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Glucose absorption inhibitors given during insulin withdrawal in type 1 and type3c diabetes

Submission date
28/12/2019

Recruitment status
No longer recruiting

Registration date
02/01/2020

Overall study status
Completed

Last Edited
07/08/2020

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Diabetes is a lifelong condition that causes a person's blood glucose (sugar) level to become too high.

Dapagliflozin is a new class of drug called a SGLT-2 inhibitor that is taken once a day. It is currently prescribed as a glucose lowering medication in people with type 2 diabetes. The drug may also be beneficial in people with type 1 diabetes to reduce the frequency of low blood glucose levels (<4.0mmol/L) and reduce insulin requirements.

Diabetic ketoacidosis occurs when the body is unable to use blood sugar (glucose) because there isn't enough insulin. Instead, it breaks down fat as an alternative source of fuel. This causes a build-up of a potentially harmful by products called ketones. Ketones are bad because they make the blood acid and other chemical processes in the cells do not work normally when the blood and tissues are too acid.

Case reports and early pilot clinical trials indicate that when SGLT2 inhibitors are prescribed in patients with known insulin deficiency they may be at risk of developing the potentially life threatening state of ketoacidosis in the presence of a normal glucose level. This condition can be very frightening and may need treatment in an intensive care unit.

When people take the study medication they may not be aware they are at risk of developing ketoacidosis because blood glucose levels may not increase, and the only sign that they have developed ketoacidosis is that their ketone levels have increased or they become unwell and start to vomit. However, unlike blood glucose levels, people do not routinely measure their ketone levels, therefore, an increase in ketones is unlikely to be detected (or may be missed).

The aim of this research is to develop an understanding of how Dapagliflozin regulates blood glucose levels in periods of insulin deficiency. The metabolic assessment day involves inducing a state of insulin deficiency in a controlled way and monitoring glucose and ketone levels. Ketone levels will rise. The study will be stopped and insulin given before the ketones produce a state of acidosis (ketoacidosis). It is not the intention to induce ketoacidosis but to understand how the drug works in insulin deficient patients.

Who can participate?
Patients with type 1 (where the pancreas doesn't produce any insulin) or type 3c (insulin deficiency following pancreatic conditions such as chronic pancreatitis or pancreatic surgery) diabetes, aged 18 – 65 years with HbA1c is greater or equal to 6.5% and less than 9%.

What does the study involve?
Participation in the study will last approximately 64 days.
Participants will be required to attend three visits. One will be a screening visit and the other two visits will be metabolic assessment days. Participants will need to attend at 22.00 the night before the metabolic study day and will go home the next evening around 18.00.
Participants will be randomly allocated to receive Dapagliflozin or placebo for seven days, after which they will have a metabolic assessment. Later, the participants will receive the opposite treatment, again for seven days, followed by another assessment.
To prevent developing ketoacidosis during the metabolic assessment day, the study will be stopped in the event of blood glucose rising above 18mmol/L, bicarbonate dropping below 15mmol/L or if blood becomes acidic, evidenced by venous pH falling below 7.35 or point of care capillary 3-beta Hydroxybutyrate level of >5.0.

What are the possible benefits and risks of participating?
The results of the study will potentially provide a better understanding of how the class of drug works in people with type 1 and type 3c diabetes. Participants' diabetes control may change while taking the study drug and they will receive advice on blood sugar control from the study clinician. Participants are not likely to experience any immediate benefits but there may be benefits for future people with type 1 and type 3c diabetes.

Where is the study run from?
Royal Surrey County Hospital, Guildford, UK

When is the study starting and how long is it expected to run for?
January 2018 to August 2019

Who is funding the study?
1. Diabetes UK
2. AstraZeneca, UK

Who is the main contact?
Dr Roselle Herring
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-002094-38

Integrated Research Application System (IRAS)
215268

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
3, IRAS 215268

Study information

Scientific Title
Metabolic effects of an SGLT2 inhibitor (dapagliflozin) during a period of acute insulin withdrawal and development of ketoacidosis in people with type 1 diabetes

Acronym
SIDS

Study objectives
1. Treatment with Dapagliflozin will result in a statistically significant difference in fasting plasma glucose concentration at 600 minutes following insulin cessation (or at last measured concentration prior to rescue) when compared to treatment with placebo in each of two independent studies performed on Type 1 and Type 3c people with diabetes.
2. Treatment with Dapagliflozin will result in a statistically significant difference lipid flux of Dapagliflozin when compared to placebo following insulin withdrawal

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/02/2017, South Central - Berkshire B Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)207 104 8199; nrescommittee.southcentral-berkshireb@nhs.net), ref: 17/SC/0005

Study design
Phase IV single centre randomized double-blind controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 1 diabetes and Type 3c diabetes

Interventions
Participants received in random order 7 days of placebo or dapagliflozin.

The expected duration of participant participation is approx. 64 days.

Randomisation procedure:
The participant will be assigned a study identification number and randomised to receive in random order Dapagliflozin or placebo.

To prevent developing ketoacidosis during the metabolic assessment day, the study will be stopped in the event of blood glucose rising above 18mmol/L, bicarbonate dropping below 15mmol/L or if blood becomes acidic, evidenced by venous pH falling below 7.35 or point of care capillary 3-beta Hydroxybutyrate level of >5.0.

Intervention Type
Drug

Phase
Phase IV

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

Primary outcome(s)
Plasma glucose concentration at 600 minutes following insulin cessation or at the time of glycaemic rescue, whichever occurs first, measured by blood test

Key secondary outcome(s))
1. Endogenous glucose production
2. Peripheral glucose uptake
3. Glycerol rate of appearance
Stable isotopes of glucose and glycerol will be infused from -120 to 600 minutes. From -120 to 0 minutes, blood samples will be taken to measure glucose and glycerol enrichment

4. Urinary glucose excretion
Urine samples will be collected at 2 hour intervals for measurement of spot glucose and urinary ketones (acetoacetic acid and acetone) until 600 minutes

5. Non-esterified fatty acid production
6. Ketone body production
NEFA, and 3-beta hydroxybutyrate will be taken at 20minute intervals until 180 minutes and then at 30minute intervals until 600 minutes

Completion date
01/08/2019

Eligibility

Key inclusion criteria
1. Able in the opinion of the investigator, and willing to give informed consent obtained before any study-related activities
2. Type 1 diabetes or type 3c (chronic pancreatitis or undergone pancreatic surgery) according to clinical judgment
3. Duration of type 1 or type 3c diabetes (chronic pancreatitis or undergone pancreatic surgery) greater than 12 months
4. Current treatment basal bolus insulin regime or insulin pump therapy
5. Aged 18 – 65 years
6. BMI of less than 35
7. HbA1c of greater or equal to 6.5% and less than 9%
8. Able and willing to complete the study
9. Patients who are or who have previously been involved in research are eligible provided they have not received an investigational drug within one month of entry into the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
12

Key exclusion criteria
1. Cannot adequately understand verbal and / or written explanations given in English
2. LADA –latent autoimmune diabetes in adults due to differing nature of the illness/Type 1
3. Confirmed excessive and compulsive drinking of alcohol i.e. alcohol abuse as determined from GP medical notes by the Fast Alcohol Screening Test (FAST) or history of previous alcohol abuse
4. Restricted food intake (e.g. on VLC diets) - as this depletes the person of calories and may

affect your data. Consider excluding Individuals on a severe calorie restricted diet <800cals/day. Determined by history
5. Diagnosis of osteoporosis confirmed by DEXA scan
6. Proliferative retinopathy that has required acute treatment within last three months
7. Moderate to severe renal impairment (creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²
8. History of unstable or rapidly progressing renal disease
9. Severe hepatic insufficiency / and or significant abnormal liver function defines as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and / or alanine aminotransferase (ALT) > 3ULN
10. Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IGM, Hepatitis B surface antigen and Hepatitis C virus antibody
11. Congestive heart failure defined as New York Heart Association (NYHA) class III and IV, unstable or acute congestive heart failure. Note: eligible patients with congestive heart failure, especially:
11.1. Uncontrolled cardiac arrhythmias
11.2. Uncontrolled hypertension (BP greater than 160/90)
12. Mental incapacity
13. Pregnancy or breastfeeding women
14. Those of child-bearing potential not taking adequate contraception precautions. Adequate protection is defined as barrier protection, oral contraceptive pill or intrauterine device
15. Volume depleted patients, patients at risk of volume depleting due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status
16. History of unstable angina.
17. Recent Cardiovascular Events in a patient:
17.1. Acute Coronary Syndrome (ACS) within 2 months prior to enrolment
17.2. Hospitalisation for unstable angina or acute myocardial infarction within 2 months prior to enrolment
17.3. Acute Stroke or TIA within 2 months prior to enrolment
17.4. Less than 2 months post coronary artery revascularization
17.5. History of diabetic ketoacidosis (DKA) requiring medical intervention (e.g. Accident and Emergency and/or hospitalisation) within 1 month prior to the Screening visit
18. Known or suspected allergy to study products
19. Known lactose-intolerant
20. Any other medical or psychological conditions that would interfere with the study participation

Date of first enrolment
29/01/2018

Date of final enrolment
01/08/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Centre for Endocrinology Diabetes and Research
Royal Surrey County Hospital
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Sponsor information

Organisation
University of Leicester

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Charity

Funder Name
Diabetes UK

Alternative Name(s)
The British Diabetic Association, DIABETES UK LIMITED, British Diabetic Association

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Funder Name
AstraZeneca

Alternative Name(s)

AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	08/07/2020	07/08/2020	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes