An efficacy, safety and pharmacokinetic study on the short-term and long-term use of METFORMIN in obese children and adolescents.

Published: 07-07-2011
Last updated: 27-04-2024

The primary objective of the METFORMIN study is to determine the efficacy of metformin in combination with lifestyle-intervention in obese children and adolescents with insulin resistance versus placebo with lifestyle-intervention. The secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39499

Source
ToetsingOnline

Brief title
Metformin in obese children and adolescents

Condition

- Other condition

Synonym
excess body fat, Obese

Health condition

Bariatrie (Obesitas)

Research involving

Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: adolescents, children, metformin, obese

Outcome measures

Primary outcome

Primary study endpoint for efficacy is the reduction in BMI, which is calculated from the anthropometric measurements.

Other primary endpoints for efficacy are insulin resistance, calculated by the HOMA-IR, which is a generally accepted index to determine insulin resistance in children and adolescents, percentage of body fat measured by bio-impedance, HbA1C value, β-cell function, calculated by HOMA-β%, oral disposition index, insulin secretion calculated by the insulinogenic index, physical fitness measured by validated fitness tests, basal metabolic rate measured by calorimetry and quality of life measured by validated quality of life questionnaire.

Secondary outcome

Secondary outcome parameters for safety of metformin treatment are hepatic and renal function tests, and for tolerability the number of adverse effects (in relation to the achieved dose level).

Tertiary outcome parameters are the pharmacokinetic parameters of metformin in

obese children and adolescents. These parameters are estimated using population PK-PD modelling techniques in which a comprehensive covariate analysis will be performed allowing to account for variability in PK parameters on the basis of individual characteristics such as age, bodyweight, BMI, percentage of body fat, gender, Tanner stage and genetic constitution.

Quaternary outcome parameters for long-term efficacy and long-term safety and tolerability of metformin are BMI, insulin resistance calculated by the HOMA-IR, percentage of body fat measured by bio-impedance, HbA1C, β-cell function, calculated by HOMA-β%, oral disposition index, insulin secretion calculated by the insulinogenic index, physical fitness measured by validated fitness tests, quality of life measured by validated quality of life questionnaire, hepatic and renal function tests and number of side effects. In addition, the percentage of patients that has developed impaired fasted glucose, impaired glucose tolerance (2-hrs plasma glucose during an OGTT), T2DM and the development of micro-vascular complications detected by micro-albuminuria and macro-vascular complications detected by using pulse wave velocity (PWV) and augmentation index (AIx) is evaluated.

Study description

Background summary

The prevalence of obesity in children and adolescents is increasing rapidly and is associated with significant medical and psychosocial consequences persisting into adulthood.
Obesity may lead to metabolic complications, such as insulin resistance, which

can progress via impaired fasted glucose and impaired glucose tolerance to type 2 diabetes mellitus (T2DM) and to the development of micro- and macro-vascular complications.

Metformin, an oral anti-diabetic licensed for adults and children from 10 years onwards, is already used off label in obese children and adolescents with insulin resistance, even though the specific effects of metformin in these obese children and adolescents have not been elucidated, particularly upon long-term use.
The rationale for this study is based on the hypothesis that metformin may reduce body mass index (BMI), insulin resistance and percentage of body-fat in obese children and adolescents with insulin resistance. Further more it is anticipated that metformin may delay the progression to T2DM and thereby micro- and macro-vascular complications in obese children and adolescents with insulin resistance.

The rationale for this study is based on the hypothesis that metformin may reduce body mass index (BMI), insulin resistance and percentage of body-fat in obese children and adolescents with insulin resistance. Further more it is anticipated that metformin may delay the progression to T2DM and thereby micro- and macro-vascular complications in obese children and adolescents with insulin resistance.

Study objective

The primary objective of the METFORMIN study is to determine the efficacy of metformin in combination with lifestyle-intervention in obese children and adolescents with insulin resistance versus placebo with lifestyle-intervention.

The secondary objective of the METFORMIN study is to determine the safety and tolerability of metformin in combination with lifestyle-intervention in obese children and adolescents with insulin resistance versus placebo with lifestyle-intervention.

The tertiary objective of the METFORMIN study is to study the population pharmacokinetics (PK) of metformin in obese children and adolescents.

The quaternary objective of the METFORMIN study is to determine the long-term efficacy and long-term safety and tolerability of metformin in obese children and adolescents with insulin resistance.

Other objectives are to compare body fat measured using bio-impedance with a body fat measured using dual energy X-ray absorptiometry (DEXA scan), to compare insulin sensitivity measured by the whole body insulin sensitivity index (WBISI) with insulin sensitivity using HOMA-IR in obese children and adolescents .

Study design

The proposed multi-centre project is divided in two consecutive studies: a double-blind randomized placebo-controlled study (study of 18 months duration) and an open study (follow up study of 18 months duration), when metformin will be offered to all patients, for whom metformin is still indicated.

Intervention

In the initial study, the study population will be assigned to either placebo or Metformin. All subjects will follow the same lifestyle-intervention program during the entire study period of 18 months. Metformin and placebo will be administered in increasing dosages. The initial dose is 500 mg and will be increased weekly with 500 mg to a maximum dose of 1000 mg bid. The dose of 1000 mg bid will be administered till the end of the study unless the study subject develops adverse effects.
In the follow up study metformin will be offered to all study subjects, if indicated.

Study burden and risks

Metformin is licensed for children >= 10 years with T2DM while there is world wide experience with off-label use of metformin in obese children and adolescents with and without insulin resistance.
The potential benefits of using metformin are faster stabilisation of weight or weight loss and possibly slower progression to T2DM and the development of micro- and macro vascular complications.
Expected adverse effects of metformin are mainly gastro-intestinal symptoms, such as diarrhoea, nausea and vomiting.

During the initial study of 18 months, there are three extra visits with two extra blood samples (extra blood collected 50 ml) compared to children and adolescents that are being prescribed metformin in an off-label manner. Total number of visits is 9, during which at 8 visits blood will be collected (6 times by venous puncture and twice using a venous catheter for OGTT and metformin day-curve). Total amount of blood taken will be approximately 125 ml over 18 months). There are no extra OGTTs compared to treatment with off-label metformin.

Compared to current lifestyle intervention program, the subjects are offered a 18 months fitness program instead of 6 months, and undergo a validated fitness test (30 minutes) during the first training, in week 37 and at the end of the initial and the follow up study.
The subjects have to fulfil a quality of life questionnaire, dietary questionnaire (approximately 30 minutes) at study entry, week 37 and at the end of the initial and the follow up study.

During the follow up study, there will be 6 times contact with the subjects. Children using metformin will visit the hospital every 3 months, this number of visits is similar to children and adolescents that are being prescribed metformin in an off-label manner. Children not using metformin, will visit the hospital 3 times and will receive phone calls in between the visits. Total number of visits is including blood sampling is 3(twice by venous puncture and once using a venous catheter for OGTT), this is equal for all children, and similar to children and adolescents that are being prescribed metformin in an off-label manner. Total amount of blood taken will be approximately 50 ml over 18 months.

Contacts

Public
Sint Antonius Ziekenhuis

Koekoekslaan 1
Nieuwegein 3435 CM
NL
Scientific
Sint Antonius Ziekenhuis

Koekoekslaan 1
Nieuwegein 3435 CM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

The inclusion criteria are subject*s age >= 10 and <= 16 years at study entry, from Caucasian descent, with obesity defined as BMI SDS > 2.3 and with insulin resistance defined as HOMA-IR >= 3.4. In addition an obtained informed consent from subjects and/or parents/caregivers.

Exclusion criteria

The exclusion criteria are presence of T2DM (American Diabetes Association criteria); presence of endocrine disorders with steroid therapy; suspicion of polycystic ovarium syndrome; height < -1.3 SD of target height; psychiatric illness and eating disorders in particular; use of anti-hyperglycaemic drugs; pregnancy (pregnancy test will be performed, if applicable); (history of) alcohol abuse; impaired renal and/or hepatic function (defined as GFR<80ml/min and ALAT >= 150% of normal value for age); use of ritonavir; use of ACE inhibitors; insufficient knowledge of the Dutch language.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-08-2011
Enrollment:	144
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	07-07-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-05-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-023980-17-NL
CCMO	NL34811.100.11