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Title: Effects of Intramuscular Oxytocin on Pupil Diameter and Heart Rate Variability

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BACKGROUND

A large body of evidence in animals and in humans suggest that oxytocin can produce analgesia to experimental pain stimuli and relieve pain in acute and chronic clinical pain states. For the past 8 years we have, under an NIH MERIT award, tested the role of the spinal cord in oxytocin's actions by studies in rodents and clinical trials, 3 of which are ongoing, of spinally injected oxytocin.

The Pain Mechanisms Laboratory at Wake Forest is now in the process of assembling an NIH program project grant (P01) on the topic of oxytocin sites, mechanisms, and clinical applications for analgesia, and Dr. Eisenach will lead the clinical project in that proposal. In order to acquire adequate preliminary data to support this application, we are examining the effects of oxytocin in several small clinical studies. The first one of these (IRB 00056413) has been completed, and described the pharmacokinetics of oxytocin, 10 IU, after intravenous administration in men and women. The second one (IRB00056660) is ongoing and examines intramuscular oxytocin, 10 IU, compared to placebo in a double blinded study on sensory changes after controlled UV-B sunburn. We have obtained a waiver of IND from the FDA for oxytocin at these doses by these routes of administration in men and women.

The goal of this third protocol is to test central effects of Intramuscular oxytocin on noninvasive measures which can be easily and repeatedly assessed. The first two studies are providing information related to dosing of oxytocin and measurement of its effects on sensory nerves in the periphery. Oxytocin also enters the central nervous system after systemic administration, and the goal of the current study is to test the effects of oxytocin on heart rate variability and pupil diameter, both of which affect subtle effects on autonomic tone and which have been proposed in earlier studies by others to be altered by oxytocin. Taken together, these 3 studies will provide most of the information required to support larger clinical studies to be proposed in the P01 application.

RATIONALE

Nearly all clinical studies of oxytocin involve intranasal administration, which results in minimal or no increase in circulating oxytocin concentration, but effects that are presumed to reflect actions in the brain. The focus of most of these studies involves

presumed social effects of oxytocin, typically measured by brain activity or subjective report when viewing images of differing social valence. These studies universally show an effect of oxytocin, although their rigor has been questioned because of extremely small sample size and lack of *a priori* statistical analysis plan [16]. Most studies demonstrate small effects of oxytocin close to a threshold P value of 0.05 for statistical significance, and these measures can typically only be assessed once, requiring a between subject design inappropriate to pharmacokinetic-dynamic modeling. For these reasons we do not plan to use these kinds of outcome measures to assess central effects of oxytocin.

This protocol focuses on two measures of autonomic control, both in use in current studies by our group, to quantify central actions of oxytocin. First, we propose to examine the influence of oxytocin on heart rate variability with focus on its effect on high frequency variability, most commonly ascribed to parasympathetic nervous system activity acting to brake sympathetic tone. Intranasal oxytocin has been demonstrated to have a large effect size on this measure which can be repeated at frequent intervals [7]. As a secondary assessment of parasympathetic activity, we will measure high frequency fluctuation in pupil diameter, termed hippus, which also reflects parasympathetic nervous system activity [14]. This outcome measure can be assessed in 3 seconds using equipment currently being used under IRB approved protocols.

Protocol

Effects of intramuscular oxytocin on pupil diameter and heart rate variability

PRIMARY GOAL: Provide an estimate of effect size of intramuscular oxytocin on tests of parasympathetic nervous system activity using variations in pupil diameter and in heart rate.

GENERAL METHODS: Equal numbers of healthy adult men and women will be recruited (22 total) and will have 2 visits in the Pain Research Unit at Piedmont Plaza 2. A non-invasive, chest band heart rate monitor will be applied and baseline pupil diameter measures obtained with a pupilometer. Subjects will receive an intramuscular injection of either oxytocin (Pitocin®), 10 IU, or saline. The study will be randomized and double blind and all subjects will receive both treatments.

STUDY DESIGN

Inclusion Criteria: We request permission to study up to 30 subjects so that we will have 22 evaluable subjects who have completed both visits.

1. Male or female > 18 and < 66 years of age, Body Mass Index (BMI) <40.
2. Generally in good health as determined by the Principal Investigator based on prior medical history, American Society of Anesthesiologists physical status I or II
3. Normal blood pressure (systolic 90-140 mmHg; diastolic 50-90 mmHg) resting heart rate 45-100 beats per minute) without medication
4. Female subjects of child-bearing potential and those < 1 year post-menopausal, must be practicing highly effective methods of birth control such as hormonal methods (e.g., combined oral, implantable, injectable, or transdermal contraceptives), double barrier methods (e.g., condoms, sponge, diaphragm, or vaginal ring plus spermicidal jellies or cream), or total abstinence from heterosexual intercourse for a minimum of 1 full cycle before study drug administration.
5. All subjects must be vaccinated against SARS-CoV-2, with proof via vaccination card or the NC HHS form.

Exclusion Criteria:

1. Hypersensitivity, allergy, or significant reaction to any ingredient of Pitocin®

2. Any disease, diagnosis, or condition (medical or surgical) that, in the opinion of the Principal Investigator, would place the subject at increased risk (active gynecologic disease in which increased tone would be detrimental e.g., uterine fibroids with ongoing bleeding), compromise the subject's compliance with study procedures, or compromise the quality of the data

3. Women who are pregnant (positive result for urine pregnancy test at screening visit), women who are currently nursing or lactating, women that have been pregnant within 2 years.

4. Subjects with neuropathy, chronic pain, diabetes mellitus, or taking benzodiazepines or pain medications on a daily basis.

5. Subjects with history of eye surgery, with cataracts, or taking medications for eye conditions.

Study Visit 1: The participant will report to Piedmont Plaza 2. The participant will review and sign the Informed Consent. After informed consent is adequately obtained, a detailed medical history will be obtained from the participant, female participants will provide a urine sample to determine pregnancy status. The research nurse will have the subject place the chest belt for heart rate monitoring, familiarize the subject with the pupilometer, and calibrate the system for gaze by having the subject look at each of 9 gray Xes on a monitor located in front of the chin rest and pupilometer camera.

Baseline blood pressure, heart rate and respiratory rate will be measured. Pupil diameter measurements will be obtained for 20 seconds every 5 minutes for 20 minutes. The subject will only need to position their head with chin on the chin rest during times of pupil measurements. During the pupil measurements we will record the measurements using an infrared camera.

The subject will then receive an intramuscular injection of oxytocin (Pitocin®), 10 IU or the same volume (1 ml) of saline. Pupil measurements will be made for 20 seconds every 5 minutes until 120 minutes after study drug administration.

Study Visit 2

All procedures from Study Visit 1 will be repeated with the cross-over study drug solution. The visits will be at least 24 hours apart.

Safety and Monitoring: Given that oxytocin is available over the counter in much larger systemic doses than proposed in this application and since multiple scientific reports have examined much larger systemic doses than in this application using only subjective reporting, we propose to only request subjects to report any unusual sensations and query them at the end of each drug administration study day if they experienced any unusual sensations. Blood pressure, heart rate and respiratory rate will be measured at both study visits at baseline and then at 30, 60, and 90 minutes after the injection.

RISKS

Risks of intramuscular injection include pain and bruising. Risks of oxytocin are primarily restricted to uterine contraction in the presence of pregnancy, since oxytocin receptors are not present in the non-pregnant uterus (Package insert attached). Additionally we noted in our previous study of intravenous oxytocin there is the possibility of a feeling of being flushed, headache and increased heart rate with no significant change in blood pressure during or immediately after the infusion. These events were reported by previous participants in the intravenous study, but were short lived, lasting approximately 12-15 minutes. We have received no reports of these effects in our current study of intramuscular oxytocin. The use of infrared video camera will does not expose participants to a greater amount of light than expected in normal use of an infrared camera.

Data Safety Monitoring Plan

Although the use of oxytocin in this protocol is outside FDA approval for oxytocin administration during the postpartum period, the dose to be studied is similar to or less than that of multiple recent studies in healthy volunteers with intranasal oxytocin purchased over the counter in the US [1-6; 8-13; 15-19] and without description of

adverse events. For these reasons, we do not propose a data safety monitoring committee or special safety evaluation beyond those required by IRB regulations.

Minority, Gender, and Children Participation

Both sexes and races and ethnicities will be actively recruited in this small study. Children under age 18 are not included in these protocols because this protocol because the safety of this product has not been established in children.

Volunteer Payment

Participants will be paid a total of $200 according to the following payment schedule which we have used throughout the last 2 cycles of this grant's protocols. We believe that this payment schedule is fair and appropriate, paying for each procedure attempted and an additional payment for completion of the entire study.

Completion of study visit 1: $50

Completion of study visit 2: $150

Long-term Follow-up

Volunteers will be contacted one and 7 days after the last study visit and questioned about adverse events from the study.

Data Share Plan Stanford Pilot Data

Scope of Work: The Dr. Steven Shafer at Stanford University will establish and direct a pharmacokinetic/dynamic (PK/PD) modeling to facilitate future modeling in a NIH grant to be funded late 2021/early 2022. The PK/PD modeling will generate a mathematical model of oxytocin uptake, distribution, and elimination following intravenous delivery in humans. The PK/PD Core will use these mathematical models to describe the relationship between concentration at the site of effect and therapeutic response. The models will facilitate dosing regimens for future studies. The dose effect of intramuscular oxytocin will be modeled by the relationship noted on pupil diameter and heart rate variability and pupillary hippus measurements.

STATISTICAL RATIONALE

Co-Primary outcome measures are magnitude of power at the dominant frequency in the Fourier transform of pupil diameter in the .1-2 Hz range, termed hippus, and heart rate variability in the high frequency range (HF-HRV). These are complementary measures which are both affected by parasympathetic nervous system activity and by non-overlapping other factors. We request a convenience sample of 22 subjects for the purpose of preliminary data to provide variance and effect size estimates that will inform federal grant submission for use of this model to a larger sample size to adequately test the plasma concentration response of computer controlled infusions of oxytocin to targeted plasma concentrations with intravenous infusions. Thus, we propose descriptive statistics as the primary analysis of this pilot study.

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