The effect of short term Topiramate treatment on insulin secretion, glucose- and lipid metabolism in obese women

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•To determine the effect of short-term Topiramate treatment on glucose metabolism including endogenous glucose production, whole body glucose disposal and glucose oxidation in obese women. •To determine the effect of short-term Topiramate on lipid...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON31914

Source
ToetsingOnline

Brief title
Effect of Topiramate on glucose and lipid metabolism in obese women

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
metabolic syndrome, obesity

Health condition

obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Top Institute Pharma
Source(s) of monetary or material Support: Top Institute Pharma

Intervention

Keyword: Insulin resistance, obesity, Topiramate

Outcome measures

Primary outcome

•Anthropometric: Weight, height, waist and hip circumference, Bioelectrical impedance analysis

•Glucose metabolism: Endogenous glucose production, Ra and Rd of glucose by infusion of [6,6-2H2]glucose two-step hyperinsulinaemic euglycaemic clamp

•Lipid metabolism: Ra glycerol by infusion of [2H5]glycerol

•Indirect calorimetry: resting energy expenditure and RQ, glucose and lipid oxidation rates

•Plasma concentrations: Total cholesterol, HDL-C, LDL-C, Triglycerides, Glucose, insulin, glucagon, free fatty acid, total glycerol, Isotope enrichment of [6,6-2H2]glucose and [2H5]glycerol, lactate, cortisol, Growth Hormone

•ß-cell sensitivity: Early and late response of insulin secretion (hyperglycemic clamp)

•Actimety: Resting energy expenditure, diet induced thermogenesis, active energy expenditure and total energy expenditure.

•Diary: Calorie intake, Physical activity

Secondary outcome

none

Study description

Background summary

Both obesity and type 2 diabetes mellitus are serious and growing global problems. Over 80% of type 2 diabetic patients are overweight or obese. Both obesity and type 2 diabetes mellitus are characterized by insulin resistance of the liver, skeletal muscle and adipose tissue. Therefore, it is likely that insulin resistance is the major underlying pathogenetic defect in obese type 2 diabetic patients. The most common treatment for obesity is life-style changes, such as changing diets and/or increasing physical activity. However, this is often insufficient to obtain the desired amount of weight loss. Lately, the development of antiobesity agents has progressed rapidly. One of the medicines tested is Topiramate.
Topiramate is a registered broad-spectrum neuro-therapeutic agent. Patients show a striking dose dependent weight reduction after long-term treatment with Topiramate (up to 6.3% weight loss). Furthermore, Topiramate treatment increases the odds ratio of having normal glucose tolerance compared to placebo after 60 weeks of treatment. However, patients treated with long-term high-dose Topiramate show significant side effects. The exact mechanism behind the drug-induced weight loss is not yet known, animal studies show a decrease in food intake and an increase in total energy expenditure after long-term Topiramate treatment.
Animal studies show that short-term Topiramate treatment has an insulin-sensitizing effect in female obese rats independently of the decrease in food intake or weight loss. Zucker diabetic fatty rats, who were fed Topiramate 100 mg/kg for 7-9 days, showed an increase in whole body glucose disposal of 35%, as well as a 40% increase in the ability of insulin to suppress endogenous glucose production without losing weight.
Other animal studies in rodents show that beside an insulin sensitizing effect, Topiramate also exert direct action on insulin secreting cells, in particular it improves the obesity associated ß-cell dysfunction. Topiramate treatment counteracts hyperglycemia and increases insulin levels upon glucose tolerance tests in obese rodents.
This study is meant to elucidate the effect of short-term low-dose Topiramate treatment on insulin sensitivity, lipid metabolism and insulin secretion, independently of weight loss, in obese women. If this study demonstrates an improvement of insulin sensitivity in liver, skeletal muscle and adipose tissue and improvement glucose stimulated insulin secretion of the ß-cell, it may be worthwhile to further study the mechanism of action of Topiramate and develop Topiramate analogues, for the treatment of obesity, the metabolic syndrome and type 2 DM. Since these conditions are emerging into worldwide epidemics, it is of the utmost importance to find improve and extend the treatment options for these conditions.

Study objective

•To determine the effect of short-term Topiramate treatment on glucose metabolism including endogenous glucose production, whole body glucose disposal and glucose oxidation in obese women.
•To determine the effect of short-term Topiramate on lipid metabolism including whole body lipolysis, lipid oxidation and blood cholesterol levels in obese women.
•To determine the effect of short-term Topiramate on ß-cell sensitivity to glucose, divided in the early and late response of insulin secretion.

Study design

Double blind randomized cross-over placebo controlled intervention study.

Intervention

4 weeks Topiramate (first week 25 mg od (evening); second week 25 mg bid; third and fourth week 25 mg od (morning) + 50 mg od (evening)) and 4 weeks Placebo.

Study burden and risks

Subjects will be admitted at the research center for two whole days (8 hours) and two half days (4 hours). During the study days, subjects will lie in bed and blood will be drawn from an infusion. No adverse events are expected from this.
Subjects will be asked to take both Topiramate and Placebo for four weeks. We will monitor side effects weekly.

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

Female volunteers
Age > 18 years and < 70 years
BMI > 27 kg/m2 and < 44 kg/m2
Fasting serum glucose (FSG) 6.1-7 mmol/L

Exclusion criteria

FSG >7 mmol/L
Psychiatric disorders and/or use of antipsychotic or antidepressants drugs at present or in the past.
Any significant chronic disease
Any significant abnormal laboratory results found during the medical screening procedure
Renal, hepatic or endocrine disease (including DM)
Use of medication known to influence glucose and/or FFA metabolism
Premenopausal women who do not use oral contraceptives or intrauterine device
Recent weight changes or attempts to loose weight (> 3 kg weight gain or loss, within the last 3 months)
Difficulties to insert an intravenous catheter
Smoking
Severe claustrophobia (ventilated hood)
Recent blood donation (within the last 3 months)
Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2008
Enrollment:	13
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Topiramate
Generic name:	Topiramate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	21-02-2008
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
EudraCT	EUCTR2006-004373-10-NL
CCMO	NL21926.058.08