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Study of Glucophage® SR iin patients with type 2 diabetes and moderate Kidney dysfunction

Submission date
01/03/2012

Recruitment status
No longer recruiting

Registration date
07/03/2012

Overall study status
Completed

Last Edited
31/05/2019

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The purpose of the study is to determine the safety, tolerability and effectiveness of the tablet Glucophage® SR (commonly known by the name metformin) in patients with type 2 diabetes and slightly reduced kidney function. Glucophage® SR (a slow release form of metformin) is an important drug in the treatment of type 2 diabetes. At present, the British National Formulary guidance states that metformin should be used with caution if the marker for flow of blood through the kidney (known as estimated glomerular filtration rate) falls below 45 ml/minute/1.73m2 but remains above 30 ml/minute/1.73m2. No studies exist that can form the basis of this advice. More importantly, the current research evidence points in the direction that this advice may even be wrong and Glucophage® SR can be quite safe in the above mentioned range of kidney dysfunction. In the interest of patients with type 2 diabetes and kidney disease, it is an important question that should be answered through a proper research study. This question is important because at present Glucophage® SR is sometimes discontinued from the patients treatment when the estimated glomerular filtration rate reaches a range between 30 ml/minute /1.73m2 and 45 ml/minute/1.73m2. At present this treatment strategy of patients is purely hypothetical and not based on a good scientific background. In certain situations these decisions deprive the patient of the beneficial effects of Glucophage® SR. The aim of this study to generate scientific data for safe and sound decision making for patient treatment.

Who can participate?
Patients with (adult onset) type 2 diabetes with moderate kidney dysfunction.

What does the study involve?
The study will start with a screening visit, where data will be collected on age, sex, height, weight, body mass index (BMI) and duration of diabetes, blood samples will be taken and a complete physical examination will be done. Between study visits, patients will be asked to check their blood glucose whenever they feel the symptoms of hypoglycemia (low blood glucose) and record it with date and time. Patients will be given education on how to do home glucose monitoring (HGM), and will be given a HGM booklet and a glucose meter. Patients will be advised to do HGM (pre-breakfast, pre-lunch, pre-evening meal and pre-bed) three days prior to every study visit. Patients will be advised to continue the HGM as before taking part in the study. If indicated a pregnancy test will be carried out at the screening visit.

Two weeks later at the randomization visit the HGM diary with blood sugar readings will be reviewed. Blood samples will be taken and the number of hypoglycemia episodes will be counted and recorded. If indicated, insulin dosages will be adjusted. Patients will then be randomly allocated to take either Glucophage® SR or a placebo (dummy). For additional safety, patients will be advised to contact the research team if they feel unwell in any way. Patients will then attend three visits at which the tolerability and side effects of Glucophage® SR will be evaluated and recorded. Patients will then attend six further visits, 4 weeks apart. One week later there will be an end of study visit. On this visit a physical examination will be carried out to ensure that the patient is doing well. Patients will be switched back to their pre-study medications. A follow-up appointment will be arranged for the patients to be reviewed in the diabetes clinic within 2 months, during which the study results will be discussed and if the results are found to be favourable patients will be offered to start Glucophage® SR treatment.

What are the possible benefits and risks of participating?
It is expected that if you are in the Glucophage® SR group, it is likely that your glucose control will improve. It is also expected that this improvement will not come at the cost of an increase in hypoglycemic episodes. Even if you are in the control group, it is likely that your blood glucose control will be better at the end of the study. This is because we will monitor you very closely and adjust your insulin and other diabetes-related medications meticulously. This would mean a reduced risk of developing the problems that are caused by high levels of blood glucose, including retinopathy (an eye disorder), progression of nephropathy (i.e. further damage to the kidneys) and neuropathy (damage to nerve endings which, in severe cases, can lead to amputations and sexual problems). However, taking part in the study is no guarantee that your risks of developing these complications will be reduced. In addition, if the results are encouraging you may be allowed to continue the same treatment after the study. This will be discussed with you about two months after the end of study visit.
There is a small risk of hypoglycemia with use of Glucophage® SR in combination with insulin. To minimize any risk you will be provided with thorough education prior to taking part in the study. You will also be provided with a glucose meter to monitor glucose levels when experiencing hypoglycemia and you will be educated on how to reverse these episodes. As stated above, there is a chance of developing lactic acidosis (i.e. development of acid in the body). However, we have looked at the available scientific evidence and the chances of this happening are very low. For additional safety, during the research process, we will monitor the patients very closely with blood tests about acid build up with regular blood tests in the laboratory. Even if it happens the Glucophage® SR tablet will be withdrawn immediately and the episode of acid build up will be completely reversed to normal. You may experience some pain and discomfort at the time of taking bloods.

Where is the study run from?
The study will be conducted in West Wales (Glangwili) Hospital, Carmarthen and Singleton Hospital/ILS building, Swansea University, Swansea (UK).

When is the study starting and how long is it expected to run for?
May 2012 to December 2014

Who is funding the study?
NISCHR, a funding body of Welsh Assembly Government

Who is the main contact?
Dr Atir Khan
atirsultanali.khan@wales.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Dr Atir Khan

Contact details
Diabetes Centre
West Wales Hospital
Carmarthen
United Kingdom
SA31 2AF
+44 (0)7729 691 018
atirsultanali.khan@wales.nhs.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Version - 1

Study information

Scientific Title
Safety, tolerability and effectiveness of Glucophage® SR in patients with type 2 diabetes and chronic Kidney disease

Acronym
GlucoKid

Study objectives
To study safety, tolerability and effectiveness of Glucophage® SR in patients with type 2 diabetes and chronic kidney disease (eGFR 30 to 45mL/minute/1.73m2)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Double-blind randomized placebo-controlled phase II 6 months study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes and chronic kidney disease

Interventions
Glucophage® SR versus placebo

This will be a multi-centre study. First centre for the study will be: Diabetes centre, Glangwili Hospital, Carmarthen. The second centre will be Diabetes unit in Singleton hospital, Swansea.

The study will start with a screening visit. Patients will attend in a non-fasting state and will be asked to sign an ethics committee approved consent form.

Also, at the screening visit data will be collected on age, sex, height, weight, body mass index (BMI), duration of diabetes. The inclusion and exclusion criteria will be checked. Blood samples will be taken for HbA1c, venous pH, blood lactate, venous bicarbonate (VHCO3) urea and electrolytes (U&E), plasma levels of Glucophage® SR and liver function tests (LFTs). A complete physical examination will be done. Between study visits, patients will be asked to check the blood glucose whenever they feel the symptoms of hypoglycemia (defined as capillary blood glucose < 4.0mmol/L) and record it with date and time. Patients will be given education on how to do home glucose monitoring (HGM), will be given a HGM booklet and a glucometer. Patients will be advised to do HGM (pre-breakfast, pre-lunch, pre-evening meal and pre-bed) three days prior to every study visit. Patients will be advised to continue the home glucose monitoring (HGM) as before taking part in the study. If indicated a pregnancy test will be carried out at the screening visit.

Following the screening visit there will be an up to two week run-in period. During the run-in period patients eligibility to participate in the study will be assessed.

The 2-week run-in period will end with the randomization visit. Patients will attend in a non-fasting state and data will be collected on weight, body mass index (BMI), incidence of hypoglycemia and HGM diary with blood sugar readings three days prior to the randomization visit will be reviewed. Blood samples will be taken for HbA1c, venous pH, blood lactate, venous bicarbonate (VHCO3) urea and electrolytes (U&E), plasma levels of Glucophage® SR and liver function tests (LFTs). Number of hypoglycemia episodes during run-in period will be counted and recorded. If indicated insulin dosages will be adjusted using the insulin titration chart (see

below). Patients will be randomized (double blind), using a computer generated sequence, to Glucophage® SR or placebo arm of the study. Randomization will occur at a remote single site and study medications will be delivered by the pharmacy department of Glangwili Hospital, Carmarthen OR pharmacy department of Singleton hospital, Swansea. Patients will start with Glucophage® SR 500mg twice daily (or equivalent in the placebo arm) on the randomization visit. For additional safety, patients will be advised to contact the research team if they feel unwell in any way.

From the date of randomization visit, patients will attend at week-1 (day-7), week-2 (day-14) and week-3 (day-21). At each of these three visits the number of hypoglycemia episodes will be counted. HGM diary with blood sugar readings three days prior to the each visit will be reviewed and if patients are on insulin then insulin dosages will be titrated using the insulin titration chart (see below). If patient is tolerating the 500mgtwice daily dose without any side effects, at visit week-1 (day-7) the Glucophage® SR will be increased to 500mg three times daily (TDS), or equivalent in the placebo arm. On each visit the tolerability and side effects of Glucophage® SR will be evaluated and recorded. On each visit blood samples will be taken for venous pH, blood lactate, U&E, plasma levels of Glucophage® SR and VHCO3.

Following the visit on week-3 (day-21), future 6-visits in the study will be every 4weeks from the date of randomization visit (visits 1, 2, 3, 4, 5 and 6). At each of these visits patients will attend in a non-fasting state and data will be collected on weight and body mass index (BMI) and incidence of hypoglycemia. HGM diary with blood sugar readings three days prior to the each visit will be reviewed and if patients are on insulin then insulin dosages will be titrated using the insulin titration chart (see below). Patients who at the time of randomization were not on insulin but were on Glimepride or Gliclazide, will enter the study on the their "current (pre-study)" Glimperide / Gliclazide doses and then from visit1 doses will be up-titrated at 1-mg every 4-weeks in case of Glimepride and 40mg BD every 4-weeks in case of Gliclazide; if the mean of fasting blood glucose readings three days prior to the study visit is > 7.0mmol/L (to a maximum dose of 6mg daily for Glimepride and 160mg BD for Gliclazide). On each visit blood samples will be taken for HbA1c, venous pH, blood lactate, venous bicarbonate (VHCO3), U&E, plasma levels of Glucophage® SR and LFTs. For patients not on insulin at the time of randomization, if the mean of fasting blood sugars readings three days prior to the study visit is >10mmol/L on two consecutive visits despite being on maximum doses of Glimepride (6mg OD) / Gliclazide (160mg BD), then Humulin M3 insulin twice daily will be added to the treatment. Starting dose of Humulin M3 insulin, will be individualized for every patient, and will be decided by the research team.

One week after the visit 6 there will be an end of study visit. On this visit physical examination will be done to ensure the patient is doing well. Patients will be switched back to their pre-study medications. As this is a double blind study, the full results are unlikely to be available at the end of study visit. Therefore, a follow up appointment will be arranged for the patients to be reviewed in the Diabetes clinic within 2 months. During the follow up appointment in Diabetes clinic study results will be discussed and if the results are found favorable patients will be offered to start Glucophage® SR treatment.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Glucophage® SR

Primary outcome measure
1% Change in HbA1c at the end of study from baseline in the Glucophage® SR group of the study, compared to placebo

Secondary outcome measures
1. Change in eGFR from baseline
2. Incidence of lactic acidosis and tolerability (measured by number of patients completed the study) in the Glucophage® SR group of the study compared to placebo

Overall study start date
01/05/2012

Completion date
31/12/2014

Eligibility

Key inclusion criteria
1. Age > 18 years
2. Male or female
3. Patients with Type 2 diabetes
4. Suboptimal glycaemic control {HbA1c ≥ 7.5% (IFCC equivalent ≥ 58mmol/mol)} at the screening visit
5. Chronic kidney disease with Estimated Glomerular Filtration Rate (eGFR) ≥ 30mL/minute/1.73m2 to ≤ 45mL/minute/1.73m2 at the screening visit
6. Stable renal function (eGFR) in the last 3 months
7. Willing and able to comply with the study protocol

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
50 (25 in each group)

Key exclusion criteria
1. Previous myocardial infarction (MI) (in last 6 months)
2. Previous history of Congestive Cardiac Failure New York Heart Association (NYHA) class III or IV

3. Previous history of Chronic obstructive pulmonary disease (COPD)
4. Chronic kidney disease with eGFR < 30mL/minute/1.73m2
5. Abnormal alanine aminotransferase (ALT) (> 3fold at baseline)
6. Hypoglycaemia symptoms unawareness
7. History of hypoglycemic episodes requiring 3rd party assistance for reversal in last 12 months
8. Uncontrolled Hypertension (BP > 180/100mmHg)
9. Pregnant or likelihood of pregnancy during the study
10. Females who are breastfeeding
11. Proliferative Diabetic retinopathy and/or laser treatment in last 6 months
12. History of Diabetic ketoacidosis, lactic acidosis and gasteroparesis
13. Current treatment with metformin/Glucophage® SR
14. Treatment with metformin/Glucophage® SR in last 3 months prior to screening visit
15. History of irritable bowel syndrome
16. Previous intolerance to metformin or Glucophage® SR
17. Patients currently on dipeptidyl peptidase IV (DPPIV) inhibitors and Glucagon-Like Peptide (GLP) analogues
18. History of significant (more than one stone) weight loss in last 6 months
19. History of allergic or hypersensitivity reaction to metformin, Glucophage® SR or any insulin
20. Patients unable to tolerate minimum 1000mg daily divided dose of Glucophage® SR
21. Any other condition excluded in Summary of Product Characteristics (SPC)

Date of first enrolment
01/05/2012

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
West Wales Hospital
Carmarthen
United Kingdom
SA31 2AF

Sponsor information

Organisation
West Wales Hospital (UK)

Sponsor details

c/o Dr Atir Khan
Diabetes Centre
Carmarthen
Wales
United Kingdom
SA31 2AF
+44 (0)7729 691 018
atirsultanali.khan@wales.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.wales.nhs.uk/

ROR
https://ror.org/01cs14q41

Funder(s)

Funder type
Government

Funder Name
National Institute for Social Care and Health Research

Alternative Name(s)
Sefydliad Cenedlaethol ar Gyfer Ymchwil Gofal Cymdeithasol ac Lechyd, NISCHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration