Effect of sodium oxybate on energy metabolism in narcolepsy

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Primary objective:1. To assess the effect of 4 weeks SXB treatment on basal and cold-induced WAT lipolysis (assessed by levels of circulating free fatty acids) in narcolepsy type 1 patients. Secondary objectives:1. To assess the effects of 4 weeks...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52823

Source
ToetsingOnline

Brief title
Sodium oxybate and energy metabolism in narcolepsy

Condition

- Other condition
- Hypothalamus and pituitary gland disorders
- Lipid metabolism disorders

Synonym
hypersomnia, narcolepsy

Health condition

hypersomnieën

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: NarcolepsieNL

Intervention

Keyword: Adipose tissue, Energy metabolism, Narcolepsy, Sodium oxybate

Outcome measures

Primary outcome

The effect of 4 weeks SXB treatment on basal and cold-induced levels of circulating free fatty acids (FFA) in narcolepsy type 1 patients.

Secondary outcome

1. Baseline differences between narcolepsy type 1 patients and matched controls in:

- Indirect markers for basal and cold-induced WAT lipolysis (measured by expression of genes and (phosphorylated) proteins involved in lipolysis and lipid content).

- Serum markers for lipid metabolism metabolism (triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), free fatty acids (FFA)).

- Thermoneutral and cold-induced changes in free fatty acids (FFA).

- Serum markers for glucose metabolism (glucose, insulin, cortisol).

- Resting energy expenditure: measured by indirect calorimetry.

- Skin temperature (as a proxy of BAT activity): measured by infrared thermography.

- Fat/lean mass: measured by body composition analyzer (InBody720).

- mRNA immune gene expression: measured by microfluidic qPCR analyses on whole blood.

- Fecal microbiota composition: measured by 16S sequencing.

2. The effect of 4 weeks of SXB treatment in narcolepsy type 1 patients on all above-mentioned outcomes, excluding free fatty acids (FFA) which is already the primary outcome measure.

Study description

Background summary

From as early as the 1930s, it has been reported that obesity is more prevalent in patients with the sleep-wake disorder narcolepsy than in healthy controls. Recent observations show that narcolepsy type 1 patients lose weight when using sodium oxybate (SXB), the current therapy for the disease. A mean loss of 5.2 kg in three months has been reported in several studies (1-3). This effect appears to be more pronounced in women compared to men [3]. The available animal studies and one human study show an increase in sympathetic activity after SXB administration (4). In line with this, SXB treatment increases lipolysis in narcolepsy type 1 patients (1). Furthermore, our recent experiments in mice suggest a role for remodeling of white adipose tissue (WAT) and changes in the microbiome in the weight-losing effects of SXB. However, thus far the underlying mechanism and involved metabolic tissues mediating the weight loss in narcolepsy type 1 patients after initiation of SXB treatment remain unclear. Therefore, we aim to investigate the short-term effects of SXB treatment on metabolic tissues that importantly contribute to lipid metabolism, e.g. WAT and brown adipose tissue (BAT) as well as the microbiome in patients with narcolepsy type 1. Because the weight losing effects of SXB is more pronounced in women compared to men, only females will be investigated in this study.

Study objective

Primary objective:
1. To assess the effect of 4 weeks SXB treatment on basal and cold-induced WAT lipolysis (assessed by levels of circulating free fatty acids) in narcolepsy type 1 patients.

Secondary objectives:
1. To assess the effects of 4 weeks SXB treatment on indirect markers of basal and cold-induced WAT lipolysis (by the expression of genes and (phosphorylated) proteins involved in lipolysis, and lipid content) in narcolepsy type 1 patients.
2. To assess differences in gene and protein expression, and lipid content in subcutaneous WAT between narcolepsy type 1 patients and matched controls.
3. To assess the effect of 4 weeks SXB treatment on cold-induced lipoprotein dynamics in blood, and supraclavicular skin temperature (as a proxy of BAT activity) in narcolepsy type 1 patients.
4. To assess differences in cold-induced lipoprotein dynamics in blood, and supraclavicular skin temperature (as a proxy of BAT activity) between narcolepsy type 1 patients and matched controls.
5. To assess effects of 4 weeks SXB treatment on fecal microbiota composition and resting energy expenditure in narcolepsy type 1 patients.
6. To assess differences in fecal microbiota composition and resting energy expenditure between narcolepsy type 1 patients and matched controls.

Study design

Prospective observational study.

Study burden and risks

The subcutaneous WAT biopsy may cause pain and often causes bruising, which will disappear within several days. The feeling of fainting may occur during or shortly after the WAT biopsy and/or blood sampling. If so, the subject will be instructed to lie down immediately. The WAT biopsy scheduled after 21 days (only for patient group) will be performed on the other side of the abdomen compared to day 1. It is important to state that the risks of SXB are not added risks to this study, since subjects will be started on SXB treatment independent of this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients:
1. Narcolepsy type 1 based on ICSD-3 criteria.
2. >=18 and <40 years of age.
3. Biologically female.
4. White Caucasian descent.
5. Clinical indication for SXB treatment.
6. BMI >= 25 kg/m2

Matched controls:
1. Biologically female.
2. Age- and BMI-match with patient.
3. White Caucasian descent.

Exclusion criteria

Patients and matched controls:
1. Previous use of SXB.
2. Contraindications for SXB treatment.
3. Sleep-wake disorders other than narcolepsy type 1.
4. Renal, hepatic or endocrine disease.
5. Use of medication known to influence glucose and/or lipid metabolism or brown adipose tissue activity (e.g. β-adrenergic receptor blockers).
6. Participation in an intensive weight-loss program or vigorous exercise program during the year before the start of the study.

7. Pregnant during the study days (due to unreliable body composition measurements on the InBody machine)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2024
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	07-12-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL74154.058.20