

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient
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INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 11-CH-0208 PRINCIPAL INVESTIGATOR: Lynnette Nieman, M.D.

STUDY TITLE: Effects of the Glucocorticoid Antagonist, Mifepristone, on Glucose Intolerance in Obese and Overweight Individuals

Continuing Review Approved by the IRB on 11/29/16
 Amendment Approved by the IRB on 12/16/15 (Q) Date Posted to Web: 12/17/16
 Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Nature of the Study

Cortisol, a hormone produced by the adrenal glands, is an important regulator of metabolism. Blood levels of cortisol have a natural day-to-night pattern so that the highest levels occur in the morning and lowest levels at night. This diurnal rhythm is maintained by a normal "feedback" so that the body recognizes when there is enough cortisol and turns off production and when levels get low, cortisol production is switched back on. The switch that increases cortisol is a hormone called ACTH, which is made by the pituitary gland located at the base of the brain. ACTH levels increase or decrease to cause the changes in cortisol secretion.

Some studies have shown that individuals with central obesity and insulin resistance have higher than normal cortisol levels (either in the blood or at the tissue level), lose the natural diurnal rhythm, and have abnormal dynamic cortisol tests. It is therefore thought that cortisol abnormalities may play an important role in the development of glucose intolerance and

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insulin resistance.

Mifepristone is a drug that blocks the actions of cortisol in the body. This study is designed to better understand the role of cortisol in the development of glucose intolerance.

Study Design

Your Involvement

We invite you to participate in this study if you are between the ages of 35 to 70 years are overweight or obese, and have abnormal glucose levels. You may not enter the study if you have conditions that may affect the study results. This includes use of estrogen therapy, use of medications for treatment of diabetes, sleep disorders, certain psychiatric disorders, severe kidney, liver or heart problems, known history of infection with human immunodeficiency virus (HIV) and history of cancer of the uterus or unexplained vaginal bleeding.

Screening Visit

Potential participants first will be seen at the Clinical Center to assess if they may enter the study. This will include measurement of height, weight, waist and hip circumference, blood pressure, electrocardiogram (heart rhythm tracing) and a history and physical examination. After an overnight fast, blood will be drawn for glucose, hormone levels to assess for postmenopausal state, and other basic blood tests to examine your general health status. Women will also undergo a transvaginal ultrasound test to look at the thickness of the lining of their uterus and will have a blood pregnancy test. A magnetic resonance imaging (MRI) scan will be performed ONLY IF the transvaginal ultrasound is unable to provide an accurate measurement of the thickness of the lining of the uterus. MRI uses a strong magnetic field and radiowaves instead of x-rays to obtain images of body organs and tissues. Since x-rays are not used, there is no risk of radiation exposure. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie still on a table that can slide in and out of the cylinder. Scanning time may vary from 20 minutes to an hour. Individuals with fear of confined spaces may become anxious during this procedure. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at anytime. As part of the MRI study, you may receive a contrast agent into your vein that is gadolinium-based. These agents are approved by the FDA for use with MRI imaging.

An oral glucose tolerance test also will be performed at the screening visit in the morning after a 12-hour fast. As part of this test, you will be asked to drink a sweet beverage over a 5 minute period and blood samples will be drawn from an intravenous catheter (IV) placed in your arm. The results of the test will tell us how high your blood sugar levels go and this will be used to make the diagnosis of pre-diabetes and diabetes. Some people do not like the sweetness of the beverage and may feel nauseated.

Individuals who are eligible for the study will continue with the visits below. Women will have a blood pregnancy test 1 – 2 days before initiation of testing at each admission. Only women with a negative result will continue in the study.

Study Outline

The study involves testing before and after seven days of treatment with each of two study medications - placebo every 6 hours or mifepristone 50 mg every 6 hours. Each person will take both the placebo and mifepristone treatments, but you will not be told which treatment you are receiving and you will undergo each treatment only once. As a result you will be studied on each of the two treatment arms exactly once in a random order.

Each treatment involves 3 days of baseline testing before beginning the study drug, then seven days of treatment with the study drug, followed by 3 days of post-treatment testing. There will be a gap of at least six and no more than eight weeks

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between the two treatments and therefore the total duration for the study will be at least nine weeks. You will be asked not to start on any new diet or exercise regimen during the entire study.

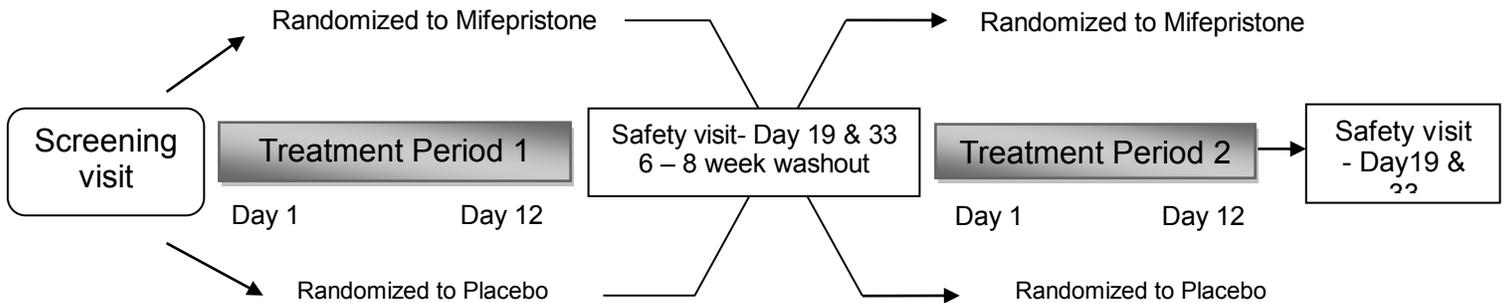


Figure 1: Study Design Overview

Study Procedures

For each treatment, you will be admitted to the 5SWN metabolic unit in the Clinical Center on a Sunday for testing to begin the following day.

Day 1 (Monday): Body Measurements, blood drawing for glucose, cortisol and ACTH, 24 hour urine
 Height, weight, waist, hip and neck circumference and blood pressure (mean of three measurements) will be recorded. Blood pressure will be measured after you have been laying down for at least 5 minutes. You will be asked to not smoke or drink caffeine (found in coffee, tea and some soft drinks) for 30 minutes before the blood pressure measurement. After a morning fasting blood draw, an IV will be inserted into a vein in the arm at 8 am. We will be using this IV line to draw blood every hour from 9 AM on Monday to 9 AM on Tuesday for measurement of cortisol and ACTH levels. During this 24 hours of blood draws, you can choose to sit or lay down. You may get up at any point to use the bathroom. You will be allowed to use a computer or watch TV if the programs will not stress or excite you too much. Getting either too excited or stressed can affect the cortisol levels that will be studied. A 24 hour urine collection for measurement of cortisol and its break down products will also be done on the same day. Blood will also be drawn before and two hours after breakfast, lunch and dinner for glucose measurements. You will be allowed to take water, but no food or drinks with calories after 8 PM.

Day 2 (Tuesday): Testing for how the body reacts to intravenous glucose and insulin
 After finishing the 24 hour urine collection and the hourly blood draws, you will undergo a frequently sampled intravenous glucose tolerance test (FSIVGTT). This test will help us find out how your body reacts to insulin. In the morning, two IVs will be placed, one in each arm. At the start of the test, glucose will be given to you through the IV over one to two minutes. Twenty minutes later, a small dose of insulin will be given through the IV. You will be monitored very carefully while blood samples are taken for the next three hours. The risks from this test include the possibility of slight arm tenderness during the glucose infusion, flushing and mild nausea during the glucose infusion and low blood glucose levels after the insulin is given. With low blood glucose, people may get hungry, have a headache, feel shaky or dizzy or may sweat or become drowsy. If low blood glucose does occur, the test will be stopped and you will be given juice or glucose by vein to raise the blood glucose to normal. After completion of the intravenous glucose tolerance test, you will be allowed to go on pass if you can return the next morning by 8 AM.

Day 3 (Wednesday): Testing for how body reacts to glucose load by mouth

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A 3-hour 75-gram oral glucose tolerance test, as described earlier, with blood draws every 30 minutes will be performed on the third day of testing before and after the study drug.

After the conclusion of the day 3 study, you will be provided with the study drug and allowed to go out on pass with instructions to begin taking the study drug at 6 PM, and continue to take it every 6-hours (midnight, 6AM, noon and 6PM).

Day 4 – 9 (Thursday – Tuesday): You will continue taking the study drug as instructed for seven days and will return to the 5SWN metabolic unit for admission on day 9 of the study (Tuesday), bringing the remaining study medication and the pill bottles with you.

Day 10– 12 (Wednesday-Friday): After an overnight fast, all study procedures indicated for day 1 - 3 will be repeated on day 10 - 12. You will continue taking the study drug until the completion of all study procedures on day 12.

Day 19 and 33 (± 5 days): Approximately one week and then three weeks after the last day of study drug intake, you will return for follow-up safety visits where you will undergo a brief history and physical exam and blood will be drawn for measurement of blood chemistries and blood counts.

These study procedures will be repeated for the second treatment after a gap of 6-8 weeks. The pre-study drug testing (Days 1 through 3) for each treatment can be done on days other than as specified above as long as it is done no more than 10 days before you start taking the study medication.

Testing for how cortisol is handled by the body

This study will be performed only once during the study- at least one and no more than two months after completion of the second treatment arm. An IV will be placed for blood drawing to measure 11-beta hydroxysteroid dehydrogenase (11BHSD) activity. 11BHSD is an enzyme that changes cortisol to active and inactive forms. After placement of the IV line, we will give a bolus dose followed by continuous infusion of deuterated (deuterium labeled) cortisol for a period of 3 hours and 20 minutes. During this time we will draw blood every 60 minutes for 3 hours and then every 5 minutes for 20 minutes to measure the change of the labeled cortisol into inactive and active forms. The deuterated isotope of cortisol is not radioactive and there are no additional side-effects other than those associated with placement of an IV.

Medications Used in the Study

Mifepristone is a drug that blocks the action of cortisol in the body. By blocking glucocorticoid action it can increase cortisol levels. High daily doses of mifepristone have been used safely to treat a few subjects with tumors causing excessive cortisol production as well as certain kinds of cancer, gynecological diseases, and psychiatric disorders. No major safety issues have been raised from these clinical studies. Mifepristone has been used safely in many countries for more than ten years at a single dose of 600 mg to terminate early pregnancy as well as for induction of labor at term. Women who have not undergone menopause and can become pregnant will be asked to use a non-hormonal contraceptive method if they are sexually active during the study and for one month after stopping the study medication.

Alternatives to Participation in this Study and Rights Upon Refusal or Withdrawal From this Study

The choice to enter or not enter this study is entirely voluntary. Before you make a decision to enter or not, you should understand what the doctor has explained and what you have read about the research study. If you decide not to participate, your enrollment in any other protocol will not be affected. If you are not sure that you wish to participate in this study, let us know at any time. You are free to withdraw from the study at any time. This study is not intended to be a

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long-term treatment of metabolic syndrome or diabetes. The usual treatments for metabolic syndrome and diabetes include lifestyle changes with diet and exercise as well as medications to lower blood sugar levels like metformin and insulin.

Risks and Discomforts

Most procedures of the study, such as blood drawing, urine collection, and an oral glucose tolerance test represent basic medical interventions with some discomfort and minimal risk while the intravenous glucose tolerance test is associated with greater than minimal risk. Mifepristone is an experimental agent with minimal side-effects at doses being used in the study.

1. Phlebotomy may cause bruising and there is a small chance of fainting, infection, or inflammation of the vein. These will be minimized using a clean technique and by placing you in a seated or lying position.
2. Hypoglycemia or a low blood sugar level can be associated with insulin administration used in the intravenous glucose tolerance test. The dose of insulin will be calculated carefully to reduce this risk and the test will be performed in strictly monitored setting. If a low blood sugar develops you will be treated to increase the blood sugar.
3. Anemia is a possible risk of phlebotomy. No more than 425 ml of blood will be taken over a 6 week period and therefore it is unlikely that you will develop a low blood count because of the study.
4. Discomfort associated with transvaginal ultrasound. Insertion of the ultrasound vaginal probe is usually well tolerated but occasionally may be uncomfortable. The sound waves from the ultrasound machine are painless and do not pose a medical hazard to you.
5. Mifepristone administration, at the doses and time period used in the study, has minimal risk. Long-term side-effects may include adrenal insufficiency, endometrial thickening and vaginal bleeding; however this study does not include chronic use. Termination of pregnancy is a risk associated with mifepristone. A pregnancy test will be performed prior to participation in the study. Women who have not undergone menopause and can become pregnant will be asked to use a non-hormonal contraceptive method if they are sexually active during the study and for one month after stopping the study medication.
6. Risks associated with an MRI scan if performed:
MRI uses a strong magnetic field and radiowaves instead of x-rays and therefore is not associated with any risk of radiation exposure.

Patients are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves and cochlear implants), implanted delivery pump or shrapnel fragments. Welders and metal workers may also be at risk for injury because of possible small fragments in the eye which they may be unaware of. You will be screened for these conditions prior to the study, and if you have any of these conditions, you will not receive an MRI scan. If you have a question about any metal objects being present in your body, you should inform the physician. In addition all magnetic objects (for example, watches, coins, jewellery, credit cards) must be removed before entering the MRI scan room. All women of child bearing potential will have a pregnancy test performed which must be negative before proceeding with the MRI. You will be asked to complete an MRI screening form, and to sign a separate MRI consent form.

Gadolinium-based contrast agents are approved by the FDA for use with MRI imaging. The vast majority of patients receiving gadolinium-based contrast agents have no symptoms related to the injection of this medication. Mild symptoms that may occur include coldness in the arm at the time of injection, a metallic taste, headache and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium-based contrast agents if you previously had an allergic reaction to them and will be asked about this before administration of any contrast agents.

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7. Tests conducted during this study may uncover a medical condition that could affect your health in the future. Any illness that we detect during these tests will be discussed with you. If a condition is discovered that prevents your participation in this study, you will not be eligible for treatment of that condition under this protocol. However, records of tests obtained during the screening may be forwarded to a physician of your choice to help further evaluation and treatment.

Benefits

You may benefit personally by undergoing a basic physical examination and basic blood tests. In addition, this study will contribute to our current understanding of the role of cortisol and the pathophysiology of metabolic syndrome and may lead to development of treatment modalities for various components of metabolic syndrome.

Remuneration

You will be taking an investigational drug for a short period of time and will have the inconvenience of travel to the NIH for study visits. Thus we propose to remunerate you for participation according to NIH guidelines. As recommended, we will be paying according to the level of inconvenience of the study procedures. We will take into account the fact that you will be undergoing: multiple blood draws, urine collection, brief hospital stay, and drug administration. The total compensation would be \$900 if you complete the study.

Confidentiality and Use of Retained Tissue Specimens

We will record your name with your blood and urine specimen. Initially, these samples will be used as described above for studies at the NIH. Additionally, the samples could be stored for a long time, with your name, and used for different studies than those we originally plan. For example, if we discover new effects of cortisol on a protein in the blood, we may evaluate that effect in your stored samples. However, such studies would be limited to evaluation of the effects of cortisol and/or mifepristone. The researchers conducting these studies will not contact you for more information. These future studies will not benefit you personally, and are not needed for your medical care. If you decide in the future that you no longer want your sample to be used for research, please contact the study doctors and any remaining sample will be destroyed. Please indicate your preference regarding future use of your samples by initialing one of the choices below.

<p>_____ These samples may be used for future studies related to cortisol and/or mifepristone</p>	<p>_____ I agree that my blood may be used in future studies for other conditions if I am contacted in advance and can rescind this authorization if I choose.</p>	<p>_____ Under no circumstances should these samples be used for future studies. Samples should be discarded once the present study is complete.</p>
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If you agree to possible future use of the samples, it is possible that those studies may involve sharing your samples with other investigators. If this is done, information about your medical condition may also be shared for the purpose of the future study. Information about you would be sent with a coded identification so that your name would not be linked to the information received by the other investigators. These studies would only involve investigations related to cortisol.

Your medical records are kept confidential to the extent allowable by law. Results of tests performed with the blood obtained from you will be kept confidential. However, access to your records will be allowed to individuals carrying out this study, so that appropriate information can be collected and possibly published in scientific journals.

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The results of research tests performed with the blood obtained will not routinely be provided to you. By agreeing to participate in this study you do not waive any rights that you may have regarding access to and disclosure of your records.

Other Interested Parties and Collaborators

The NIH has a Cooperative Research and Development Agreement (CRADA) with Laboratoire HRA Pharma, 15 rue Béranger, 75003 Paris, France to develop mifepristone through a joint study with the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of mifepristone. As part of this CRADA, HRA Pharma supplies the mifepristone for this study.

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