ROYAL ADELAIDE HOSPITAL

Do short acting glucagon-like receptor agonists (GLP-1 RAs) attenuate the 'gastric' counter-regulatory response to hypoglycaemia in type 2 diabetes?

Research Ethics Committee Protocol Application
Royal Adelaide Hospital

1. Title

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INFORMATION SHEET

PROTOCOL NAME: Do short acting glucagon-like receptor agonists (GLP-1 RAs) attenuate the 'gastric' counter-regulatory response to hypoglycaemia in type 2 diabetes?

YOUR PARTICIPATION IS VOLUNTARY

You are invited to take part in a research study conducted by Dr Chinmay Marathe, Dr Ryan Jalleh, Dr Daniel Quast, Dr Tejaswini A Murthy, A/Professor Marianne Chapman, Professor Karen Jones, Ms Jacqueline Grivell, A/Professor Adam Deane, Ms Michelle Bound, Ms Seva Hatzinikolas, Ms Deanna Sabadin , Dr Palash Kar, Professor Michael Horowitz, and Professor Chris Rayner.

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way. Also you may withdraw from the project at any time after you have commenced.

WHAT IS THE PURPOSE OF THE TRIAL?

Treatment with insulin is often required for optimal control of blood sugar in people with advanced type 2 diabetes. However, a common adverse effect of insulin treatment is ‘hypoglycaemia’ or an abnormally low blood sugar. A low blood sugar can be dangerous if it's not treated promptly, although you can usually treat it easily yourself. The human body has built-in (‘counter-regulatory’) mechanisms to restore blood sugar to a normal range. These include releasing stress hormones making one alert to the problem, creating a subjective desire to eat and increasing the rate of stomach emptying. The latter helps in increasing delivery of (carbohydrate-containing) food to the small intestine where it is absorbed aiding to get blood sugar back to normal.

Exenatide is a drug that has been shown to reduce blood sugar (glucose) levels in people with type 2 diabetes. It is a member of the GLP-1 agonist class of drugs and is commonly used for treatment of type 2 diabetes in Australia. Exenatide is given by injection under the skin (or subcutaneous) into the thigh, abdomen or upper arms two

times daily, within 1 hour (60 min) of your two main meals (for most people, the meals will be breakfast and tea/dinner).

A combination treatment of exenatide and insulin has now been approved for use in Australia. Slowing of stomach emptying is likely to be the dominant mechanism by which exenatide reduces blood sugar levels after a meal. However, the effects of exenatide during combination treatment with insulin on stomach emptying, and particularly in the setting of low blood sugar is not known. The aim of this study is to study the effects of exenatide on stomach emptying in the setting of low blood sugar in people with type 2 diabetes.

WHAT WILL YOU HAVE TO DO?

This study involves one screening visit and four test days. At an initial screening visit, prior to entering the study, you will be asked to fill out a consent form for the study and we will ask you about your medical history. Specifically, we will attempt to exclude any stomach disorders, as well as epilepsy, heart disease and previous/present allergies. You will also need to inform us of any medication that you are currently taking and how much alcohol you consume. If you are a patient with type 2 diabetes taking metformin, you will be asked to refrain from taking your medication for the 48 hours prior to the gastric emptying studies. You will be advised to recommence the metformin at the meal following the gastric emptying study. You will also have a blood sample (10mL) collected for the assessment of liver and kidney function and the normal components of blood.

You will receive 'exenatide + usual treatment' for 4 weeks or 'placebo + usual treatment' for 4 weeks (in random order). After a 1 week washout period, the participants receiving 'exenatide + usual treatment' for 4 weeks will then switch to 'placebo + usual treatment' for 4 weeks and vice versa, thereby ensuring each participant receives 4 weeks of exenatide treatment.

Stomach emptying will be measured on four occasions – two measurements at the end of 'Period 1' of the intervention and two after 'Period 2' of exenatide or placebo treatment. Both periods will be 4 weeks each. The stomach emptying measurements at the end of each period will be performed once in the setting of normal and once in low

blood glucose. All studies will be performed in the Royal Adelaide Hospital. Each study day will take approximately five hours, beginning at about 8.30 am on each day. For each test, you will be asked to have a standardized lasagna meal (which will be provided in advance by the study team) on the prior evening and then fast (14 hours for solids and 12 hours for liquids) till you arrive to the research center the next morning. Smoking will be prohibited for 12 hours prior to and on each study day.

Cannulation

On the morning of the study, cannulas (needles) will be inserted into forearm vein – one in each arm (which may be associated with minor, temporary, discomfort) for periodic measurement of blood sugar levels and hormones as well as infusing glucose and insulin.

Measurement of stomach emptying

You will be seated in semi-recumbent position with a special camera positioned above your stomach region that will measure the rate at which your stomach empties a solid meal containing beef patty and water. The beef patty will also contain a small amount of radiation (which can be detected by the camera) and your stomach emptying will be measured for approximately 180 minutes (i.e. 3 hours). You will be given an injection of exenatide/placebo within 60 min of the study mean. At the end of each study day, you will be offered a cold buffet-style lunch. Feelings of hunger and fullness will be evaluated using questionnaires throughout the study days.

Glucose-insulin clamp

A glucose-insulin clamp sometimes simply referred to as the ‘clamp’ will be performed on each of the study days. This is called a clamp as your blood sugar level will be ‘clamped’ or ‘maintained’ at a specific concentration (in this study, at either 6 mmol/L or 2.6 mmol/L). This is achieved by infusing both insulin (a hormone which lowers blood glucose) and glucose. Insulin will be infused at a steady, continuous rate. Blood sugar will be measured every 5 min, so that enough glucose can infused to keep blood glucose just right. Thus, glucose infusion rate will be variable and dictated by your latest blood glucose level. The ‘clamp’ will last while the emptying of the stomach is measured. The visits when blood sugar is maintained at a ‘low’ level (2.6 mmol/L) will be referred to as the ‘hypoglycaemic’ clamp and this state will be maintained for 60

min. For the remainder of the period of measurement of stomach emptying, blood sugar will be maintained at 'normal' blood glucose i.e. 6 mmol/L.

Blood sampling

The amount of blood taken over the four study days plus the screening visit, in total, will be approximately 450mL. For comparison, the amount taken in an Australian Red Cross blood donation is between 350mL to 470mL. Your hemoglobin levels (i.e. your body's red cell count) will be tested prior to the study; in a patient with normal levels of hemoglobin, this amount of blood loss will not cause any adverse effects. You should refrain from blood donation for the period of 10 - 12 weeks both prior to and following the study in line with the Australian Red Cross guidelines.

At the end of the study, the cannulas will be removed. We will monitor your blood sugar level before sending you home to ensure that they are at a normal level.

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

RISKS AND DISCOMFORTS

Placement of the needle in the vein of your arm may be associated with some minor, and temporary discomfort; bruising, infection or thrombosis may also occur due to the insertion of the needle. Exenatide has been approved by the Therapeutic Goods Administration (TGA) of the Commonwealth Department of Health and Ageing for use in the management of diabetes and the dose of exenatide we are administering has been used in other studies, without causing any serious side effects. At higher doses than we plan to use in this study, exenatide has been associated with nausea and vomiting which has been transient. Should you experience any side effects, we will discontinue the study. As exenatide is given as an injection under the skin (subcutaneous), skin puncture may be associated with some minor, and temporary discomfort; bruising, and in rare and extreme cases, inflammation or infection. Exenatide is being taken only for

the purpose of the study. The study doctor will provide you with a document that contains additional information about exenatide (Byetta ®).

This research study involves exposure to a very small amount of radiation- approximately 2 milliSieverts (mSv) in total for the four studies. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 mSv each year. At this small dose, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be very low and the level of radiation considered safe for you as long as you have not also been exposed to radiation in other research projects in the last twelve months. Please discuss this with the investigator if you have had any exposure to radiation as a research project volunteer in the last twelve months.

The clamp will be performed by medical and research staff trained in this technique and a medically trained doctor will always be present. Your blood sugar level will be kept at 'moderately' low blood sugar (2.6 mmol/L) levels for 60 minutes on two study visits. You may experience some symptoms during low blood sugar levels including pounding heart, shakiness, sweating, headache and difficulty thinking. The degree (2.6mmol/L) and duration (60 min) of the low blood sugar level are not considered hazardous. Participants who have had high blood glucose levels (poorly controlled) for a long period, may experience increased symptoms. The research trolley will be stocked with emergency management for low blood glucose.

WHAT IF SOMETHING GOES WRONG?

You will be asked about discomfort frequently during the study and should you experience any significant side effects, we will discontinue the study immediately. Any adverse events that occur during the study and may, or may not be, related to the study will be dealt with immediately by a fully qualified doctor.

In the event that you suffer a study-related injury, care will be provided to you through the public hospital system. You will be monitored and then a taxi may be organised to take you home. You should contact us if any of the side effects persist or concern you.

RESEARCH RELATED INJURY

In the event you believe you have sustained any injury or side effects from this study, you should contact the investigators using the telephone numbers listed below. If hospital assessment or treatment is needed as a result, you would receive care within the public hospital system. The study has been indemnified by SA Health and the University of Adelaide but in the case of a study-related injury you also have the right to seek compensation through the legal system.

WITHDRAWING FROM THE STUDY

You are free to withdraw at any stage of the study. If you decide to withdraw, we will cease the hypoglycaemic clamp immediately and provide intravenous and/or oral source of glucose to return the blood glucose to normal baseline levels. Your blood glucose will be monitored and ensured that it is in the normal range prior to discharge. We will ensure that you are asymptomatic and feeling well prior to discharge and therefore it is necessary that you remain at the study centre until it is safe for you to leave.

IS THERE ANYTHING TO GAIN FROM PARTICIPATING?

This study is designed to provide information about the effect of the drug, exenatide, on stomach emptying during low blood sugar levels, in people with type 2 diabetes and will not directly benefit you. However, if our hypothesis proves right, the results have the potential to change current practice of prescribing combinations of medications for type 2 diabetes in the future. We estimate you will spend approximately five hours in the hospital on each study day. Payment for your participation is by way of an honorarium at the rate of $20 per hour. If you withdraw from the study prior to completion, you will be reimbursed for the period of your involvement.

CONFIDENTIALITY AND DATA SECURITY

Your participation in this study is strictly confidential, and will not be disclosed to other medical or research staff unless you agree, or if disclosure is required by law. Once you have been enrolled in our study, you will be given a study participant code, and only study investigators will have access to your name and personal details. If information

that we gather from this study is published in any form, it will be done so in a way that does not allow you to be personally identified in any way.

The data collected will be in the form of demographic details and blood specimen of human participants. It will be de-identified in the public domain and will be kept at the premises of Adelaide Medical School until the results of the study are published in peer-reviewed journals and potentially for longer duration so as to facilitate follow-up studies. The data will be accessible, under normal circumstances, only to the investigators. The specimens will, under normal circumstances, be used by the investigators only and all analyses will be performed locally. Rarely, specimens may be shipped to academic institutions globally, to analyse for special investigations not available locally.

In addition to the processes described above, data may otherwise be discoverable through processes of law or for assessing compliance with research procedures. You have a right to access the information collected and stored by researchers about you. You also have a right to request that any information with which you disagree be corrected. You have a right to ask that any stored specimens be destroyed but should be aware that data which has already been derived from those specimens may not be able to be destroyed.

NAMES AND CONTACT NUMBERS OF INVESTIGATORS

Should you have any questions or concerns before or after the study, please contact *Dr Chinmay Marathe (ph: 8313 6497. Email: chinmay.marathe@adelaide.edu.au)* .

INDEPENDENT CONTACT

The Human Research Ethics Committee (HREC) of the Central Adelaide Local Health Network has approved this study. If you would like to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also like to contact the Chairman Mr Ian Tindell, Human Research Ethics Committee of the Central Adelaide Local Health Network (CALHN HREC) on **7117 2229** or email: Health.CALHNResearchEthics@sa.gov.au.

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CONSENT FORM

PROTOCOL NAME: Do short acting glucagon-like receptor agonists (GLP-1 RAs) attenuate the 'gastric' counter-regulatory response to hypoglycaemia in type 2 diabetes?

INVESTIGATORS: Dr Chinmay Marathe, Dr Ryan Jalleh, Dr Daniel Quast, Dr Tejaswini Murthy, A/Professor Marianne Chapman, Professor Karen Jones, Ms. Jacqueline Grivell, A/Professor Adam Deane, Ms Michelle Bound, Ms Seva Hatzinikolas, Ms Deanna Sabadin, Dr Palash Kar, Professor Michael Horowitz and Professor Chris Rayner.

The nature, purpose and the risks of the research project has been explained to me. I understand them and agree to take part.

1. I understand that I will not benefit from taking part in the study.
2. I understand that while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
3. I understand that I can withdraw from the study at any stage and that this will not affect my medical care, now or in the future.
4. I understand the statement concerning payment to me for taking part in this study, which is contained in the **Information Sheet**.
5. I have not been a volunteer in any other research projects that have involved radiation exposure in the last twelve months.
6. I have not donated blood in the last 12 weeks.
7. I have had the opportunity to discuss taking part in this investigation with a family member or friend.
8. I have adhered strictly to the dietary instructions given to me and my consent is given voluntarily.
9. I also have not been smoking for at least 12 hours prior to the study.
10. (For female participants) I understand that I should not be pregnant to take part in the study. In the event of a pregnancy occurring, I agree to notify the investigators as soon as practically possible.

Name of Participant:

Signed:

Dated:

FOR THE USE OF STUDY MEDICAL PRACTITIONER:

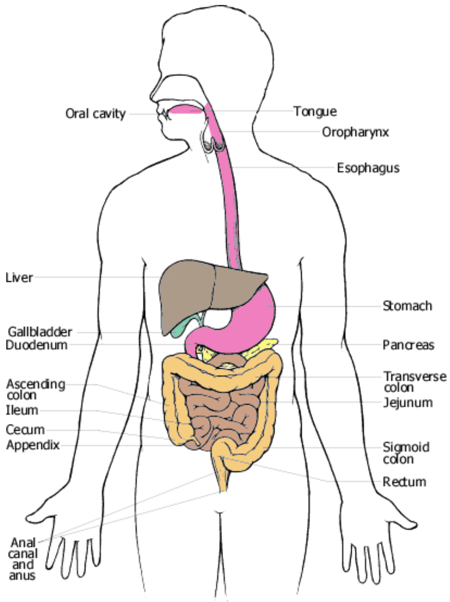
I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

Signed: _____

Date_____

ARE YOU INTERESTED IN TAKING PART IN A DIABETES RESEARCH STUDY?

The Faculty of Health and Medical Sciences, Adelaide Medical School is conducting studies to understand the effect of exenatide (a drug used in the management of diabetes) on the stomach during low blood sugar levels



You may be eligible if you:

- **Have type 2 diabetes**
- **Are aged 40 - 65 years**
- **Are diet controlled or on metformin**
- **Do not have any other significant medical illnesses: *(e.g. gastrointestinal or heart disease)***

If you are interested in taking part in a research project, please call Ms Jacqui Grivell (8313 6691)

Study participation is voluntary, however, an honorarium will be given for time spent in our department.

This study is approved by the Royal Adelaide Hospital Ethics Committee

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