Official Title: Defining a Pharmacokinetic and Pharmacodynamic Model for Peripheral Analgesia after Intravenous Oxytocin
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Create a PK/PD Model for Peripheral Oxytocin Effect

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Rationale for current application

Both preclinical and clinical evidence suggests that oxytocin may serve as a novel pain therapeutic and potential disease-modifying agent to prevent the transition from acute to chronic pain. This follows from observations that pain resolves quicker in women after cesarean delivery than other surgeries [1], and that hypersensitivity resolves quicker in rodents when neuropathic injury is performed after delivery, an effect blocked by inhibition of oxytocin action [2, 3]. Oxytocin may act peripherally to affect pain after injury. Since chronic pain is usually reduced acutely by peripheral nerve block, peripheral input is necessary, but most research assumes that input is normal and pain reflects ongoing central sensitization. We and others challenge these ideas, showing that touch sensitive nerve fibers are desensitized after injury whereas fast conducting pain nerve fibers are sensitized [4]. In rodents, oxytocin acutely moves these two abnormal signals after injury towards normal [5], suggesting a disease-modifying potential of oxytocin as a 'vaccine' against chronic pain after injury.

Oxytocin itself is the only clinically available tool for translational studies in many areas – neuroprotection, anxiety, sleep, social behaviors, addiction, and pain. Most rodent and human studies of oxytocin are small, lack strong scientific rigor, and only half of the clinical studies examining pain demonstrate efficacy. Thus, we have minimal ability to understand oxytocin effects across species. A critical problem is the complete lack of fundamental pharmacologic characterization for oxytocin, which is used clinically in obstetrics by titration-to-effect. There are few PK and no PK/PD modeling studies of oxytocin in the literature, and the PK studies use RIA and ELISA assays which are unreliable [6].

Under IRB00056413 we measured plasma oxytocin concentrations after IV administration, using an LC/MS assay [7]. **Figure 1A** shows individual (thin lines) and group (thick lines) after oxytocin, 10 IU (17 μg). The first 3 individuals received a 1 min infusion, which was accompanied with headache and sensation of flushing (red lines) and the remaining 8 volunteers received a 10 min infusion with 5 of 8 subjects experiencing symptoms. These data were well fit to a 2-compartment PK model using NONMEM. Note the large discrepancy between these data and a recent report [8] in which the same dose of oxytocin was infused over 10 min and plasma oxytocin measured by radioimmunoassay (RIA).

To assess peripheral effects, we used pain report to 5 minute exposure to a heat stimulus, since our studies in rodents shows that prolonged noxious heat sensitizes and increases activity the fast conducting pain fibers which are sensitive to oxytocin [9]. **Figure 1B** shows the modeled plasma oxytocin concentrations in the 11 subjects in **Figure 1A** and pain

report to a 5 min noxious heat exposure. The data were nicely fit to a PK/PD model yielding parameters of 25 min to peak effect, an EC50 of 10 pg/ml, and steepness of concentration response (γ) of 1 (green dashed lines). The goal of this PK study was to determine oxytocin PK and to explore a potential effect on pain from skin heating. Under IRB00066136 we examined the time course of analgesia to skin heating by slower infusion of IV oxytocin (0.47 µg/min for 30 min for a total dose 14 µg) in 10 volunteers. There were no adverse events with this dosing regimen, and the PK/PD model from the first study accurately predicted the time course of onset of analgesia during infusion and maintenance of analgesia after the infusion was stopped (**Figure 1C**).

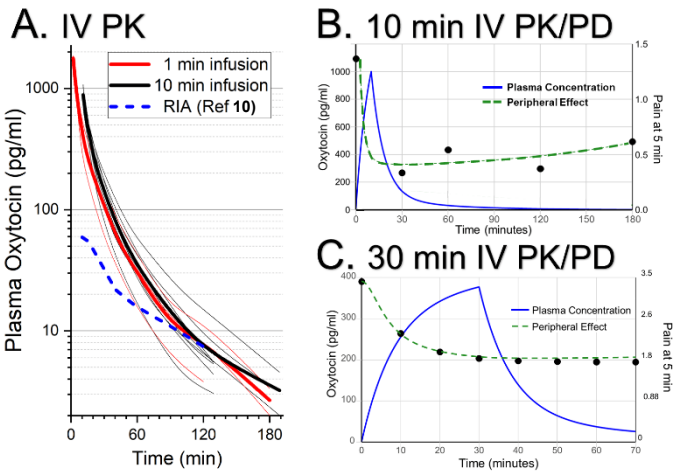

Figure 1. A) plasma oxytocin concentrations with LC/MS (red/black lines) compared to plasma by RIA (blue lines. **B)** modeled plasma oxytocin concentrations (blue line) and observed (circles) and modeled (green dash) pain scores after 10 min infusion of 17 µg oxytocin. **C)** as in B) but after 30 min infusion of 14 µg oxytocin

Based on this model, we predicted that 10 min infusions of oxytocin, 0.3, 1.3, and 7 µg would produce approximately 20, 50, and 80% maximum effect to reduce pain from 5 min application of heat. We completed that study (IRB00079629) in February, 2023 and observed minimal impact on pain by of these infusion doses. A more thorough modeling evaluation of the original preliminary data revealed a consistent oxytocin effect across both previous intravenous infusion studies and suggested that the original modeling led us to use doses below the threshold to achieve analgesia. The revised modeling forms the basis for the oxytocin dosing to administered in the current application.

Protocol

Objective. The primary objective of the current IRB application is to define the time course of change in pain score after 5 min heating of the skin applied at intervals during and following infusion of intravenous oxytocin in order to create a PK/PD model for oxytocin-induced analgesia. The proposed study design will advance the preliminary data by use of a dosing regimen predicted to produce the maximum achievable effect with oxyticn in a manner that will validate and more precisely describe PK/PD model from prelimary data.

A secondary objective is to test for effects of subject sex or age on oxytocin effect.

Overview. Equal numbers of adult men and women, age 18-75 will be recruited. Subjects will report to the Pain Clinical Research Unit (CRU) or the CTSI CRU for four visits, the first to confirm consent and train the individuals in all heat pain procedures, the second to infuse oxytocin intravenously, record heat pain ratings at 15 min intervals for 2 hr, then once more at 3 hr, and the third and fourth to record heat pain ratings approximately 24 hr and 5-7 days after oxytocin infusion. A PK/PD model will be generated from these PD measures (heat pain ratings). We will not withdraw blood and measure oxytocin for PK in these subjects nor in subsequent studies to be submitted to the IRB. Rather, we will use the population PK model of intravenous oxytocin established from a past study of 11 volunteers and an ongoing study in 24 other volunteers.

Phase II trials

Setting

The training visit will occur at either the Pain CRU at Piedmont Plaza 2 or the CTSI CRU. Drug study visits will occur on the main campus at CTSI CRU.

Subjects selection criteria

The study will enroll healthy subjects.

Inclusion Criteria

1. Male or female ≥ 18 and < 75 years of age, Body Mass Index (BMI) <40.
2. Generally in good health as determined by the Principal Investigator based on prior medical history, and as assessed to be American Society of Anesthesiologists physical status 1, 2
3. For healthy volunteers, normal blood pressure (systolic 90-140 mmHg; diastolic 50-90 mmHg) resting heart rate 45-100 beats per minute) without medication. For those with hypertension, blood pressure controlled with anti-hypertensive medication and with a resting heart rate 45-100 beats per minute.
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.

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 (located in any body location that is being treated), diabetes mellitus, or taking benzodiazepines or pain medications on a daily basis.
5. Subjects with current or history of ventricular tachycardia, atrial fibrillation or prolonged QT interval.
6. Subjects with past or current history of hyponatremia or at risk for hyponatremia; anyone taking thiazide diuretics, loop diuretics, combination diuretics, lithium, carbamazepine, enalapril, Ramipril, celecoxib, temazepam, gliclazide, glimepiride, glibenclamide, glipizide, omeprazole, pantoprazole, desmopressin, SSRI's, MAOI, or the recreational drug ecstasy.
7. Subjects with a known latex allergy.

Sample Size

The projected sample size is 24 evaluable subjects with complete data sets. We request to enroll up to 26 subjects. Our current estimates indicate that the confidence interval for studies of 21 individuals with pain intensity ratings in two preliminary studies will determine the pharmacodynamic parameters with a corrected confidence range < 20%. A corrected confidence range < 20% implies that mixed effect analysis will distinguish covariate effects in the range of 40% in a study with 21 or more subjects. This is the range at which the covariate effect may be clinically consequential. In practice, mixed-effects analysis with NONMEM is often sensitive to covariate effects smaller than predicted by preliminary analyses. The sample size is increased to 24 to provide covariate assessment for age, weight, and sex.

Interventions and Interactions

At all study visits participants will be queried regarding recent history of symptoms commonly associated with COVID-19 or recent close contacts with anyone with a positive COVID-19 test.

Study Visit 1:

The participant will report to the Pain CRU or the Wake Forest CTSI CRU. 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 have a urine pregnancy test performed to determine pregnancy status. Vital signs to include blood pressure (BP), heart rate (HR), respiratory rate (Resp) and oxyhemoglobin saturation by pulse oximetry (POX) will be measured and recorded along with height and weight.

Once eligibility has been determined the participant will be trained in study procedures. This will include pain ratings to brief (5 sec) heat stimuli on the lateral calf to 39, 41, 43, 45, 47, and 49ºC and then a pain intensity rating each minute for 5 mins during heating to 45ºC. If the pain report to 45ºC is ≤ 2 at the end of the 5 min, a second trial using 46ºC will be done. If the 46ºC results in pain intensity ≤ 2, a third trial with 47ºC will be performed, and if that trial results in pain intensity ≤ 2, a third trial with 48ºC will be performed. Subjects who have pain intensity ≤ 2 with the 48ºC 5-min stimulus will not be further studied. The duration for visit 2 will be approximately 2 hours.

Study Visit 2

On the second visit, the participant will report to the CTSI CRU. Baseline vital signs (BP, HR, Resp, POX) will be obtained for a baseline measurement, a catheter inserted into a peripheral vein in the upper extremity and pain report to 5 min heating of skin on the calf at the temperature determined in Visit 1 will be recorded. Subjects will then receive two 30 min infusion of oxytocin, 17 μg (provided by the research pharmacy), with infusions separated by 30 min. Pain ratings to 5 min heat pain testing will be performed at 15 min intervals for 2 hr, then at 3 hr after initiation of the first infusion. The first 5 min heat stimulus will end at 15 min after beginning the first oxytocin infusion in the first 8 subjects. In the event that there is no effect of oxytocin on heat pain, we will stop recruitment and assess whether protocol amendment or termination will be requested. If there is an effect, the remaining 16 subjects will be randomized to have the first 5 min heat stimulus end at 10 or 20 min after the first oxytocin infusion begins. In this fashion there will be 3 cohorts of 8 subjects each, thereby providing pain rating measurements in 8 subjects every 5 min after the first 5 minutes of the infusion. The duration for study visit 2 will be approximately 4 hours.

Study Visit 3

On the third visit, the participant will report to the CRU approximately 24 hr after the beginning of the infusion (acceptable range 20-28 hr) and heat pain ratings acquired on 3 trials separated by 10 min. The duration for study visit 3 will be approximately 1 hour.

Study Visit 4

On the fourth visit, the participant will report to the CRU 5-7 days after the day of oxytocin infusion and heat pain ratings acquired on 3 trials separated by 10 min. The duration for study visit 4 will be approximately 1 hour.

Safety and Monitoring:

Assessment of Side Effects*:* Peripheral oxyhemoglobin saturation, BP and HR will be measured non-invasively before and 5,10, 30, 60, 90 and 120 minutes after oxytocin infusion. Subjects will informed to report any subjective sensations during or after oxytocin administration and will be queried at the same intervals as vital sign monitoring for any subjective sensations.

Treatment of Side Effects: Significant cardiorespiratory side effects include:

a. Decreased BP with symptoms of hypotension (e.g., dizziness or lightheadedness)
b. Blood pressure or HR changes >20%
c. Pulse oximetry less than 94% that does not correct with several deep breaths.

Treatment of BP elevations > 20% of baseline will be treated with labetalol 5-15 mg IV incrementally until BP elevation <20% elevated. Treatment of symptomatic hypotension or BP reductions >20% will be treated with incremental ephedrine 5-20 mg, IV. Heart rate (HR) reductions or elevations > 20% of baseline will be treated with incremental glycopyrrolate 0.2 mg IV or propranolol 0.2 mg IV, respectively. Peripheral oxyhemoglobin desaturation (< 90) will be treated with supplemental oxygen, nasal cannula, face mask, or non-rebreathing mask depending upon the degree desaturation and the response to therapy.

Regardless of whether any treatment is required, subjects with significant side effects will be monitored more frequently (every 5 min for BP and HR; continuously for POX) until symptoms or signs resolve.

Serious adverse events: In addition to treatment, as described above, and timely reporting as required to the DSMC, IRB, and FDA, emergency treatment will be available within the CRU itself. As such, an ACLS-certified health care professional will be on site or within 5 minutes of the CRU during each treatment session, and a crash cart containing medicine and equipment for emergency resuscitation, and an automated external defibrillator will be located on-site.

Study Stopping Criteria: Should significant cardiorespiratory or other side effects occur during oxytocin administration, the IV infusion will be stopped and the subject treated as indicated in Treatment of Side Effects.

The study will be stopped if more than 2 individuals exhibit significant cardiorespiratory side effects or after any serious adverse event and future conduct of the study will be determined by recommendations from the DSMC, IRB, and FDA.

Outcome Measure(s)

Primary Outcome Measure

Name: Average verbal pain score (0-10) at one min intervals during the 5 min of skin heating

Type: Primary

Time Frame: For 180 minutes after the beginning of oxytocin infusion

Description: Pain scores are measured each minute during 5 min heating of the skin of the calf, with temperature of the probe determined in visit one to obtain a pain score at the end of this period of > 2.

Analytical Plan

The primary analysis will use NONMEM to create a PK/PD model of oxytocin on average pain ratings each min for 5 min during the noxious heat stimulus. To do so, pain scores over time will first be modeled using NONMEM with derived parameters of maximum effect (Emax), predicted concentrations from the PK/PD model to produce a 50% and 90% maximum drug effect (C50 and C90, respectively), the steepness of the dose response curve (γ), and the time to peak effect. Inter-subject variability (e.g., biological variability) will evaluate additive, proportional, and exponential models. Residual intrasubject variability (e.g., noise) will typically require an additive and multiplicative error model. The influence of covariates (e.g., age, sex, weight) on model parameters will be analyzed by serial inclusion / exclusion, with significance determined by the likelihood ratio test ($p < 0.01$ if the decrease in -2 log likelihood exceeds 6.6 ($\chi^2_{0.99}, \mathrm{df} = 1$)). Parameters will be estimated using first-order conditional estimate with η-ε interaction.

Covariate effects deemed significant by likelihood ratio test will be validated using jackknife cross-validation [10]. Jackknife cross-validation provides an estimate of the utility of the covariate to inform the pharmacodynamics in a future individual, rather than merely characterize the pharmacodynamics in the individuals from which the model was derived. The jackknife cross-validation divides the data into N subsets. Each subset leaves out a single individual. The parameters of the model are re-estimated for each subset with and without the covariate being validated. The inaccuracy (mean ((|measured – predicted|) / predicted)), of the model with and without the covariate is measured in the excluded individual. The covariate is only being included in the final model if it the improvement in model accuracy in the N iterations is significantly greater than 0. Jackknife cross-validation helps compensate for NONMEM's ability to identify very small covariate effects that do not meaningfully contribute to accuracy in future patients.

Expected outcomes. Based on pain ratings and an estimate of the PK/PD model from preliminary data (Fig 1), we anticipate that the maximum oxytocin effect is a 50-60% reduction in pain rating from the 5 min heat stimulus.

Human Subjects Protection

Subject Recruitment Methods

Healthy subjects will be recruited from our current database of volunteers BG05-468, word of mouth and Be Involved website; The research nurses; Regina Curry, RN and Vonda McGee, LPN will conduct the recruitment of study subjects.

Potential subjects from the database will be contacted via phone or email, per their request. Potential subjects from the Be Involved website will be contacted according to the information they provide.

Informed Consent

Signed informed consent will be obtained from each subject. Regina Curry, RN or Vonda McGee, LPN will obtain consent. Potential subjects will be consented in the CRU. A private room will be utilized during the consent process and all study visits.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 3 years after closure of the study, in confidential shredding disposal bins consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

The DSMP outlined below will provide appropriate oversight and monitoring to ensure the safety of participants, the validity of the data, and make intermittent recommendations whether to continue, modify or stop the study. The DSMP will utilize an independent DSMB to ensure the effective institution of the DSMP.

This DSMB will have discretion to unblind any results, or conduct any inquiry needed to ensure the safety and efficacy of the trial at the request of the DSMB chair. The committee will maintain a written record of its meetings.

Scope of Data Monitoring

The primary source of the data will be adverse event reporting.

Study admission data

Monitoring of admission data will include the number of subjects requesting participation in the study, number of subjects screened and number of subjects admitted to the study. The DSMB may request a report of the reason why subjects were disqualified from participating in the study. For subjects admitted to the study, the DSMB will review eligibility criteria for admitted subject, any protocol deviations and/or violations, and the demographic distribution of the subjects by group.

Protocol Compliance

The DSMB will monitor the data to assess compliance with the protocols including the adherence to the randomization schedule. The DSMB will also monitor the quality and completeness of the data being collected, including the frequency of missing or erroneous data, and presence and frequency of outliers.

Safety Data
Monitoring of safety data will include review of Adverse Events (AEs) and Serious Adverse Events (SAEs), trial retention, and reason for drop out. Safety information will be reported to the DSMB in an unblinded manner. Formal statistical analyses of the safety data may be requested by the DSMB. For SAEs, data will include all the adverse event data meeting the FDA definition of serious adverse events. In the assessment of SAEs, the DSMB will review each individual case including treatment group assignment. After each meeting of the DSMB, the secretary will forward a summary report of all serious and unexpected adverse experiences to the principal investigator to summarize the DSMB's review of the serious and unexpected adverse events reported. Furthermore, the DSMB will make a recommendation to continue, modify or halt the study protocol. This report will be transmitted to the Wake Forest University IRB and NIH. Safety data will be prepared for review following the enrollment of each 24 subjects.

Establishing a DSMB Board membership
The DSMB will be appointed by Dr. Eisenach and Dr. Ririe with the purpose of reviewing, approval, and monitoring the implementation of the DSMP. The DSMB will have two members encompassing multidisciplinary expertise who are not involved in the study protocol. Board members will have no financial and/or scientific ties to the outcome of the clinical trials to avoid any real or perceived conflict of interest. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data. The DSMB will include the following physicians; Laura Dean, M.D., Associate Professor of Anesthesiology and Director of Obstetric and Gynecologic Anesthesiology and Ashish Khanna, M.D., Associate Professor and Vice Chair for Research in Anesthesiology, Wake Forest School of Medicine.

Board meeting schedule
The board will have scheduled meetings twice a year and expedited meetings to review unexpected SAEs or other urgent issues that may arise during the trial. Unscheduled meetings may be initiated by the DSMB chair, Dr. Eisenach, or Dr. Ririe. The data to be reviewed by the DSMB will be available to the Board members.

DSMB Recommendations:
DSMB recommendations will be made in writing by The DSMB chair to Dr. Eisenach. The secretary will prepare meeting minutes for inclusion in the DSMB report. The draft report will be reviewed by all Board members prior to issuance of the final report. DSMB recommendations will then be forwarded to the NINDS program officer and Wake Forest University IRB.

Volunteer Payment

Participants will be paid a total of $500 according to the following payment schedule which we have used throughout the last 10 years. 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
Study visit 2: placement of IV-$25, IV infusions and thermal testing-$125
Study visit 3: thermal testing-$100
Study visit 4: thermal testing-$100
Completion of all study related procedures: $100

If an IV cannot be placed on Study visit 2: subject will be compensated $50 and subject replaced.

Long-term Follow-up

Volunteers will be contacted daily within the following week and questioned about adverse events from the study.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB, DSMC and the FDA if appropriate.

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