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Pharmacokinetic profile, safety and tolerability of Sildenafil (REVATIO®) in cardiac surgery patients with chronic kidney disease

Submission date
20/11/2012

Recruitment status
No longer recruiting

Registration date
10/01/2014

Overall study status
Completed

Last Edited
26/10/2016

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
We are carrying out a study of 36 patients with kidney disease who are scheduled to have heart surgery. Our goal is to find the ideal dose of the drug named Sildenafil (REVATIO®) to protect the kidneys during heart surgery with a heart-lung machine. We want to look at the levels of Sildenafil in the bloodstream, and the way the body removes it. Other aims of this study are to find out how safe this medicine is and what side effects it causes, if any.

Who can participate?
Adult men or women with kidney disease, having heart surgery at three study centres in England can take part in this study.

What does the study involve?
Over a period of six months patients who are planned to undergo heart surgery at a participating centre will be asked to take part in the trial. If they provide consent, patients will receive a single dose of Sildenafil during surgery. The amount of Sildenafil given to the participants will be increased with each six participants; there will be six groups in total. This will enable us to find the optimum dose to protect the kidneys during surgery. Blood samples will be collected at regular intervals during surgery to study the levels of the medication in the bloodstream and how quickly it is removed by the body. Blood and urine samples will also be collected at regular intervals during the hospital stay after the operation and tested for several chemicals that will give us an idea of how well different parts of the body, e.g. your brain, heart and kidneys, worked during and after the operation. At the end of the study, we will compare the amount of medication in the bloodstream and how long it stayed present between the six different groups. We will also compare measures of well-being and kidney function between groups.

What are the possible benefits and risks of participating?
We believe that this drug has the potential to benefit patients at risk of postoperative acute

kidney injury, who would otherwise be at higher risk, and has a very low risk profile. Potential participants will need to weigh up the possibility of benefit from the intervention against the risk of harm.

Where is the study run from?
The study has been set up by the University of Leicester and University of Oxford, UK in collaboration with the British Heart Foundation.

When is study starting and how long is it expected to run for?
The recruitment started mid-2013. Participants will be enrolled on the study for a period of six weeks, until they return to hospital for a routine follow-up appointment.

Who is funding the study?
This study is funded by the British Heart Foundation, UK.

Who is the main contact?
Miss Veerle Verheyden, vv46@le.ac.uk
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Contact information

Type(s)
Scientific

Contact name
Miss Veerle Verheyden

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Additional identifiers

Protocol serial number
RCSCKD - 001

Study information

Scientific Title
A phase I study to determine the pharmacokinetic profile, safety and tolerability of Sildenafil (REVATIO®) in cardiac surgery patients with chronic kidney disease

Acronym

REVAKI-001

Study objectives
1. To evaluate the pharmacokinetic profile of Sildenafil in cardiac surgery patients with chronic kidney disease.
2. To determine the safety and tolerability of Sildenafil in cardiac surgery patients with chronic kidney disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Phase I multi-centre open-label non-randomised single-dose study

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Cardiac surgery patients with chronic kidney disease

Interventions
Patients will be screened by the investigators to assess eligibility for entry into the study. Eligible patients undergoing cardiac surgery with CPB who consent to participate will be consecutively allocated, in a 6:6:6:6:6:6 sequence to:

Treatment group 1: Sildenafil 2.5 mg bolus IV (3.125 mL)
Treatment group 2: Sildenafil 2.5 mg bolus IV + Sildenafil 2.5 mg as a 2hrs continuous infusion (6.250 mL)
Treatment group 3: Sildenafil 5.0 mg bolus IV (6.250 mL)
Treatment group 4: Sildenafil 5 mg bolus IV + Sildenafil 2.5 mg as a 2hrs continuous infusion (9.375 mL)
Treatment group 5: Sildenafil 10 mg bolus IV (12.5 mL)
Treatment group 6: Sildenafil 10 mg bolus IV+ Sildenafil 2.5 mg as a 2hrs continuous infusion (15.625 mL)

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Sildenafil

Primary outcome(s)

1. Safety will be assessed by means of the following:
1.1. Physical examination at screening and clinical outcome monitoring during hospitalization and at 4-6 weeks follow-up visit
1.2. Vital sign measurements during study drug administration
1.3. Clinical laboratory assessments including haematology, biochemistry and urinalysis (at screening and at 6 hrs, 24 hrs, 48 hrs and 96 hrs after study drug administration and at hospital discharge)
1.4. Adverse events and concomitant medications/therapies
2. Pharmacokinetic assessments will include evaluation of plasma levels of Sildenafil and N-desmetyl-Sildenafil (at start of infusion, end of the bolus infusion and at 15 min, 30 min, 45 min, 1 hr, 2 hrs (end of CPB), 4 hrs (CICU admission), 6 hrs and 24 hrs after end of bolus infusion
3. Plasma levels of Sildenafil and the following pharmacokinetic parameters calculated from it:
3.1. Incremental recovery (peak recorded within the first hour after infusion)
3.2. Maximum plasma concentrations (Cmax)
3.3. Time to Cmax (Tmax)
3.4. Terminal half-life (t1/2)
3.5. Terminal elimination rate constant (kel)
3.6. Area under the plasma time versus concentration curve from time 0 to time of last measurable concentration (AUC(0-t)); linear trapezoidal method
3.7. Area under the plasma time versus concentration curve from time 0 to extrapolated to infinity (AUC(0-∞))
3.8. Clearance (CL)
3.9. Apparent volume of distribution (Vz)
3.10. Mean residence time (MRT)

Key secondary outcome(s))
No secondary outcome measures

Completion date
01/10/2013

Eligibility

Key inclusion criteria
1. Adult cardiac surgery patients (>16 years and <80 years) undergoing cardiac surgery with moderately hypothermic cardiopulmonary bypass (CPB) (32-34°C) and blood cardioplegia
2. eGFR >15 and <90ml/min (International classification of Chronic Kidney Disease, CKD, Stage 2-4)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Emergency or salvage procedure
2. Ejection fraction <30%
3. CKD Stage 1, defined as eGFR>90ml/min
4. CKD Stage 5, defined as eGFR<15ml/min or renal replacement therapy
5. Administration of potent CYP 3A4 inhibitors within 1 month prior to study participation
6. Any ongoing malignancy, or prior malignancy that currently requires treatment.
7. Patients allergic to any other PDE-5 Inhibitor
8. Patients who are participating in another interventional clinical study

Date of first enrolment
01/04/2013

Date of final enrolment
01/10/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Leicester
Leicester
United Kingdom
LE3 9PQ

Sponsor information

Organisation
University of Leicester (UK)

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (UK)

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results:	01/04/2017		Yes	No