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A Study of Oxytocin Pharmacokinetics after Intravenous and Intranasal Administration in Healthy Subjects

Informed Consent Form to Participate in Research
James C. Eisenach, M.D., Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to evaluate the change of oxytocin in the blood after administration of oxytocin by intravenous (IV) route and the amount of oxytocin in the blood after intranasal (i.n.) oxytocin is administered. You are invited to be in this study because you are a healthy subject. Your participation in this research will involve 2 visits and last approximately 3 to 4 hours per visit.

Participation in this study will involve IV administration and i.n. administration of oxytocin and blood sampling. All research studies involve some risks. Risks to this study include discomfort or bruising from IV placement, nasal irritation from the oxytocin spray, changes in your blood pressure or heart rate from oxytocin which may require treatment, and headache or a feeling of flushing from oxytocin. These are more described in the risk section of this consent.
You may or may not benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. This is not a treatment study and there are no additional choices. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is James C. Eisenach, M.D. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: James C. Eisenach, M.D.
[redacted]

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Wake Forest University Health Sciences Research Subject Advocate at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you are a healthy adult. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to evaluate the level of oxytocin in the blood after administration of oxytocin (naturally occurring hormone made in the brain that transmits messages) by intravenous (IV) route and intranasal (i.n.) route.

Oxytocin has been approved by the US Food and Drug Administration (FDA), but it has not been approved for use in this manner, at this dose, for this condition, for administration by this route.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

In order to identify the 24 subjects needed, we may need to screen as many as 100 because some people will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

You will have 2 study visits. All study visits will be conducted in the Clinical Research Unit (CRU) at Atrium Health Wake Forest Baptist Health. The first study visit will last approximately 4- 5 hours and the second study visit will last approximately 2-3 hours.

If you take part in this study, you will have the following tests and procedures:

PROCEDURES

Vital Signs: we will monitor your blood pressure, heart rate, respiratory rate and oxygen saturation (amount of oxygen in your blood).

Laboratory Testing: female participants of child-bearing potential will provide a urine sample to determine that they are not pregnant.

Intravenous injection of Oxytocin: we will place an intravenous catheter and administer a dose of oxytocin.

Intranasal Oxytocin: you will administer oxytocin spray into each side of your nose.

Blood Sampling for Oxytocin amounts: we will place a second intravenous catheter for taking a small sample of your blood (1 teaspoon) at multiple times through the visits.

You will have approximately 1 teaspoon of blood withdrawn from a vein 10 times at visit 1 and 11 times at visit 2. Total amount of blood withdrawn during the study (including both study visits) will be approximately 8 tablespoons.

Study Visit 1

You will report to the Clinical Research Unit (CRU) at Atrium Health Wake Forest Baptist, in the morning after having had nothing to eat or drink since midnight. You will review and sign the Informed Consent. After informed consent is adequately obtained, a detailed medical history will be obtained, female participants of child bearing potential will have a urine pregnancy test performed to determine pregnancy status. Vital signs will be taken including blood pressure (BP), heart rate (HR), respiratory rate (Resp) and peripheral oxygen saturation (POX) will be measured and recorded along with height and weight.

Once eligibility has been determined; two intravenous catheters will be inserted, one in each arm, baseline vital signs (BP, HR, Resp, POX) will be obtained before the initiation of the infusion and then at the following intervals after the infusion has been initiated; 5, 10, 30, 60, 90 and 120 minutes. Then 14 micrograms oxytocin (Pitocin®), will be obtained from the research pharmacy, and infused over 30 min through one of the catheters. Blood (1 teaspoon) will be sampled from the other catheter at 2, 5, 10, 20, 30, 40, 50, 65, 90, and 120 minutes from starting the infusion. The intravenous catheters will be removed after all data collection and you will be discharged from the CRU. The duration for study visit 1 will be approximately 4 hours.

Study Visit 2

On the second visit, you will report to the CRU, in the morning after having had nothing to eat or drink since midnight. Vital signs (BP, HR, Resp, POX) will be obtained for a baseline measurement and then at the following intervals after the intranasal oxytocin: 10, 20, 30, 60, 90 and 120 minutes. One intravenous catheter will be inserted. Then you will self-administer oxytocin obtained from the research pharmacy, by nasal spray. For this you will administer one spray in each nostril and 5 minutes later, one more spray in each nostril. The total dose is 102 micrograms. Blood (1 teaspoon) will be sampled from the IV catheter at 1, 2, 5, 7, 10, 15, 20, 25, 35, 45, and 60 minutes after the administration of the oxytocin. The intravenous catheter will be removed after all data collection and you will be discharged from the CRU. The duration for study visit 2 will be approximately 3 hours.

How Long Will I Be in the Study?

You will be in the study for 2 visits, approximately 7 hours total.
We will contact you daily for 7 days after each study visit to ask how you are doing.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to this study and oxytocin include:

Needle Insertions
You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions.

Oxytocin
Intravenous oxytocin is not approved by the Food and Drug Administration (FDA) for use in men or in women other than in obstetric and certain gynecologic indications and intranasal oxytocin is not approved by the FDA for any indication. This study is being performed under Investigational New Drug oversight by the FDA. We will monitor you for many possible problems such as changes in your blood pressure, how fast your heart is beating, and your urge to breathe. We will treat any side effects that you may experience if the changes are enough to concern us.

There is the possibility of a feeling of being flushed (warm feeling), headache and increased heart rate with no significant change in blood pressure during or immediately after the infusion. These events have been reported by previous participants but were short lived, lasting approximately 12-15 minutes.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

Blood Draws
You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).
If you donate blood to the American Red Cross, you should talk with the study doctor about whether or not it is safe to do so while participating in this study. You should not donate blood more than 2 times per week and no more than approximately one pint (about 500 ml) of blood in an eight week period.

There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks to your health.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study to identify possible safety issues to participants and to provide advice and recommendations on possible changes to the research study for the protection of participants.

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, OrthoEvra patch, NuvaRing, intrauterine devices (IUD), Nexplanon implant, DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because NO method of birth control is 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from taking part in this research study. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

All study costs, including any study products or procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required or permitted by law, or necessary to protect the safety of yourself or others.

Your information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

_____ *Please initial if you agree to the following statement for text messaging contact*

TEXT MESSAGE COMMUNICATION. I give permission to Atrium Health, Wake Forest University Health Sciences, and their respective affiliated entities and representatives (including third-party agents if applicable) to contact me by text message at the number I provided to send information, reminders, and to communicate with me about the research study. I understand that I am responsible for the standard text message rate of my carrier. I also understand that text messaging is not a secure form of communication and I accept the risk that individuals not involved in the research study may be able to access the text messages. I also understand that texting is not to be used for emergency situations.

_____ *Please initial if you agree to the following statement for email contact*

EMAIL COMMUNICATION. By providing my email address, I give permission for Atrium Health, Wake Forest University Health Sciences, and their respective affiliated entities and representatives (including third-party agents if applicable) to send me information, reminders, and messages about the research study by email. I understand that these email messages may not be encrypted, and I understand and accept the risks that individuals not involved in the research study may be able to access unencrypted email messages. I also understand that email is not to be used for emergency situations.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $500 if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid according to the description below.

Study Visit 1: 2 PIV $25/each ($50); $100 for PK sampling
Study Visit 2: 1 PIV $25; $100 for PK sampling + $225 for completion of study visit 2 PK sampling

If 2 peripheral intravenous catheters cannot be placed on Visit 1 you will be compensated $50 and we will not be able to include you in the study.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the National Institutes of Health. The sponsor is providing money or other support to the researchers to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Wake Forest University Baptist Medical Center maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of injuries or illnesses to some participants in certain research studies. To the extent research insurance coverage is available under this policy, the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. To the extent research coverage is not available, you or your insurance company may be charged for the costs of medical care. You may receive care at Wake Forest University Baptist Medical Center and/or Atrium Health.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call James Eisenach at [redacted] or after hours

you should call the study coordinator at [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** medical history and medication history.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with the health care operations of Atrium Health, Wake Forest University Health Sciences, and their respective affiliated entities.

We will take steps to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and Atrium Health Facilities; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS), the National Institutes of Health (NIH) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs, videotapes, audiotapes or other recorded media which are identify you unless we you're your written authorization.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to your medical record for verification of clinical trial procedures or data to the extent permitted by other

applicable laws. These monitors, auditors, and other individuals are also required to maintain the confidentiality of your protected health information.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire.

You can tell Dr. James C. Eisenach that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

James C. Eisenach, M.D.
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Atrium Health, Wake Forest University Health Sciences, or their respective affiliated entities will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. Authorization to access this part of the medical record will only be available to people who have a need to know this information in order to perform their job-related duties. If you are not a patient of these health care facilities, a medical record will be created for you anyway to provide access to this important information to providers in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.
As part of the Clinical Trials Registry, a Data Sharing Plan will be included on the website. The following data will be made available are oxytocin dose administered, time blood sampling

occurred (relative to the start of dosing), plasma oxytocin concentrations at the sampling times for each subject, and age, weight, and sex for each subject.

Laboratory test results and other clinically relevant medical reports created as a result of your participation in the research study may be entered into the computer systems of Atrium Health, Wake Forest University Health Sciences, and/or their respective affiliated entities. These results and reports will be kept secure in compliance with applicable laws, with permission to access this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A medical record will be created for all study participants seen on-site and if a medical record doesn't already exist. Information about your participation in the study will be placed in the medical record, along with any routine medical test results that were obtained as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

This study will be enrolling students from Atrium Health and Wake Forest University School of Medicine. In addition to your rights as a research participant noted in the previous section, as a student, you are under no obligation to participate in this study. You may refuse to participate or withdraw from the study at any time and for any reason without affecting your grades, performance evaluations, or assignments. You will not be pressured into participating in this research study by any statements or implied statements that your grades, performance evaluations or assignments will be affected by your willingness to enroll in the study. Your medical records/information will not be used by the faculty, administration or study staff to make decisions regarding the status of your medical benefits. If you have questions regarding your enrollment in the study and your status as a student, please contact the research subject advocate for additional information.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study

investigator, Dr. James Eisenach at [redacted] or after hours you should call the study coordinator by calling [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____

Date: _____ Time: _____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent: _____

Date: _____ Time: _____ am pm