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IRAS ID: 277675
Study Number: A095470

Participant Identification Number for this trial:

PARTICIPANT INFORMATION SHEET

Title of Project: Effects of serotonin receptor agonism blood glucose lowering: Proof of concept in humans
Name of Researcher: Dr Rajna Golubic

Invitation and brief summary

We would like to invite you to participate in our research study.

This project is aiming to examine a new approach to improve the regulation of blood glucose and we are looking for overweight but otherwise healthy adults. Sumatriptan is a drug widely used for migraine treatment and data from mouse models show that it decreases appetite and lowers glucose. This glucose lowering effect of sumatriptan has not been studied in humans yet. In this study, we aim to establish in healthy overweight adults whether a single tablet of sumatriptan can improve:

1. sensitivity of the body to insulin (a hormone which regulates your blood glucose level), and/or

2. release of insulin from the pancreas

The results of this study might help design more targeted studies in people with diabetes. If ultimately proven effective, sumatriptan or similar treatments could be used in diabetes (including those treated with insulin as an "add-on" treatment) to improve glucose levels and reduce the risk of complications and substantial healthcare costs associated with this.

Taking part is entirely your decision. Before you decide whether or not you wish to take part, please read the information below carefully. You may wish to discuss it with your family, friends or healthcare team. If you would like any more information, have any questions, or something is unclear, please feel free to contact the research team using the details at the end of this document.

What is involved?

The study will take place in the Translational Research Facility (TRF) which is embedded in the NIHR/Wellcome Trust Clinical Research Facility affiliated with the Cambridge University Hospitals NHS Foundation Trust. Participation will involve a screening visit (to determine if you are eligible) and 2 visits at which you will have a single dose of either sumatriptan or placebo (tablet without active drug) and studies with glucose and insulin infusions will be performed together with blood tests as detailed below. These studies are called Botnia clamps. Drugs will be given in a random order (first sumatriptan and then placebo or *vice versa*) one at visit 1 and one at visit 2. This study is blinded so neither you nor the study doctors and nurses will know which tablet you had at which visit. This will allow us to assess the effects of the drug using a rigorous scientific approach. During the study you will be looked after by healthcare professionals (doctors and research nurses) trained in clinical research and the methods described below and they will be with you during the entire procedure.

We wish to examine how the body handles glucose and insulin in overweight healthy volunteers (aged 18-65 years) after taking a single dose of sumatriptan or placebo. There will be three visits (please also see the Table at the end of this document):

1. Screening visit

We will assess if you are eligible to participate by asking questions about your medical history, and performing a clinical examination. Your height and weight will be measured and a sample of your blood and urine will be taken. The results will be reviewed, and you will be informed if you are eligible to

attend the subsequent visits. The visit is expected to take around 1 hour. If significant abnormalities are noted on the screening visit both you and your GP will be notified by letter or telephone call and appropriate follow up arranged..

2. Visit 1

Visits will take place in the morning and you will need to come fasted (nothing to eat or drink except water from approximately 22:00 h the night before the visit). At the visit you will be given the assigned medication (sumatriptan or placebo) and asked to rest on a bed during the procedure. One intravenous cannula will be placed in each arm. The whole study visit will be performed over approximately 3 hours (Botnia clamp). You will first receive an infusion of glucose and blood samples will be taken at pre-defined time points (from the cannula, this will be around 10 times in the first hour). After 1 hour you will receive an infusion of insulin and blood samples will be taken at pre-defined time points approximately every 5 minutes. You will simultaneously receive an infusion of glucose to keep your blood glucose stable until the end of the procedure for the next 2 hours.

3. Visit 2

This is the same as Visit 1, the only difference being that the assigned medication will be the opposite of what you had at Visit 1 (i.e. if you had sumatriptan you will receive placebo and vice versa). All the visit procedures will be repeated as described in Visit 1 above.

At all visits you will be looked after by healthcare professionals (doctor and research nurses) trained in clinical research and the method described above. This study plan has been reviewed by our diabetes Patient and Public Involvement group (GRACED- Group for Research and Clinical Experience in Diabetes)- an independently chaired and functioning group established from volunteers attending the Wolfson Diabetes Endocrine Clinic in Cambridge.

The total volume of blood taken during all 3 visits is estimated to be about 150 mL . Blood samples for glucose will be analysed on the day of the procedure while the samples for insulin and the remainder of the blood taken will be stored safely in a freezer according to the standard operating procedures and analysed later. The samples will be stored for possible future ethically approved research into metabolism and diabetes for up to 5 years while maintaining security and integrity in keeping with the current legal framework. Your personal data will always be pseudonymous and will not be shared.

Do I have to take part?

No. Participation is completely voluntary and you can withdraw from the study at any point. If you would like to take part we will ask you to sign a consent form (last page of this document) to show that you have agreed to take part. There will be no consequences if you decline to take part.

What are the possible benefits of taking part?

As this is a research project,this study will not benefit you directly . However, the results of this study and your experience will help us develop targeted studies in people with diabetes to further explore the impact of sumatriptan on glucose levels in diabetic populations and if shown to be effective sumatriptan has the potential to be used as one of the treatment options in diabetes.

What are the possible disadvantages and risks of taking part?

The procedure risks include. not being able to insert an intravenous cannula on the first attempt, bruising, skin irritation and infection. Well trained staff, standardised protocols and aseptic technique are used to minimise these risks. Other risks include well established side effects of sumatriptan. Side-effects of sumatriptan occurring between 1/100 to 1/10 people include: dizziness, sensation disturbance, temporary increase in blood pressure, flushing, shortness of breath, nausea and vomiting. However, the likelihood of these side-effects is very small given that only one dose is taken in this study and if these do occur they are likely to last for a short period. Glucose infusion may cause nausea and if this happens the procedure will be stopped. Furthermore, we would like to advise you not to take a type of drug called selective serotonin reuptake inhibitor (SSRI; used for the treatment of depression) immediately after the procedure as there is an extremely small risk of developing serotonin syndrome (high blood pressure, fast heart rate, increased temperature, tremor, sweating, diarrhoea) if sumatriptan and SSRI are used together. We will review your medication at each visit to identify any potential risk and advise you accordingly.

Can the study be stopped, or can I be taken out of it?

If we find out important new information about the study, the study doctor will tell you as soon as possible, and will ask if you want to carry on being in the study. You may be taken out of the study even if you are willing to carry on. Possible reasons include: your study doctor thinks it is better for you to stop; you do not follow the study instructions; health authorities, the ethics or regulatory agencies decide that the study must be stopped.

Will it cost me anything to take part?

You will receive £100 to helpcompensate your time participating in this study (screening and subsequent two visits). To be eligible for £100 you will need to complete all visits. Travel costs will be reimbursed additionally.

Who is funding this research?

The Diabetes Research and Wellness Foundation (https://www.drwf.org.uk/)

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the _____ Research Ethics Committee and approval has been granted by the Health Research Authority.

How will we use information about you?

We will need to use information from you, your medical records, and your GP (if required) for this research project.

This information will include your initials, NHS number, name, contact details, and the values of the parameters we are interested in. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information at:

- www.hra.nhs.uk/information-about-patients
- by asking one of the research team
- by sending an email to gdpr.enquiries@addenbrookes.nhs.uk, or
- by ringing us on 01223 74847.

Who can I contact if I have a complaint?

If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer. The research team can give you details of the right Data Protection Officer. If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

What if something goes wrong?

If there are any problems during your participation in the study you can contact the research team directly.

What happens if I get injured or ill while I am in the study?

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the study caused

through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the study, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the study.

Complaints

If you have a concern about any aspect of this study, please speak to the study nurse or study doctor. They will do their best to answer your questions (contact details are provided below). If you are still unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure via the Patient Advice and Liaison Service (PALS) at pals@addenbrookes.nhs.uk and telephone number 01223 216756. NHS Trusts are responsible for clinical negligence and other negligent harm to individuals that are under their duty of care.

If you have health-related insurance, please check with your insurance company that taking part in this study will not affect your policy.

Who should you contact with questions?

You will be given a copy of this information sheet and the signed consent form to keep. The research team will keep another copy of this information sheet and the signed consent form for their records. If you have any problems or questions about this study or your rights as a patient in clinical research you should contact:

Doctors : Rajna Golubic (Tel No 07704279255; email: rg380@medschl.cam.ac.uk); Mark Evans (mle24@cam.ac.uk)

Study Nurse: Jane Kennet: (Tel No 01223 74847; email: jk605@cam.ac.uk)

24 hour contact number: 07704279255

The 24h contact number can be used out of working hours (9am – 5pm) in the event where you need you contact a hospital doctor immediately.

We would like to thank you for reading the Patient Information Sheet and for considering taking part in this clinical study. If you have any further questions please talk to the study doctor before

considering entry into this clinical study.

Contact for further information

If you have any questions concerning your rights as a study participant, you may wish to visit the INVOLVE website available at: http://www.invo.org.uk/ or contact the INVOLVE team on 023 8059 5628.

Tests and procedures that will be taken during the study

	When?		
	Screening visit	**Visit 1**	**Visit 2**
	Day -28 to -1	**Day 0**	**Day 7 to 31**
What happens?	**x**		
Informed consent	**x**		
Medical history	**x**		
Physical examination	**x**		
Weight measurement	**x**	**x**	**x**
Height measurement	**x**		
Vital signs	**x**	**x**	**x**
Bloods sample collection	**x**		
Intravenous cannula insertion		**x**	**x**
Pregnancy test (women only; urine sample)	**x**	**x**	**x**
Substance abuse screen (urine sample)	**x**	**x**	**x**
Fasted overnight		**x**	**x**
Study drug administration		**x**	**x**
Botnia clamp study		**x**	**X**
Adverse event review		**x**	**x**
Concomitant medication	**x**	**x**	**x**

NB Sumatriptan and placebo will be taken in a random order.

Overview of tests during the study

Screening visit

Blood tests at the screening visit include full blood count, urea and electrolytes, blood borne viruses (hepatitis B and C and HIV) and HbA1C (marker of glucose control over the last 2 months). Urine will be taken for a pregnancy test (women only) and to screen for drugs of abuse (such as marijuana, cocaine, amphetamines, barbiturates, opiates and benzodiazepines).

Visit 1 and Visit 2

As outlined above, Botnia clamp is a 3h-study involving intravenous glucose infusion followed by intravenous insulin with variable glucose infusion while maintaining blood glucose level stable. Blood samples will be taken frequently during the study to determine the levels of glucose and insulin in your body at specified time points.

IRAS ID: 277675
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Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Effects of serotonin receptor agonism blood glucose lowering: Proof of concept in humans
Name of Researcher: Dr Rajna Golubic

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared pseudonymouslywith other researchers. ☐

5. I consent to have blood and urine samples collected as part of this research study. ☐

6. I consent to keeping my blood samples stored pseudonymously for any future analyses that might be useful in ethically approved studies into diabetes and metabolism. ☐

7. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me or my data in any publications. ☐

8. I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the General Data Protection Regulation (GDPR). ☐

9. I agree to take part in the above study. ☐

OPTIONAL POINTS

10. I agree to my General Practitioner being informed of my participation in the study. I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team (optional). ☐

11. I understand that the information held and maintained by the Cambridge University Hospitals NHS Foundation Trust may be used to help contact me or provide information about my health status (optional). ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

NB Please file the original in the investigator site file, return a copy of the completed form to the participant and ensure a copy is filed in the participants medical records.