Effects of randomized, double blind, multiple dose administration of olanzapine versus concurrent administration of olanzapine plus topiramate in healthy males.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22772

Source
Nationaal Trial Register

Brief title
Olanzapine vs olanzapine/topiramate study

Health condition

Weight gain and calory intake induction in subject taking Olanzapine are treated with Topiramate for reversal off effects

Sponsors and support

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

Intervention

Outcome measures

Primary outcome

To compare the effects of 14 days of daily dosing of 10 mg olanzapine with or without topiramate on body weight in healthy male subjects.

Secondary outcome

To assess if olanzapine at a dose of 10 mg daily for 14 days with or without topiramate has an effect on thyroid function, glucose and lipid metabolism in healthy male subjects.

Study description

Background summary

Anti-psychotics, i.e. olanzapine, have become the “drug of choice” for the treatment of schizophrenia and other chronic psychotic disorders. They are highly effective, but unfortunately they are paralleled by a large increase in body weight and other metabolic changes implicated in the development of metabolic syndrome. The most common side effects, besides weight gain, are hyperglycemia, a lower insulin sensitivity, hyperphagia, hypercholesterolemia, bradycardia, elevated plasma corticosteron and hypothermia.

This gain in weight can be remarkably large and frequently leads to development of diabetes mellitus. Schizophrenic patients already have a predisposition of developing diabetes mellitus without treatment with anti-psychotic agents.

Olanzapine is a thienobenzodiazepin derivate and it is thought to exert its effects through antagonism of the serotonergic 5HT2, 3 and 6 receptors, partial agonistic-like effects action at dopamine D2 receptors and an antagonist-like activity at D1 receptors. The underlying mechanism which causes the unwanted side effects is still unknown and are investigated in this study.

Olanzapine treatment in rats lowers the nocturnal plasma levels of melatonin. This has been confirmed in female rats in which nocturnal plasma levels of melatonin were lowered by 55%. Daily oral melatonin replacement, administered to return nocturnal melatonin to normal. Also reversed body weight and visceral adiposity to normal. This suggests that a metabolic effect of olanzapine could be related to changes in melatonin secretion.

It was recently discovered that topiramate, an anticonvulsant prescribed mainly for the treatment of epilepsy, is able to control olanzapine-induced weight gain in schizophrenic patients without aggravation of psychotic symptoms. When topiramate was administered in combination with olanzapine, none of the side effects were observed. In fact, co administration of topiramate exerts weight loss, reduction of appetite, higher insulin sensitivity and a decrease in fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and leptin.

From the literature it is known that topiramate can up-regulate energy expenditure and lead to an increment in body heat production. It is temptative to hypothesize that the metabolic changes exerted under olanzapine treatment are explained by a subclinical hypothyroid state, with all the changes in the fat metabolism as.

Increased food desire occurs under olanzapine treatment even at such a typical manner, that it is characterized as an eating behavior which we call “binch eating”. This consuming behavior shows great resemblance with a disturbed satiation response which could be explained by the serotonergic component of olanzapine.

In the proposed clinical study in healthy volunteers our main purpose is to investigate if under olanzapine treatment a change in body weight can be observed together with changes in thyroid function or melatonin blood levels and whether the healthy volunteers who will use olanzapine combined with topiramate will not display these effects.

Study objective

Topiramate leads to reduced olanzapine-induced weight gain and calory intake .

Study design

Before study and after 14 days of treatment with olanzapine and topimarate or placebo and 28 days after start dosing of olazapine.

The following measurements are used:

Pharmacodynamics (in blood): Glucose, insulin and C-peptide, T3, T4, thyroid stimulating hormone (TSH) and T1AM, melatonin, oxyntomodulin and glucagons, triglycerides and free fatty acids, total cholesterol, high-density lipoprotein-bound cholesterol [HDL cholesterol], low-density lipoprotein-bound cholesterol [LDL cholesterol] and apolipoprotein B [ApoB].

Pharmacodynamics (in urine): Proteomics and peptidomics.
Other measurements are body temperature, body weight, VAS questionare, actometer and metabolic rate via doubly labeled water test.

Intervention

Group 1: An oral dose of 10 mg olanzapine once daily on Days 1-14 and 1 capsule of placebo twice daily on Days 1-6 and 2 capsules of placebo twice daily on Days 7-14.

Group 2: On Days 1-6: an oral dose of 10 mg olanzapine once daily and an oral dose of 25 mg topiramate (encapsulated tablet) twice daily. On Days 7-14: an oral dose of 10 mg olanzapine once daily and an oral dose of 50 mg topiramate (2 encapsulated tablets) twice daily.

Contacts

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Eligibility criteria

Inclusion criteria

1. Gender: Male;

2. Age: 20-55 years, inclusive;

3. Body mass index (BMI): 22-30 kg/m2;

4. Ability and willingness to abstain from alcohol, methylxanthine-containing beverages or

food (coffee, tea, cola, chocolate, "powerdrinks"), grapefruit (juice) and tobacco products from 48 h prior to entry in the clinical research centre until discharge;

5. Medical history without major pathology;

6. Blood pressure and resting pulse rate showing no clinically relevant deviations as judged by the Medical Investigator (MI);

7. Computerised (12-lead) electrocardiogram (ECG) recording without signs of clinically relevant pathology or showing no clinically relevant deviations as judged by the MI;

8. All values for haematology and for clinical chemistry tests of blood and urine within the normal range or showing no clinically relevant deviations as judged by the MI;

9. Have serum prolactin and serum ALAT, ASAT, alkaline phosphatase and bilirubin values at screening less than upper limit of normal (ULN);

10. Willingness to sign the written Informed Consent Form (ICF);

11. Understanding of written and spoken Dutch language.

Exclusion criteria

1. Evidence of clinically relevant pathology;

2. Mental handicap;

3. History of psychiatric diseases with or without medical treatment;

4. Significant psychopathology (=admission to psychiatric facility) in first grade family members;

5. History of relevant drug and/or food allergies;

6. Regular/routine treatment with non-topical medications within 30 days prior to drug administration;

7. Have an abnormally low blood pressure with significant orthostatic change (systolic blood pressure decrease of >30 mm Hg on standing up for 3 minutes;

8. Smoking (less than 60 days prior to drug administration);

9. History of alcohol abuse or drug addiction (including soft drugs like cannabis products);

10. Use of concomitant medication, except for acetaminophen (paracetamol), which is

allowed up to 3 days before entrance into the research facility. All other medication (including over the counter medication, health supplements, and herbal remedies such as St. John’s Wort extract) must have been stopped at least 14 days prior to the first dose. The use of a limited amount of acetaminophen is permitted;

11. Participation in a drug study within 60 days prior to drug administration. Participation in more than 3 other drug studies in the 10 months preceding the start of this study (this is the first administration of study drug);

12. Donation of more than 50 mL of blood within 60 days prior to drug administration. Donation of more than 1.5 litres of blood in the 10 months preceding the start of this study;

13. Positive screen on drugs of abuse (opiates, methadone, cocaine, amphetamines, cannabinoids), barbiturates, benzodiazepines, tricyclic antidepressants and alcohol;

14. Intake of more than 24 units of alcohol per week (one unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits);

15. Positive screen on HBsAg;

16. Positive screen on anti HCV;

17. Positive screen on anti HIV 1/2;

18. Illness within 5 days prior to the first drug administration.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-04-2010

Enrollment:	30
Type:	Anticipated

Ethics review

Positive opinion Date:	21-05-2010
Application type:	First submission

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
NTR-new	NL2206
NTR-old	NTR2330
Other	Top Institute Pharma : TPA111EC-101111

Study results

Summary results
N/A