequency range in quantitative EEG analysis increased, whereas slower activity decreased (Friess et al., 1997). During early pregnancy progesterone plasma levels increase. It is thought that this change prompts tiredness in pregnancy (Lancel et al., 1996; Driver and Baker, 1998). The menopausal transition is discussed to contribute to impaired sleep (Moline et al., 2003; Dzaja et al., 2005; NIH State-of-the-Science Statements, 2005; Polo-Kantola, 2011) and is characterized by loss of both estrogens and progesterone. Estradiol is also known to promote sleep in animals. In the ovariectomized marmoset estradiol replacement prompted higher EEG delta power pointing to improved sleep intensity (Gervais et al., 2016). Sleep homeostasis was investigated during the estrous cycle of the rat. In the light period

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slow wave sleep activity exhibited high values (Schwierin et al., 1998). In postmenopausal women estrogen replacement therapy induced normalization of sleep-EEG pattern (Antonijevic et al., 2000). Progesterone restored normal sleep in postmenopausal women when sleep was disturbed (Caufriez et al., 2011). In a previous study (Schüssler et al., 2008) we investigated in a randomized double blind cross over design with two treatment intervals of 21 days the effects of a daily oral dose of 300 mg micronized progesterone in healthy post-menopausal women. After progesterone intermittent time spent awake decreased. During the first third of the night rapid eye movement (REM) sleep increased. No significant changes of EEG power spectra were observed. In contrast to oral medication intranasal administration circumvents the intestines and liver (Ducharme et al., 2010) and is an effective method to modulate brain activity (Dhuria et al., 2010; Fréchou et al., 2015). The intranasal route of administration delivered in mice progesterone to blood and brain (Ducharme et al., 2010). Progesterone and GABA A-active substances were reported to modulate nocturnal growth hormone (GH) and melatonin secretion (Caufriez et al., 2011 Hajak et al., 1996; Morera et al., 2009). After diazepam cortisol decreases (Pomara et al., 2005). The effect of intranasal progesterone administration on progesterone plasma levels in humans is unknown.

The objective of our study was to compare the effects of intranasal administration of two dosages of progesterone (MPP22), placebo and of oral administration of the hypnotic zolpidem on sleep EEG, subjective sleep. and on sleep related hormone secretion of cortisol, growth hormone (GH), melatonin and progesterone.

1.1. Trial design

This was a monocentric, randomized, placebo and comparator controlled cross over-study with double dummy conducted at the Max-Planck-Institute of Psychiatry, Munich, Germany. The study is registered with EudraCT number. 2009-013051-30.

1.2. Participants

The subjects consisted of 12 healthy paid postmenopausal women (mean age ± S.D.: 59.6 ± 1.3 years, range 52–67, range of body mass index between 18.97-28.15 kg/m^2). Eleven women were naturally and 1 woman was surgically postmenopausal since at least 4–23 years. Follicular stimulating hormone plasma concentration (FSH) was in a range between 43.2 and 111.7 mU/ml reflecting the postmenopausal status. The subjects were recruited by newspaper advertisement and did not report poor sleep quality as motivation to participate in this trial. All subjects did not take any medicine including hormone replacement therapy for at least 3 months and entered the study after passing rigid psychiatric, physical (including gynecologic and rhinal) and laboratory examinations. Reasons for exclusion from the study were: major chronic diseases (e.g. diabetes, heart failure, hepatitis), previous chronic neurological or psychiatric disorder in the own or family history, stressful life events, a transmeridian flight during the past 3 months, shift work, aberrancies in the blood chemistry or in the waking EEG or electrocardiogram. All subject underwent a polysomnographic examination in the sleep laboratory to exclude sleep disorders including sleep related respiratory disorders (e.g. sleep apnea) and sleep related movement disorders (e.g. restless legs syndrome). Other exclusion factors were abuse of drugs, nicotine (more than five cigarettes per day), alcohol, and caffeine. Caffeine was restricted to 200 ml coffee in the morning.

The experiment was approved by the Ethics Committee of the Faculty of Medicine of the University of Munich. After the purpose of the study had been explained to the subjects, all of gave their written informed consent according to the tents of the declaration of Helsinki.

1.3. Interventions

The study was performed between June 2010 and December 2012 in our sleep laboratory with four sessions separated by at least one week, maximum 14 days. Each session consisted of two nights in the sleep laboratory, one adaptation and one study night. During study nights, the following medications were administered according to randomized schedule:

A.) 4.5 mg MPP 22 intranasally and placebo orally (p.o.)
B.) 9.0 mg MPP 22 intranasally and placebo p.o
C.) Placebo intranasally and 10 mg zolpidem p.o.
D.) Placebo intranasally and placebo p.o.

The study medication was obtained by M et P Pharma AG, Emmetten, Switzerland. MPP 22 is a proprietary formulation for intranasal application containing natural progesterone, intranasal placebo is the matrix of MPP 22 without active ingredient. 9.0 mg MPP 22 was the certified maximum dose available at the time of beginning the study. Oral zolpidem (Stilnox®, immediate release) and oral placebo were blinded by encapsulating them into identical capsules.

All subjects were administered either treatment A, B, C or D once in accordance with the randomisation schedule during each of the four study nights, respectively. For intranasal application MPP22 dose was divided into two equal halves in 2 containers, i.e. 2 × 2.25 mg, 2 × 4.5 mg or 2 x placebo, respectively and administered to the left and to the right nostril. The test substances were given intranasally at 22.05 and orally at 22.55. The gap between the each study period was at minimum 7 days to maximum 14 days.

1.4. Outcomes

Primary outcome were the conventional sleep-EEG variables total sleep time (TST), sleep period time (SPT), sleep efficiency index (SEI), sleep onset latency (SOL), amount of wake after sleep onset (WASO), the time spent in the various sleep stages and the power spectra derived from quantitative sleep-EEG.For definitions see 2.3.2. Secondary variables were subjective sleep variables and nocturnal hormone secretion. These variables were assessed by the following methods.

1.4.1. Sleep EEG recordings

Electrodes for polysomnographic recordings (Comlab 32 Digital Sleep Lab, Brain Lab V3.3 Software, Schwarzer GmbH Munich, Germany) were fixed between 21.00 h and 22.00 h. Subjects were not allowed to sleep until the lights were turned off at 23.00 h. Polysomnographic recordings were performed from 23.00 h to 07.00 h according to the international 10–20 electrode system (F3, F4; C3, C4, P3, P4, O1 and O2, all referenced against the contralateral ear lobe), with an electrooculogram and a chin electromyogram. The sampling rate for EEG channels was 250 Hz with a band-pass filter from 0.53–70 Hz.

1.4.2. Analysis of conventional sleep EEG parameters

Related to two EEG channels (C3-A2, C4-A1), EOG and EMG, sleep stages (awake, Stage 1–4 sleep [stage 3 and 4 mean slow wave sleep, SWS] and rapid eyemovement sleep (REM) were scored visually according to the standard guidelines by Rechtschaffen and Kales (1968). The raters were unaware of the treatment for all consecutive thirty-second intervals (epochs) from 23.00h-07.00 h. Sleep continuity parameters referred to TST (total time spent in REM and NonREM sleep during sleep period time), SPT (time between sleep onset and final awakening in the morning), SEI (sleep period time divided by time in bed), SOL (time between lights off and the first occurrence of stage 2 sleep), WASO (time spent awake after sleep onset until end of bedtime) and the time spent in different sleep stages. Sleep-EEG parameters were analyzed for SPT, as well as for the night half and the night thirds (time interval 23.00h-07.00 h)