

Gut derived hormones, body composition and metabolism in Prader-Willi Syndrome

INFORMATION FOR PERSON RESPONSIBLE

Introduction

The person for whom you are responsible for making medical decisions (hereinafter called "your relative/friend") is invited to take part in a research study into how appetite regulating hormones are disturbed in individuals with Prader-Willi Syndrome. The objective is to investigate whether the abnormal eating behaviour in these individuals is a result of disturbances of the hormones that control satiety and hunger, and whether this disturbance might be the cause of developing obesity and related complications.

Furthermore, the study will examine the appetite regulating effects of the drug Exenatide (Byetta®) which has been approved in Australia in September 2007 for the treatment of type 2 diabetes. Because it also reduces food intake and causes weight loss, it also is a promising drug for subjects with Prader-Willi Syndrome and obese individuals without diabetes.

The study is being conducted within this institution by

- Prof. Lesley Campbell, Diabetes & Obesity Research Program, Garvan Institute of Medical Research, Darlinghurst

in collaboration with:

- Associate Professor Kate Steinbeck and Georgina Loughnan, Prader-Willi Syndrome Clinic, Royal Prince Alfred Hospital

The study is being supported by the Prader-Willi Syndrome Association of NSW.

Study Procedures

If you allow your relative/friend to participate in this study, you will be asked to sign the Person Responsible Consent Form.

You and your relative/friend will then be invited to come to the Garvan Institute of Medical Research on two different occasions for metabolic studies and a meal test as described below. These tests altogether will take a maximum of 8 hours on each occasion. It is important that your relative/friend has fasted (ie nothing to eat or drink except clear water) for at least 8 hours, from midnight the day before. The study will usually start at 8.00am.

If your relative/friend is of childbearing age we will perform a quick urine pregnancy test. If pregnant, she cannot enter the study.

You will need to arrive at the clinical research facility at 8.00am. A cannula will be placed in a vein in your relative/friend's arm for blood sampling.

Thereafter, a single injection of either the drug Exenatide or placebo (saline) will be injected into the fat under the skin (abdomen or thigh) with a fine needle. Since we will be assessing the effect on your relative/friend's appetite, it is important that we do not let your him/her know which substance he/she receives on which visit.

Then a defined meal will be served to your relative/friend. The meal should be eaten within 15 minutes together with 500 ml of water. During the next 4 hours we will take blood samples for testing blood glucose, insulin, different hormones and lipid levels.

Before and 4 hours after the meal we will measure the energy expenditure/metabolic rate (calorimetry). A ventilated plastic hood will be placed over your relative/friend's head and shoulders for about 20-30 minutes during which samples of inspired and expired air will be collected to estimate the degree of oxygen consumption and carbon dioxide production. The resting metabolic rate gives us an indication of how many calories the body burns even while resting.

Appetite will be assessed before and after the meal with a visual analogue scale (appetite rating on a score from 0 to 10).

Arterial stiffness will be measured before and continuously every 30-60 min after the meal by a tonometer (sensor for pressure) which will be placed over the radial artery, compressing, but not blocking, the artery against the underlying bone. The arterial blood flow allows us to calculate its stiffness, where a high stiffness has been shown to be a risk factor for future cardiovascular diseases. The procedure is non-invasive and completely painless.

On the same day of only the first visit, we will also perform a scan (DXA-scan) of the body to determine your friend/relative's body fat composition. This is entirely non-invasive. It is the most common test used to assess bone density in relation to osteoporosis.

Your relative/friend will be lying on a table wearing a hospital gown while the scanner emits low energy x-rays and a detector passes along the body. The scan takes about 5 minutes and the radiation dose is low (equal to about 12 hours of background radiation).

At the end of the study day (approximately at 4.30 p.m.) we will provide a light snack. After that, the study day is finished and you can leave the unit.

During the visit we would like to ask you as a parent/carer to fill out two short questionnaires (each lasting about 5 minutes) about excessive food intake and other behaviour traits of your relative/friend. You will also be given a short follow-up questionnaire to assess possible effects of Exenatide on your friend/relative during 24 hours after the visit.

The blood samples will be frozen for later analysis in our laboratory. From the blood samples we will measure the different hormones that are known to be important in the regulation of hunger and satiety. These hormones are called Peptide YY, Ghrelin, Pancreatic Peptide and Glucagon-like Peptide-1. There are other hormones which might also have a role in the regulation of satiety.

In addition, the researchers would like to have access to your relative/friend's medical record to obtain information relevant to this study.

Discomfort, inconveniences and risks of participating in the study

Discomfort and risks that your relative/friend may experience during the study are expected to be mild.

1. Blood sampling: Your relative/friend may experience slight pain when we insert the needle for blood sampling. If you wish, we can apply an anaesthetic cream to the skin before inserting the needle. Risks: There is a low risk however that irritation of the skin will occur after placing intravenous cannulae. The drip can occasionally cause some mild irritation or clotting of the vein or bruising, but these are usually temporary and are expected to resolve completely.

2. The subcutaneous injection of Exenatide or placebo could cause slight pain and minor bruising of the skin. Although we are only injecting a single dose of Exenatide we cannot entirely exclude the occurrence of the known side effects of this drug, including nausea and vomiting, diarrhoea, stomach ache, headache, dizziness and low blood sugars. Although these side effects are unlikely to occur, we will monitor for them closely during the study. Occurrence of these symptoms is usually not linked to a harmful effect on your body. Inflammation of the pancreas gland (pancreatitis) has been reported as a very rare complication of Exenatide. Pancreatitis may cause severe abdominal pain which may be accompanied by nausea and vomiting. Pancreatitis has never been reported after single dose Exenatide as we use in this study.

3. Calorimetry: your relative/friend will be asked to lie flat for 30 minutes for the measurement of the resting metabolic rate. A hood will be placed over the head and shoulders for approximately 20 minutes. If your relative/friend find confined space or lying flat anxiety-provoking, please discuss this with us.

4. DXA scan: The radiation exposure associated with the DXA scan is less than 5 microsieverts (units commonly used to quantify radiation). This is a very small amount of radiation. To put this in perspective, radiation exposure is approximately 50 microsieverts from a chest x-ray and 8 microsieverts from background radiation in an average day. Harmful effects of radiation have not been demonstrated at this dose and the risk of any harmful effect is minimal. If your friend/relative has participated in other research studies involving x-rays or nuclear medicine tests (in addition to those which were required as part of normal medical treatment) in the last 5 years please inform one of the study coordinators of these details. There is a radiation dose limit for volunteers of 10 milli-sieverts per 5 year period.

For women in the childbearing age we will exclude a possible pregnancy with a quick test before this investigation.

Benefits

While we intend that this research study furthers medical knowledge and may improve treatment of *Prader-Willi Syndrome* in the future, it will not be of direct benefit to your relative/friend.

The drug Exenatide will not be available for your relative/friend after the study finishes. Because this is a pilot study with only a single injection of Exenatide, further studies are warranted before approval of its use in individuals with Prader-Willi Syndrome can be expected.

Costs

You will not be paid for participation in this study. However, we will reimburse you for travel to the Garvan Institute (train, bus, taxi, parking, etc.) up to a limit of 50 AUD, negotiable on prior arrangements with us. If you are living outside NSW, we will contribute to the expenses for air fares and accommodation according to prior arrangements with our study coordinator *Trish Humphreys*.

Voluntary Participation

Participation in this study is entirely voluntary. Your relative/friend does not have to take part in it. If they do take part, you can withdraw them at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your friend/relative's medical treatment or relationship with the staff who are caring for them. Of the people treating them, only Kate Steinbeck, Georgina Loughnan and the nursing staff from the Metabolism & Obesity Services and The Prader-Willi Syndrome Clinic at Royal Prince Alfred Hospital will be aware of your relative/friend's participation or non-participation.

Confidentiality

All the information collected from your relative/friend for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Further Information

When you have read this information, *Dr. Alexander Viardot* or Trish Humphreys will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact them on (02) 9295 8313 (*Dr. Viardot*) or (02) 9295 8257 (*Trish Humphreys*).

This information sheet is for you to keep.

Ethics Approval

This study has been approved by the Human Research Ethics Committee of St. Vincent's Hospital. If you have any questions about the rights as research participant, please contact, Executive Officer, St Vincent's Hospital Research Ethics Committee (phone 8382 2075, fax 8382 3667, e-mail research@stvincents.com.au) and quote protocol number H07/045.

This study has also been approved by the Ethics Review Committee (RPAH Zone) of the Sydney South West Health Service. Any person with concerns or complaints about the conduct of this study should contact the Secretary on 02 9515 6766 and quote protocol number X07-0178.