Pharmacokinetics of intravenous oxytocin and effects on sensory function in healthy volunteers

IRB00056413

NCT03929367

Version Date: 6/11/2019

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. This IRB protocol is meant to obtain preliminary data critical to that NIH application in September, 2019.

Determining the site(s) of action of oxytocin for analgesia in humans is critical to future clinical trials and drug development. We will propose to use computer-controlled intravenous infusions of oxytocin to rapidly achieve and maintain targeted plasma concentrations. By locking plasma concentrations and examining a wide concentration range, coupled with testing aimed to measure activity of oxytocin on peripheral nerves, in the spinal cord, and in the brain, we plan to identify infusion regimens that only target 1 or 2 of these sites for clinical trials.

WHY WE NEED TO DEFINE PHARMACOKINETICS OF OXYTOCIN

In this IRB protocol we take the necessary first step towards computer-controlled intravenous infusions of oxytocin. In this protocol we will describe the pharmacokinetics of intravenous oxytocin in healthy non-pregnant adult men and women. We cannot program infusion devices for targeted concentrations without knowledge of oxytocin's pharmacokinetics in this population of interest. Although much is known of the pharmacodynamics of intravenous and intramuscular oxytocin to cause uterine contraction during pregnancy and in the postpartum period, we know virtually nothing about oxytocin's pharmacokinetics in this setting and nothing in the nonpregnant population. This reflects the fact that immunoassays used to measure oxytocin for the past 3 decades suffer critical limitations because the antibodies used are confounded by binding to oxytocin degradation products, particularly those that are tightly bound to

circulating proteins and presenting a large background of antigenicity to which these antibodies bound. In a recent review of the state of our lack of knowledge regarding oxytocin disposition, it was noted that reports differ in resting and infused oxytocin concentrations in plasma by 2 to 3 orders of magnitude, and that the use of these assays essentially generate random numbers with no basis in reality [8].

Beginning in 2016 reports appeared of highly sensitive and specific assays of oxytocin in plasma and other biofluids using liquid chromatography coupled with mass spectroscopy (LC-MS) [2; 3; 6; 11]. A recent report included pharmacokinetics of oxytocin after intramuscular injection using LC-MS [3] with concentrations assayed by a commercial entity (Syneos Health, Princeton, NJ). We have secured a quote from this company and will use them to measure oxytocin in de-identified samples from this protocol sent to their facility. We note that pharmacokinetics from intramuscular administration cannot alone inform computer controlled infusion of intravenous oxytocin, necessitating data from this IRB protocol.

RATIONALE FOR OTHER MEASURES BEYOND BLOOD SAMPLES IN THIS PROTOCOL

Although the primary goal of this protocol is to model change in oxytocin concentrations in plasma after intravenous administration, we will also acquire tests of sensory function that could be modulated by oxytocin during later time periods when blood samples are widely separated by time. There are two measures which will assess two different aspects of sensory function.

MEASURE 1: LIGHT TOUCH FREQUENCY THRESHOLD

Light touch is subserved by a group of myelinated peripheral nerves with fast conduction in the Aβ range and which are capable of following high frequencies, being responsible for the sensation of vibration. This capability of individual nerve fibers to respond with high frequency also underlies our ability to sense a light touch moving across the body surface as in brushing.

In preclinical studies we have shown that, following injury, these light touch fibers lose their ability to follow high frequencies and, in some cases, no longer respond to mechanical stimulation at all [1]. Oxytocin, when perfused around the neuronal cell

bodies of these Aβ nerve fibers, partially restores their function, including their response to high frequency stimulation.

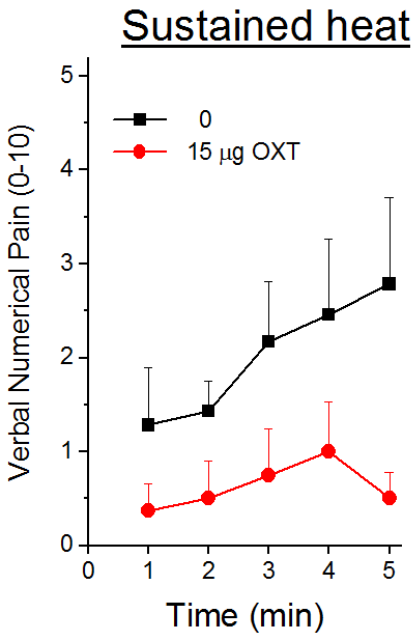
In order to determine the highest frequency that Aβ nerve fibers can respond to, we have created a simple device that produces an oscillatory / vibratory stimulus which can be used on the hand. The subject places fingertips and volar aspect of the wrist sequentially and the device is set to slowly decrease the frequency of vibration from 1 kHz until the subject first perceives this. This is repeated three times at each site and takes under 5 minutes in total. More details are provided in the Appendix.

We anticipate that oxytocin will have no effect on normal Aβ fibers and that this measure will not change after oxytocin administration. This will provide important data to contrast with the expected efficacy of oxytocin in the setting of injury, to be studied in subsequent protocols.

MEASURE 2: SUSTAINED HEAT

As part of a protocol used by us in several studies, the surface of the skin of the forearm or leg is heated to 45°C using an FDA approved, Peltier-controlled thermode for a period of 5 minutes (TSA®, Medoc, Ramat Yishai, Israel). This typically results in a slowly increasing pain experience, peaking at 5 minutes in the mild to low moderate range and has been tolerated by more than 150 subjects in studies over the past 14 years.

In an interim analysis of an ongoing clinical study in volunteers, we noted that spinal injection of oxytocin, 15 µg (equivalent to 9 IU), that pain from this sustained heat was dramatically reduced over the 5 minutes of stimulus presentation (adjacent figure). In contrast, spinal oxytocin had no effect on the stimulus-response relationship of pain to noxious heat over a 42-50°C range when the stimuli were presented for only 5 seconds. These data suggest that oxytocin reduces C-fiber mediated signaling of sustained heat pain, likely through a spinal site of action.



Drugs administered spinally have a much higher

concentration in cerebrospinal fluid than plasma. Nonetheless, spinally administered drugs are typically absorbed to an extent and with a time course similar to that after intramuscular injection, and it is conceivable that the effect on sustained heat pain we are seeing in the spinal study reflect peripheral effects via systemic absorption. Thus, if we see a similar reduction in response to sustained heat in this protocol of intravenous administration, we will conclude that oxytocin is more likely activing peripherally than spinally.

Protocol

Pharmacokinetics of intravenous oxytocin and effects on sensory function in healthy volunteers

PRIMARY GOAL: Measure oxytocin in plasma after brief intravenous infusion and model its pharmacokinetics.

METHODS: Equal numbers of healthy adult men and women will be recruited (ten total). At least 1 day prior to study subjects will be trained to rate pain in response to heat applied to the lateral calf using a Peltier controlled thermode and to indicate when they first perceive a vibratory stimulus on the fingertips and wrist.

Subjects will return for study visit two in which an intravenous catheter will be inserted in the arm and, after baseline measures of response to heat and determination of vibration frequency threshold, subjects will receive oxytocin (Pitocin®), 10 IU over 10 minutes. Venous blood samples (5 ml) will be obtained before and at 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the end of the oxytocin administration by removal of blood from the intravenous catheter.

We will abandon an individual participant's study and schedule another participant should we be unable to successfully place the intravenous catheter.

STUDY DESIGN

Inclusion Criteria: We request permission to study up to 12 subjects so that we will have 10 evaluable subjects with complete sampling at all time periods.

1. Male or female ≥ 18 and ≤ 60 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.

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 serum pregnancy test at screening visit), women who are currently nursing or lactating, women that have been pregnant within 2 years

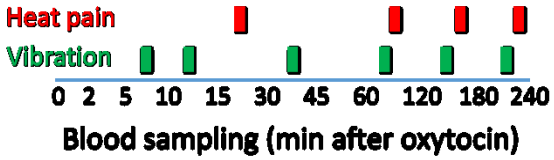
4. Subjects with neuropathy, chronic pain, diabetes mellitus, or taking benzodiazepines or pain medications on a daily basis.

Study Visit 1: The participant will report to the Clinical Research Unit (CRU) or Piedmont Plaza II at least 1 day prior to study visit 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 have a urine sampled tested to determine pregnancy status. The research nurse will train the participants to estimate pain quantitatively using a 2 cm^2 Peltier controlled thermode (TSA®) applied to a forearm with 5 sec presentation of stimuli at 39, 41, 43, 45, 47, 49, and 50°C, using a 11 point numerical verbal scale (NRS) anchored at 0 for no pain and 10 for the worst pain imaginable. Typically, the participant is exposed to temperatures between 38^0 and 51^0 C using a random staircase method. After this training, we will ask them to report pain intensity on the 0-10 NRS scale every minute for 5 minutes upon exposure to a 4 cm^2 Peltier controlled thermode at 45°C. Finally, they will place first the fingertips of their hand and then the volar wrist, on a device and report when they first perceive a sensation as the surface vibration frequency declines from 1 kHz to 1 Hz. We have found this training session significantly reduces anxiety and variability in pain and hypersensitivity ratings on subsequent study days.

Study Visit 2

On the second visit, the participant will report to the CRU, in the morning after having had nothing to eat or drink since midnight. A peripheral intravenous catheter will be inserted into a vein in an upper extremity and lactated Ringers solution infused at 1.5 ml/kg/hr for the duration of the study. After obtaining baseline measures (random presentation of 5 sec heat stimuli between 39 and 50°C, 5 minute presentation of a 45°C stimulus, and vibration frequency perception threshold as described in Visit 1), oxytocin (Pitocin®, 10 IU) will be administered intravenously over 10 minutes.

Venous blood will be sampled (5 ml) before the infusion and at 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after oxytocin injection via the indwelling intravenous catheter. We will also repeat vibration frequency perception threshold in fingertips and wrist between the samples after samples at 5, 20, 45, 60, 120, and 180 minutes. In addition, we will ask them to rate pain intensity every minute for 5 minutes with a 45° stimulus after samples at 30, 60, 120, and 180 minutes (adjacent figure) and rate pain intensity to single, 5 second duration stimuli from 39°C to 50°C after samples at 60, 120, and 180 minutes as on the first visit.



Safety and Monitoring:

Assessment of Side Effects*:* Significant side effects are defined as changes > 30% from baseline in the mean arterial pressure, HR, or oxyhemoglobin pulse oximetry < 90. Any unexpected or serious side effects will be reported to the IRB within 24 hrs. Peripheral oxyhemoglobin saturation, BP and HR will be measured non-invasively before and 15, 30, 60, 120, 180, 240, minutes after intravenous oxytocin injection. If either BP or HR change by > 30%, or oxyhemoglobin saturation decreases to less than 90, and require treatment, these vital signs will be repeated at 5-minute intervals until vital signs are stabilized.

Treatment of Side Effects: Mean blood pressure elevations greater than 30% of baseline will be treated with labetalol 5-15 mg IV incrementally until BP elevation is less than 30% elevated. Reductions in mean BP > 30% of baseline will be treated with incremental ephedrine 5-20 mg, IV. Heart rate (HR) reductions or elevations > 30% of

baseline will be treated with incremental glycopyrolate 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.

RISKS

Risks of intravenous cannulation include pain on insertion and bruising at the site. Risks from the FDA approved heat stimulus device are pain, and the subject can stop testing at any time if the pain they perceive is such that they do not want to continue. Please note that these devices are used in many pain clinics routinely and have multiple fail-safe designs to avoid thermal burn. Risks from the non-regulatory vibratory device are related only to microshock and are addressed in the Appendix.

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 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 have been reported by previous participants but were short lived, lasting approximately 12-15 minutes.

HUMAN SUBJECTS

All studies in volunteers will be performed in the CRU, which includes monitoring and resuscitation equipment and trained nursing support staff, or in in-patient settings of the Wake Forest Baptist Medical Center. All studies will be approved by the IRB and written informed consent obtained. The Project Investigators have all performed similar studies in volunteers and patients. The purpose of the study and all risks will be discussed with each volunteer, and all questions will be answered prior to obtaining written informed consent. Risks to be discussed include discomfort with needle and catheter insertion. All data acquired will remain confidential with no reference to individuals in publications.

Data Safety Monitoring Plan

Although the use of oxytocin in this protocol is outside FDA approval for oxytocin administration during labor or in 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 [4-7; 9-21] 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 $300 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 1: $25

Placement of IV: $25

Completion of entire study: $250

Volunteer must complete all of the above phases to receive this payment.

Long-term Follow-up

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

STATISTICAL RATIONALE

Primary outcome measure is the concentration of oxytocin in plasma at defined times after intravenous infusion. We request a convenience sample of 10 subjects for the purpose of preliminary data to provide variance estimates that will inform federal grant

submission for use of the pharmacokinetic parameters from this sample or proposal of a larger sample size to adequately characterize such parameters.

REFERENCES

[1] Boada MD, Gutierrez S, Aschenbrenner CA, Houle TT, Hayashida KI, Ririe DG, Eisenach JC. Nerve injury induces a new profile of tactile and mechanical nociceptor input from undamaged peripheral afferents. J Neurophysiol 2015;113(100):109.

[2] Brandtzaeg OK, Johnsen E, Roberg-Larsen H, Seip KF, MacLean EL, Gesquiere LR, Leknes S, Lundanes E, Wilson SR. Proteomics tools reveal startlingly high amounts of oxytocin in plasma and serum. Scientific reports 2016;6:31693.

[3] Fernando D, Siederer S, Singh S, Schneider I, Gupta A, Powell M, Richards D, McIntosh MP, Lambert P, Fowles S. Safety, Tolerability and Pharmacokinetics of Single Doses of Oxytocin Administered via an Inhaled Route in Healthy Females: Randomized, Single-blind, Phase 1 Study. EBioMedicine 2017;22:249-255.

[4] Gossen A, Hahn A, Westphal L, Prinz S, Schultz RT, Grunder G, Spreckelmeyer KN. Oxytocin plasma concentrations after single intranasal oxytocin administration - a study in healthy men. Neuropeptides 2012;46(5):211-215.

[5] Kessner S, Sprenger C, Wrobel N, Wiech K, Bingel U. Effect of oxytocin on placebo analgesia: a randomized study. JAMA 2013;310(16):1733-1735.

[6] Lee MR, Scheidweiler KB, Diao XX, Akhlaghi F, Cummins A, Huestis MA, Leggio L, Averbeck BB. Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay. Molecular psychiatry 2017.

[7] Leknes S, Wessberg J, Ellingsen DM, Chelnokova O, Olausson H, Laeng B. Oxytocin enhances pupil dilation and sensitivity to 'hidden' emotional expressions. SocCogn AffectNeurosci 2013;8(7):741-749.

[8] Leng G, Sabatier N. Measuring Oxytocin and Vasopressin: Bioassays, Immunoassays and Random Numbers. J Neuroendocrinol 2016;28(10).

[9] Liu R, Yuan X, Chen K, Jiang Y, Zhou W. Perception of social interaction compresses subjective duration in an oxytocin-dependent manner. eLife 2018;7.

[10] Mameli S, Pisanu GM, Sardo S, Marchi A, Pili A, Carboni M, Minerba L, Trincas G, Carta MG, Melis MR, Agabio R. Oxytocin nasal spray in fibromyalgic patients. Rheumatology international 2014;34(8):1047-1052.

[11] Quintana DS, Westlye LT, Alnaes D, Kaufmann T, Mahmoud RA, Smerud KT, Djupesland PG, Andreassen OA. Low-dose intranasal oxytocin delivered with Breath Powered device modulates pupil diameter and amygdala activity: a randomized controlled pupillometry and fMRI study. Neuropsychopharmacology 2019;44(2):306-313.

[12] Rash JA, Campbell TS. The effect of intranasal oxytocin administration on acute cold pressor pain: a placebo-controlled, double-blind, within-participants crossover investigation. Psychosom Med 2014;76(6):422-429.

[13] Rash JA, Toivonen K, Robert M, Nasr-Esfahani M, Jarrell JF, Campbell TS. Protocol for a placebo-controlled, within-participants crossover trial evaluating the efficacy of intranasal oxytocin to improve pain and function among women with chronic pelvic musculoskeletal pain. BMJ open 2017;7(4):e014909.
[14] Striepens N, Kendrick KM, Hanking V, Landgraf R, Wullner U, Maier W, Hurlemann R. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. SciRep 2013;3:3440.
[15] Tanaka A, Furubayashi T, Arai M, Inoue D, Kimura S, Kiriyama A, Kusamori K, Katsumi H, Yutani R, Sakane T, Yamamoto A. Delivery of Oxytocin to the Brain for the Treatment of Autism Spectrum Disorder by Nasal Application. Molecular pharmaceutics 2018;15(3):1105-1111.
[16] Tracy LM, Labuschagne I, Georgiou-Karistianis N, Gibson SJ, Giummarra MJ. Sex-specific effects of intranasal oxytocin on thermal pain perception: A randomised, double-blind, placebo-controlled cross-over study. Psychoneuroendocrinology 2017;83:101-110.
[17] Tzabazis A, Kori S, Mechanic J, Miller J, Pascual C, Manering N, Carson D, Klukinov M, Spierings E, Jacobs D, Cuellar J, Frey WH, 2nd, Hanson L, Angst M, Yeomans DC. Oxytocin and Migraine Headache. Headache 2017;57 Suppl 2:64-75.
[18] Walum H, Waldman ID, Young LJ. Statistical and Methodological Considerations for the Interpretation of Intranasal Oxytocin Studies. Biol Psychiatry 2016;79(3):251-257.
[19] Wang YL, Yuan Y, Yang J, Wang CH, Pan YJ, Lu L, Wu YQ, Wang DX, Lv LX, Li RR, Xue L, Wang XH, Bi JW, Liu XF, Qian YN, Deng ZK, Zhang ZJ, Zhai XH, Zhou XJ, Wang GL, Zhai JX, Liu WY. The interaction between the oxytocin and pain modulation in headache patients. Neuropeptides 2013;47(2):93-97.
[20] Zhang H, Wu C, Chen Q, Chen X, Xu Z, Wu J, Cai D. Treatment of Obesity and Diabetes Using Oxytocin or Analogs in Patients and Mouse Models. PLOS ONE 2013;8(5):e61477.
[21] Zunhammer M, Geis S, Busch V, Greenlee MW, Eichhammer P. Effects of intranasal oxytocin on thermal pain in healthy men: a randomized functional magnetic resonance imaging study. Psychosom Med 2015;77(2):156-166.