Sodium Oxybate for the Treatment of Vigilance Impairment in Narcolepsy

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Core:1. Quantify vigilance using a portable task battery three times daily during 7 days while subjects are outside the hospital 1.1 Comparing narcoleptic patients to controls 1.2 Comparing narcoleptic patients before and after treatment with sodium...

Ethical review	Approved WMO
Status	Pending
Health condition type	Sleep disturbances (incl subtypes)
Study type	Observational non invasive

Summary

ID

NL-OMON30579

Source
ToetsingOnline

Brief title
Sodium Oxybate and Vigilance in Narcolepsy

Condition

- Sleep disturbances (incl subtypes)

Synonym
Narcolepsy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: UCB Pharma

Intervention

Keyword: narcolepsy, skin temperature, sodium oxybate, vigilance

Outcome measures

Primary outcome

Core:

1. Is it feasible to measure vigilance using a portable task battery for seven days?

2. Can impaired vigilance in narcolepsy be detected when compared to healthy controls?

3. Does treatment with sodium oxybate in narcoleptics improve performance on this portable task battery?

4. Does stable treatment with sodium oxybate have an effect on activity levels as measured by wrist actigraph?

Optional Part 1:

1. Do narcoleptic patients have a different thermoregulatory profile during daily routine and during nocturnal sleep compared to controls.

2. Is the thermoregulatory profile in narcoleptic patients related to the occurrence of sleep attacks

3. Does treatment influence the thermoregulatory profile of narcoleptic patients during daily routine and nocturnal sleep.

Optional Part 2:

1. Does stable treatment with sodium oxybate have an effect on OSLER

sleep latency?

Secondary outcome

NVT

Study description

Background summary

Narcolepsy is a sleep-wake disorder characterized by excessive daytime sleepiness (EDS, tendency to fall asleep), disturbed night sleep, and rapid eye movement (REM) sleep-associated symptoms, such as hypnagogic hallucinations, sleep paralysis and cataplexy [AASM 2005, Bassetti and Aldrich 1996]. Cataplexy is a sudden bilateral loss of muscle tone provoked by strong emotions. The presence of EDS is mandatory for the diagnosis of narcolepsy. Impaired vigilance is an additional largely neglected symptom of narcolepsy that is directly related to reduced daytime performance and quality of life [Valley et al. 1981].

The Multiple Sleep Latency Tests (MSLT) and the Maintenance of Wakefulness Test (MWT) are the most common (however, cumbersome and not very specific) electrophysiological tests for the diagnosis of narcolepsy. The MSLT entails the measurement of sleep latency at five different times on one day while subjects are lying in bed in a quiet, dark room and asked to try to fall asleep. The MSLT thus assesses sleepiness. The MWT follows a similar schema, but subjects are requested to try to stay awake instead of trying to fall asleep. The MWT thus assesses the ability to remain awake. Vigilance impairment, on the other side, has been under valuated in the assessment of narcolepsy.

Recent studies suggest specific outcome measures (Sustained Attention to Response Task, SART; Psychomotor Vigilance Task, PVT) for vigilance assessment in narcolepsy [Fronczek et al. 2006, Khatami et al. submitted]. The SART and PVT are both tasks that assess vigilance by recording the subject*s responses to stimuli that are presented on a computer screen.

Sodium oxybate is a strong hypnotic that is effective in the treatment of EDS, disturbed night sleep, and cataplexy in narcolepsy [US Xyrem Multicenter Study Group 2002]. However, treatment effects on vigilance have not been evaluated thus far. In a recent study, changes in quality of life following the administration of sodium oxybate were measured with the Functional Outcomes of Sleep Questionnaire [Weaver 2006]. The nightly administration of sodium oxybate produced signi*cant dose-related improvements in the Total Functional Outcomes

of Sleep Questionnaire score, as well as in the Activity Level, General Productivity, Vigilance, and Social Outcomes subscales. Thus, the nocturnal administration of sodium oxybate in patients with narcolepsy was associated with statistically signi*cant and clinically relevant improvements in functional status, an important component of quality of life. Objective tests to measure vigilance, however, have not been applied.

An actigraph is a wrist-worn device that uses an accelerometer to measure motion. Sleep/inactivity and activity levels can thus be recorded with the extra help of sleep logs.

In this protocol, feasibility of measuring vigilance on seven days using portable versions of the PVT and the SART that can be administered while subjects are outside the hospital during normal daily, will be assessed in healthy controls and in narcoleptic patients. To objectively assess the effect of sodium oxybate, performance on this task battery will be compared before and after treatment in narcoleptic patients.

Optional Part 1:
In the field of sleep research, the relationship between skin temperature and sleep has recently received attention. Earlier laboratory studies with predefined sleep moments, showed a correlation between sleep latency and minimal changes in skin temperature. Healthy subjects whose distal skin temperature was relatively high compared to their proximal skin temperature, fell asleep faster (*warm hands and feet*). The distal-to-proximal gradient (DPG) is a measure for this thermoregulatory profile. A higher DPG is associated with a shorter sleep latency.

In a previous study we showed that the thermoregulatory profile of narcoleptic patients is continuously in a mode that is associated with sleep in healthy subjects, a *sleepy mode* (Fronczek et al, Sleep 2006). Moreover, specific manipulations of distal and proximal skin temperature and core body temperature can influence sleep latency, vigilance and nocturnal sleep (Fronczek et al, submitted). Measuring skin temperature in relationship to treatment efficacy may lead to new pathofysiological insights and a new way to measure sleepiness in narcolepsy.

In this new protocol we will study skin- and core body temperature in a non-clinical setting without fixed sleep moments. Thermoregulatory profiles and sleep-depth will be measured in both patients and controls for 24 hours.

Optional Part 2:
The OSLER test utilizes a computerized, non-assisted method for monitoring wakefulness and detecting sleep onset. The basic setting for the OSLER test is the same as for the MWT (dark room, patient sitting on the bed). The patient's dominant hand is placed on a box held in the lap. The index finger is positioned on a non-recoil proximity sensor, with a sensing distance of 1-2 mm,

transmitting finger contact to a computer. A light emitting diode (LED) is positioned 4 feet away at eye level in the frontal visual field. The light flashes regularly for 1 s every 3 s. Both the LED and hand device are connected to a personal computer located in the adjacent control room, which records the response data. The specific instructions given to each subject before the Osler test are to stay in contact with the finger to the button, and to remove the finger for 1 second when the red light flashes. The OSLER algorithm defines sleep onset when there is no response to seven consecutive flashes (>=18 s). Test ends after sleep onset or after 40 min if no sleep occurs.

Study objective

Core:

1. Quantify vigilance using a portable task battery three times daily during 7 days while subjects are outside the hospital
1.1 Comparing narcoleptic patients to controls
1.2 Comparing narcoleptic patients before and after treatment with sodium oxybate
2. Quantify activity levels using Actigraphy during 14 days while subjects are outside the hospital
2.1 Comparing narcoleptic patients to controls
2.2 Comparing narcoleptic patients before and after treatment with sodium oxybate

Optional Part 1:
1. Quantify distal and proximal skin and core body temperature using iButtons and a wireless core body temperature pill system while subjects are outside the hospital
1.1 Comparing narcoleptic patients to controls
1.2 Correlating thermoregulatory profiles to sleep attacks

Optional Part 2:
1. Quantifying OSLER sleep latency in narcoleptic patients versus controls
2. Exploring the effects of treatment with sodium oxybate on OSLER sleep latency.

Study design

Core:
The duration of this project will be 1.5 years. First subjects can be included in June 2007.

Treatment-naïve patients and healthy subjects will first be asked to wear an actigraph (appendix D) for 14 days. During this time, subjects are asked to log

bedtimes. After these two weeks, subjects will visit the hospital, where the MWT (appendix D) will be performed. This will take a full day. On that day, both the PVT and the SART (see appendix D) will be practised. After this, subjects will take home a pocket-size PDA (personal digital assistant) computer that can administer the SART, PVT and the Stanford Sleepiness Scale (Appendix D). Subjects will take this PDA with them wherever they go during the next seven days. Daily, the device can only be turned on during 1-hour-intervals around 10:00 hr, 15:00 hr and 20.00 hr (that is: from 09.30 to 10.30 hr, a.s.f.). The contents of this 15-minute task battery will be described in appendix D.

Control subjects will only follow this procedure once. Narcoleptic patients will follow this procedure before and three months after stable treatment with the normal therapeutic dose of sodium oxybate (4,5 - 9,0 g / day). All narcoleptic patients that participate in this study will thus be treated with sodium oxybate (as was already their treatment plan).

Optional Part 1:
Subjects will wear the following sensors for 24 hours. All sensors will be attached in the LUMC at 16.00 hrs on day one, and removed on at 16.00 hrs on day 2:

- Ibuttons
16x6 mm2 large, battery shaped devices that can store temperature information for 24 hours internally. They will be attached on ten different skin locations: both hands, both feet, stomach, midtigh, infraclavicularly and both ears.
- Core Body Temperature sensor
Core body temperature will be measured using a wireless temperature pill. This is a new, patient friendely method for which no rectal probe is needed. The pill can be used only once en van be swallowed just like any ordinary pill The device emits a temperature signal that can be received by a small box that test subjects can wear using a belt.
- Standard Sleep Polysomnography (PSG)
Using electrodes on the head, breast, next to the eyes and on the chin. Sleep stages will be scored by a skilled lab technician.

Test subjects are requested to go to sleep and wake up at their normal bedtime. Possible sleep attacks in narcoleptic patient will be logged in a diary.

Optional Part 2:
In addition to the core protocol described above, subjects will have to visit the hospital for one full extra day after the MWT day. On that day the OSLER will be performed.

Study burden and risks

Core:

Participation in this protocol will not harm patients or controls in any way. Narcoleptic patients who have to stop sodium oxybate can experience a slow return of their complaints. This will be evaluated and discussed with their physician. Participant will receive a gift cheque of ¤50 for each PDA test week (so narcoleptic patients will receive ¤100).

Optional Part 1:
Participation in this protocol will cost 24 hours and two hospital visits, but will not harm patients or controls in any way. Narcoleptic patients that have to stop sodium oxybate can experience a slow return of their complaints. This will be evaluated and discussed with their physician. Participant will receive a gift cheque of ¤75.

Optional Part 2:
Participation in this optional part of the protocol will not harm patients or controls in any way. Narcoleptic patients that have to stop sodium oxybate can experience a slow return of their complaints. This will be evaluated and discussed with their physician. Participant will receive a extra gift cheque of ¤50.

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

- Definite narcolepsy-cataplexy, according to international criteria [AASM 2005],
- Patients have to be treatment-naive and planning to start sodium oxybate or already using sodium oxybate and prepared to stop medication at least 14 days prior to study start

Exclusion criteria

- Younger than 18 or older than 70 years
- Cognitive impairment due to neurological disorders other than sleep-wake disorders
- Use of other hypnotics or other sleep-wake active drugs

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-05-2006
Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Leids Universitair Medisch Centrum (Leiden)

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
CCMO	NL15704.058.07