CONSENT FORM

Title: Intra-nasal Naloxone for treatment of impaired awareness of hypoglycemia

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You are being asked to be in this study as you have been identified as someone who is in good health and interested in being involved in research studies. This study is being conducted by Dr. Amir Moheet and his colleagues at the University of Minnesota.

The purpose of this form is to provide to you information regarding this clinical research study. This form may contain words that you do not understand. Please ask the study doctor, or a member of the study staff to explain any words or information that you do not clearly understand. It is important that you provide complete and accurate information concerning your medical history and any medications you are currently taking or have taken in the past. False, misleading or incomplete information that you give could have a serious effect on your health.

Why is this study being done?

Low blood sugar is also called hypoglycemia. Usually, it is mild and can be treated quickly and easily by eating or drinking a small amount of a sugar-rich food. If low blood sugar is left untreated, it can get worse and cause confusion, clumsiness or fainting. Severe hypoglycemia can lead to seizures, coma, and even death.

Some people with diabetes do not have early warning signs of low blood sugar. This condition is called hypoglycemia unawareness. It happens when the body stops reacting to low blood sugar levels and the person does not realize that they need to treat their hypoglycemia. This can lead to more severe and dangerous hypoglycemia.

The purpose of this study is to examine the effects of a drug called Naloxone on hypoglycemia. The information that is collected during this study will help researchers determine if this drug should be studied more in people with Type 1 diabetes and hypoglycemia unawareness. Naloxone is a medication that is used for the treatment of opioid overdose. It has been approved by the Food and Drug Administration (FDA) for use in the United States and is currently sold as Naloxone Injection or nasal spray. This study will evaluate the Naloxone when given as intranasal (nasal spray) administration.

How long will the study last?

Each person in this study will participate for approximately 12 weeks. The study will be done in two parts separated by approximately 8 weeks.

What is involved in the study?

If you agree to participate in this study, you will be asked questions about your medical history to make sure you are eligible to be in this study. We will ask you to not use cigarettes, alcohol, or caffeine for at least 8 hours before the start time of the study visit. In addition you will be asked not to engage in heavy exercise or strenuous physical activity 24 hours prior to your visits. The study will start in the morning after an overnight fast. You will be asked to fast for a minimum of 8 hours before arriving at the research center.

Part 1

On Day 1 of Part 1, you will be asked to come to the Clinical Research Unit (CRU) by 7AM after fasting overnight. If you are female, a pregnancy test will be done. A physical examination will be completed and will include measuring your blood pressure, heart rate and body temperature.

Two IVs will be placed in your arms. This will allow us to give you insulin, glucose and potassium and for the collection of blood samples. The arm used for blood drawing may be placed in a heated blanket for the duration of study to speed up blood flow and allow for easy withdrawing of blood.

This is a randomized, cross-over study which means that you will receive both naloxone and a placebo but which one you start with is randomly assigned. There are two parts to this study and you will start with one type of study drug (naloxone or placebo) and finish with the other (placebo or naloxone). The placebo will be saline spray.

The treatment you start with will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being starting with either treatment.

After 30 minutes, you will be given either a 4 mg or 8 mg dose of naloxone or placebo into your nose (intra-nasally). You will not be told whether you are receiving naloxone or placebo.

After the initial dose of naloxone or placebo, infusions of insulin and potassium will be started. Insulin is a hormone that your body makes naturally and it causes your blood sugar to decrease. Potassium is a salt-like substance that is present in the blood. Your blood sugar will be checked every five minutes throughout the study and we will let it fall to a value of around 50 mg/dl. Once it gets that low, we will keep it there by infusing glucose. If you received the 4 mg dose of naloxone or placebo, a second 4 mg dose will be given after 30 minutes. We will continue the insulin and potassium infusions for 120 minutes and then give you glucose to return your sugar to normal.

During the study, blood will also be collected about every 30 minutes for measurement of hormones and other chemicals. You will also be asked to complete questionnaires about any symptoms you may be experiencing. Your blood pressure will be measured during this time.

About 2 hours after your sugar is returned to normal, insulin and potassium will be started again. At this time you will receive another 4 mg or 8 mg dose of naloxone or placebo into your nose. Your blood sugar will be checked every five minutes and we will let it fall to a value of

around 50 mg/dl. Once it gets that low we will keep it there for 120 minutes similar to the morning session. After 120 minutes we will give you glucose to return your sugar to normal.

Once your sugar is in the normal range, you will be given a meal and allowed to leave the research center with the plan to return the next morning.

The following day (Day 2 of Part 1) you will arrive at the CRU by 7 AM after fasting overnight. The morning will proceed similar to the morning of Day 1, except you will not receive any study drug. Two IV lines will be placed in your arms and infusions of insulin and potassium will be started. Your blood sugar will be checked every five minutes and we will let it fall to a value of around 50 mg/dl and held at this level by infusing glucose. We will continue the infusions for 120 minutes and then give you glucose to return your sugar to normal. We will collect blood about every 30 minutes and ask you to complete questionnaires about any symptoms you are experiencing.

At the end of the study, we will return your blood glucose to a normal level and you will be given a meal and sent home.

Day 1 will be approximately 8 hours long and Day 2 will be approximately 4 hours long. You will be either reclining or lying in a bed for most of this time.

Part 2

Part 2 will be done approximately 8 weeks later. Part 2 will also consist of a Day 1 and Day 2 and will be exactly like part 1, except if you were given naloxone during part 1 you will now be given placebo. If you were given placebo during part 1, you will be given naloxone in part 2.

Risks of Being in the Study:

The study has several risks, which are understood, and measures to minimize the risks have been established:

1. Infusions/blood drawing: Occasionally individuals may have some bruises afterwards where the catheter was inserted. Some people experience a burning or cramping in their arm when glucose or potassium is infused. This feeling goes away when we reduce the rate at which the substance is given to you. Rarely an individual may experience inflammation of the vein (phlebitis). If this happens, your arm may feel sore for a couple of weeks and your vein may feel lumpy. These symptoms usually go away with local heat and elevation of the extremity. Participants will be observed closely for these complications, and if these complications occur, care will be promptly and appropriately administered. The maximum amount of blood that will be collected during each part of the study would be around 20 tablespoons and the maximum amount of blood that will be collected during the entire study (including part 1 and part 2) will be around 40 tablespoons. We will not allow you to be in the study if you have given or expect to give a similar amount of blood in the month before or after the research procedures.

2. Hypoglycemia (low blood sugar): Symptoms of hypoglycemia include sweating, shakiness, confusion, increased heartbeat and feeling "low". It is reversed within minutes by stopping the insulin infusion and by raising your blood sugar by increasing the rate of glucose infusion. When you are participating in the low blood glucose protocol of the study we expect you will develop some of these symptoms during the study. To be certain that your blood sugar level does not drop less than 30 mg/dl, we will check your blood every five minutes during the study and adjust the amount of sugar we give you by vein to keep your blood sugar at the correct level. If the blood sugar drops below 20 mg/dl, confusion, seizures, coma or abnormalities in heart rhythm can occur. With careful monitoring, it is very unlikely that your blood sugar will drop to less than 30 mg/dl.

3. Intra-nasal naloxone: Side effects of intra-nasal naloxone include increased blood pressure, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, and nasal inflammation.

Benefits of Being in the Study

There are no direct benefits of participation to you as this is strictly an experiment.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Compensation:

You will be paid $150 per day of participation to cover expenses. You will be paid this amount even if you are unable to complete the entire study or if you withdraw partway through a visit. If you complete all the parts of the study (i.e. days 1 and 2 of the two parts) total compensation would be $600.

Payment you receive as compensation for participation in research is considered taxable income. If payment from the University of Minnesota to an individual equals or exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants that equal or exceed $600 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS. You will be asked to fill out an IRS W9 form which will contain your social security number.

Confidentiality:

The records of this study will be kept confidential. In any sort of report we might present or publish, we will not include any information that will make it possible to identify you. Your records may be examined by departments of the University with regulatory authority. To that extent, confidentiality is not complete.

Protected Health Information (PHI):

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study:

Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

New Information:

If during the course of this research study, there are significant new findings discovered which might influence your willingness to continue, the researchers will inform you of those developments.

Contacts and Questions:

The researchers conducting this study are Amir Moheet, MD (612-624-3209); Lisa Coles, PhD (612-624-1861). You may ask any questions you have now. If you have questions later, you are encouraged to contact them at the numbers listed behind their names.

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 or go to https://research.umn.edu/units/hrpp/research-participants/questions-concerns. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

CONSENT FORM

Statement of Consent:

I have read the above information, asked questions and have received answers, and I consent to participate in the study.

You will be given a copy of this form to keep for your records.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

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Printed Name of Person Obtaining Consent