

Phase 1 Safety Assessment of Intrathecal Oxytocin

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ABSTRACT

Background: Preclinical data suggest that oxytocin reduces hypersensitivity by actions in the spinal cord, but whether it produces antinociception to acute stimuli is unclear. In this article, the authors examined the safety of intrathecal oxytocin and screened its effects on acute noxious stimuli.

Methods: After institutional review board and Food and Drug Administration approval, healthy adult volunteers received 5, 15, 50, or 150 μg intrathecal oxytocin in a dose-escalating manner in cohorts of five subjects. Hemodynamic and neurologic assessments were performed for 4 h after injections and 24 h later, at which time serum sodium was also measured. Cerebrospinal fluid was obtained 60 min after injection, and responses to noxious heat stimuli in arm and leg as well as temporal summation to repeated application of a von Frey filament were obtained.

Results: One subject receiving the highest dose experienced transient hypotension and bradycardia as well as subjective numbness in a lumbo-sacral distribution. No other subject experienced subjective or objective neurologic symptoms. Overall, blood pressure and heart rate increased 1 to 4 h after injection by less than 15% with no dose dependency. There was no effect on serum sodium, and cerebrospinal fluid oxytocin increased in a dose-dependent manner after injection. Pain scores to noxious heat stimuli were unaffected by oxytocin, and the temporal summation protocol failed to show summation before or after drug treatment.

Conclusion: This small study supports further investigation on oxytocin for analgesia for hypersensitivity states, with continued systematic surveillance for possible effects on blood pressure, heart rate, and neurologic function. (**ANESTHESIOLOGY 2015; 122:407-13**)

SEVERAL lines of evidence suggest that oxytocin produces analgesia and that the spinal cord is a major site for this action. Unfortunately, oxytocin enters the central nervous system to a very limited extent after systemic administration, and systemic oxytocin does not produce analgesia to acute nociception in humans although it mildly potentiates placebo analgesia.¹ In contrast, direct administration of oxytocin into cerebrospinal fluid (CSF) produced analgesia in a patient with cancer pain.² In animals, activation of oxytocin fibers descending from the paraventricular nucleus to the spinal cord participates in stress-induced analgesia³ and reduces hypersensitivity after injury.⁴ In addition, we recently showed that pain and hypersensitivity after surgery recovers more quickly in animals and humans when the surgery occurs near the time of delivery, and that this is reversed by spinal injection of an oxytocin receptor–preferring antagonist.^{5,6} Oxytocin receptors are present in the superficial dorsal horn of human spinal cord,⁷ where it engages inhibitory circuits.^{3,8,9} Thus, there is a clear rationale to test the efficacy of intrathecal oxytocin for analgesia in humans.

The purpose of this study is the first step in clinical introduction of intrathecal oxytocin for analgesia. Oxytocin has a long history of safe use by systemic administration although it can cause hypotension,¹⁰ QT interval prolongation,¹¹ and could result in hyponatremia¹² among other known side effects. In a safety assessment in dogs and rats, intrathecal injection of oxytocin produced no evidence of neurotoxicity in the spinal cord.¹³ QT interval was not measured in those studies although intrathecal oxytocin did reduce heart rate.

What We Already Know about This Topic

- There have been few advances in new drugs producing spinal analgesia
- There are oxytocin receptors in the dorsal horn of the spinal cord indicating oxytocin may be a potential spinal analgesic

What This Article Tells Us That Is New

- Subarachnoid injections of oxytocin did not produce any major adverse events or complications
- In a limited protocol for testing analgesia, no analgesic effects were apparent

In the rats, it caused intense scratching and grooming behavior, consistent with the work in mice showing an action of oxytocin on arginine vasopressin receptors to cause itching.¹⁴

New drugs for intrathecal use are typically first administered in a dose-escalating, open-label manner, beginning at doses below and extending above the presumed therapeutic range, with a focus on safety. Based on preclinical studies,¹⁵ the therapeutic dose for intrathecal oxytocin was anticipated to be 20 μg or more, and doses up to 550 μg had been studied in dogs. We therefore studied a dose range of 5 to 150 μg . On the basis of clinical observations with systemic drug administration and preclinical observations with intrathecal drug administration, we focused safety assessment on blood pressure, heart rate, QT interval, serum sodium, and presence of itching. Although we would anticipate that intrathecal oxytocin would be most effective against hypersensitivity states,

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inducing abnormal sensations complicates drug effects in phase 1 safety studies. Animal studies are conflicting whether oxytocin does^{15,16} or does not¹⁷ produce antinociception to acute stimuli in the normal state, but some data show an effect to reduce response to noxious heat.¹⁵ For this reason, we screened for analgesic effects to acute noxious thermal stimuli and to acute hypersensitivity to mechanical stimuli, recognizing that this was exploratory in nature.

Materials and Methods

The study was approved by the Wake Forest School of Medicine Institutional Review Board (Winston-Salem, North Carolina) and was performed under Investigational New Drug approval and oversight by the Food and Drug Administration and by a local data safety monitoring committee and comprised an anesthesiologist and a neurologist. We used an open-label, dose-escalation phase 1 safety design similar to that used for novel drugs for intrathecal administration.¹⁸ Written informed consent was obtained from all subjects.

We recruited adults younger than 60 yr, weighing less than 100 kg and who were healthy (American Society of Anesthesiologists physical status 1), and having normal blood pressure (systolic pressure 90 to 140 mmHg; diastolic pressure 50 to 90 mmHg) and resting heart rate of 45 to 100 beats/min on screening visit, on study visit 2, and before spinal injection. Women of child-bearing potential and those less than 1 yr postmenopausal were included if they had a negative serum pregnancy test at the screening visit and were practicing highly effective methods of birth control. We included both sexes and individuals of different races and ethnicities in accordance with the National Institutes of Health guidance. We chose a healthy, young population for this safety study to avoid interactions with other drugs or diseases. We excluded subjects who were breast feeding, had hypersensitivity, allergy, or significant reaction to any ingredient of the study drug or lidocaine, and those with 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) or would compromise the subject's compliance with study procedures. We also excluded those taking prescription medications, with the exception of birth control pills.

Study Visit 1

The participant reported to the general clinical research unit for confirmation of consent and definitive screening. A detailed medical history was obtained, and blood was drawn for pregnancy testing as appropriate. Blood pressure, heart rate, and peripheral oxyhemoglobin saturation were recorded and a 12-lead electrocardiogram obtained. Subjects were then trained to estimate pain intensity and unpleasantness from heat stimuli applied to the skin of the arm using a 2-cm² Peltier-controlled thermode (TSA-II[®]; Medoc, Ramat Yishai, Israel). Five-second periods of fixed temperatures from 39° to

51°C in 2°C increments were presented at 30-s interstimulus intervals for one cycle in an ascending temperature series and then using random presentation as previously described.¹⁹ Two to three cycles of random presentation were performed until consistent ratings (within 30% for each temperature) were obtained. The probe remained in contact with the skin for the entire cycle and was moved at the end of each cycle to avoid sensitization. The subject was blinded to temperature being applied and rated pain intensity and unpleasantness separately using a 10-cm mechanical visual analog scale anchored at no pain and the worst pain imaginable or at not unpleasant and as unpleasant as possible.

Study Visit 2

On this visit, at least 1 day after visit 1, the subject reported to the general clinical research unit in the morning, having had nothing to eat or drink since midnight. An intravenous catheter was inserted into a vein in an upper extremity and lactated Ringer's solution infused at 1.5 ml kg⁻¹ h⁻¹ for the duration of the study. After obtaining baseline measures, the volunteer was positioned in the sitting or lateral position and a #27 Whitacre spinal needle (Becton Dickinson, and Company, Franklin Lakes, NJ) was inserted in a lumbar interspace using standard, sterile technique after local infiltration of superficial tissues with 1% lidocaine. After obtaining clear, free-flow CSF, a 2-ml sample was obtained and rapidly frozen for subsequent measurement of oxytocin. Oxytocin in a 3-ml volume, diluted with sterile normal saline, was then injected over 30 s. Oxytocin powder manufactured under Food and Drug Administration oversight for human use was formulated in preservative-free solution by Anazao Corporation (Orlando, FL) and used within 48 h of shipment to Wake Forest School of Medicine. After spinal injection, the volunteer moved to the supine position and the head of the bed was elevated for the remainder of the study. Sixty minutes after injection, the subject was repositioned and a #27 Whitacre tipped spinal needle inserted at the same interspace and 2-ml CSF removed for analysis of oxytocin.

In this dose-escalation study, the first five volunteers received 5 µg of spinal oxytocin and subsequent groups of five volunteers each received 15, 50, and 150 µg of spinal oxytocin. Escalation to the next higher dose occurred only after reviewing the adverse events at the lower dose by the data safety monitoring committee. Subjects were informed that different doses of oxytocin were being studied but not which dose they received. We did not assess participant expectations of treatment effects or prior knowledge of oxytocin.

Peripheral oxyhemoglobin saturation, blood pressure, and heart rate were measured noninvasively before and 15, 30, 60, 120, 180, and 240 min and approximately 24 h after administering spinal oxytocin. The electrocardiogram was monitored continuously for 240 min after spinal injection and corrected QT (QTc) interval estimated from manual measurement of printed tracings at 15-min intervals after injection for the first hour and then hourly for 3 more hours.

A screening neurologic examination along with questioning for qualitative symptoms was performed at 45, 90, 150, 210, and 240 min and 24 h after spinal injection. The screening neurologic test consisted assessing upper and lower extremity deep tendon reflexes (biceps, knee, and ankle with standard methods and 0 to 4 standard clinical grading), response to light touch, and extension/withdrawal strength across proximal and distal major joints (plantar-dorsiflexion at the foot, flexion-extension at the knee, palmar-dorsiflexion at the wrist, and flexion-extension at the elbow with standard examiner clinical grading). On the basis of the known adverse effects of oxytocin in clinical studies and on animal data, subjects were specifically questioned whether sedation, anxiety, nausea, dizziness, gastrointestinal or genitourinary symptoms or distress, or weakness was present at the same times as the neurologic examinations. If present, they were asked to rate them on a mild, moderate, severe scale. We also asked for presence of any other symptoms. Subjects were informed through the consent document that oxytocin could cause their blood pressure or heart rate to go up or down and could produce itching, nausea, pelvic or abdominal discomfort, or altered sensations in their legs or arms.

To screen for potential analgesic effects of oxytocin to acute pain processing, we examined response to both thermal and mechanical stimuli. For the former, subjects rated pain and unpleasantness to 5-s heat stimuli between 39° and 51°C presented in random order separately on the arm and leg, using the same scales and device used on study visit 1. A stimulus response was obtained before spinal injection and 15, 30, 60, 120, 180, and 240 min and approximately 24 h after administering spinal oxytocin. At these same times, we also determined temporal summation to 10 applications of a 255-mN von Frey filament application to the arm and leg using a method previously described.²⁰ For this, the filament was manually applied briefly to the bending point once per second for a total of 10 applications and pain scores obtained with the first and last application. Temporal summation was defined as the pain score on the last application minus the first.

Subjects were discharged in the care of an accompanying adult from the clinical trials unit 240 min after oxytocin on the condition that blood pressure and heart rate were within normal limits (140/50 to 90/50 mmHg and 45 to 100 beats/min, respectively), the subject could ambulate without difficulty, and there were no adverse events that had not resolved at this time.

Study Visit 3

Approximately 24 h after the spinal oxytocin injection, the volunteer returned to the general clinical research unit for screening neurologic examination, querying of any adverse events, and measuring blood pressure, heart rate, and pain ratings in the arm and leg to thermal stimuli and repeated von Frey filament application as described in Study Visit 2. Because of concerns of potential hyponatremia after exposure

to large doses of oxytocin, a blood sample was obtained at this time for serum sodium measurement from subjects who received 50 and 150 µg oxytocin.

Long-term Follow-up

Subjects were contacted by telephone daily for 5 days after spinal injection, weekly for 1 month, and then at 6 months. They were specifically queried at these times regarding side effects from the procedure (headache or backache), for any focal or general neurologic symptoms, and for any adverse events since the time of study.

Volunteers were paid according to a graduated schedule with a total of \$400 for completion of all phases of study.

Cerebrospinal fluid oxytocin before injection was measured using an ultrasensitive, proprietary radioimmunoassay (RIAgnosis, Regensburg, Germany, limit of sensitivity 0.5 pg per sample), and CSF oxytocin after injection was measured with a commercially available radioimmunoassay (Phoenix Pharmaceuticals, Inc., Burlingame, CA, limit of sensitivity 10 pg per sample). Serum sodium was measured in a commercial laboratory (Laboratory Corporation of America, Winston-Salem, NC).

Statistical Analysis

The number of subjects at each dose level was chosen by tradition for phase 1 safety trials with intrathecal drug administration, balancing the risks associated with the invasive drug administration, and the assessment of adverse event rates. A formal power calculation was not performed.

Data are presented as mean ± SD or median [25th, 75th percentile] as appropriate. For blood pressure, heart rate, and QTc interval, a two-factor, repeated-measures ANOVA was performed with time and dose defined as the factors. For pain scores, two approaches were used. The primary analysis was a two-factor, repeated-measures ANOVA with time and dose defined as the factors and average visual analog pain score at the two highest stimuli (49° and 51°C) as the outcome measures. We chose these two because these were the only temperature stimuli to result in nonzero pain scores from all individuals at all times. We secondarily explored analgesic effects and potential sex differences in two separate generalized estimating equation models to predict pain or unpleasantness by (1) site (arm or leg), (2) dose (5, 15, 50, and 150 µg), (3) time (5 to 1,440 min), and (4) stimulus temperature (39° to 51°C). Data were first explored to determine distributions and linear associations between predictors and outcomes.

Measurements were viewed as nested within subject with repeated measures for dose, time, and stimulus temperatures. A normal distribution with identity link was specified and the robust estimator was used to provide the covariance estimation along with an independent correlation matrix. Site, dose, time, and stimulus temperature were entered into the model as fixed factors. As there were no missing values in either model, all cases were included in the analysis. The model

residuals were examined after prediction. Two-tailed P value less than 0.05 was considered statistically significant, with no attempts made to adjust for the two models. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS for Windows, version 22.0, Chicago, IL).

Results

Twenty subjects were studied between February 2012 and August 2013. They were 37 ± 12 yr old, 172 ± 10 cm tall, and 76 ± 18 kg in weight. Twelve of these subjects were women, 1 was Hispanic, 4 were African-American, and 15 were Caucasian. All subjects completed the study and none were lost to follow-up for the 6-month period of study.

Safety Measures

Sensory and motor examination as well as deep tendon reflexes in the upper and lower extremities was normal in all subjects before intrathecal injection and unchanged after injection. In response to prespecified, systematic questioning, one subject reported anxiety before and 45 min after intrathecal injection (50 μ g dose), and no subject reported weakness, sedation, nausea, itching, or gastrointestinal or bladder discomfort. Three subjects reported mild headache at the 24 h visit (two at the 5 μ g dose and one at the 150 μ g dose) which resolved spontaneously over the next few days.

There was a dose-independent effect of intrathecal oxytocin on blood pressure and heart rate, with a small (<15%)

increase in both parameters which was transient and occurred earlier for blood pressure than heart rate (fig. 1, A and B). QTc interval did not change after oxytocin injection (fig. 2), and no subject met criteria for QTc prolongation. The median serum sodium value 24 h after spinal injection was 137 mmol/l (range, 137 to 142 mmol/l) in subjects who received 50 μ g oxytocin and 139 mmol/l (range, 137 to 146 mmol/l) in subjects who received 150 μ g oxytocin. One subject who received 150 μ g oxytocin had a serum sodium of 146 mmol/l which was outside the normal range (134 to 144 mmol/l).

Serious Adverse Event

One subject had a symptomatic decrease in heart rate and blood pressure. This subject, the first to receive the largest dose (150 μ g), was noted to appear pale and felt clammy just before intrathecal injection. She denied light headedness. At the end of the injection, the subject was positioned from the sitting to the right lateral position, when blood pressure after repositioning (73/58 mmHg) was considerably below her baseline just before positioning for spinal injection (114/67 mmHg), with a heart rate of 58, no apparent change to the narrow QRS complex on electrocardiographic monitoring, but with loss of P waves. She felt better over the next 5 min, and by 15 min after intrathecal oxytocin injection, she felt normal. Although P waves were present and bradycardia resolved shortly after she was placed in the lateral position, she remained hypotensive (86/49 mmHg) 15 min after intrathecal injection. This met protocol criteria for treatment

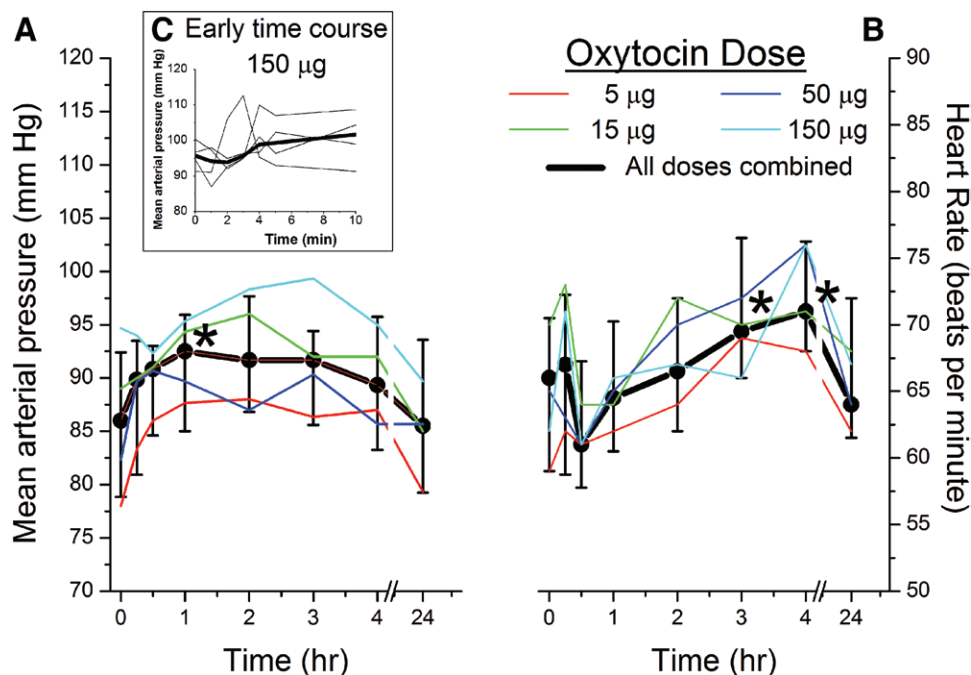


Fig. 1. (A) Blood pressure and (B) heart rate before and after spinal injections of different doses of oxytocin. There was an effect of time on blood pressure and heart rate across all groups, with no dose dependency. (C) *Inset* shows blood pressure for the first 10 min after injection of 150 μ g oxytocin in four volunteers (*thin lines*) and the median value (*thick line*). There was not an effect of time on blood pressure during this time period. For A and B, *thin lines* represent the median of five individuals, and the *thick line* represents the median \pm interquartile range of the population. * <0.05 versus time 0 by Bonferroni test, which followed a significant two-way ANOVA for repeated measures.

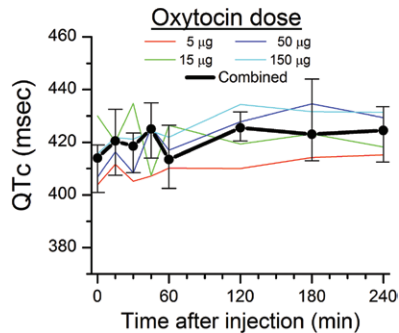


Fig. 2. Corrected QT (QTc) interval before and after spinal injections of different doses of oxytocin. Thin lines represent the median of five individuals, and the thick line represents the median \pm interquartile range of the population. No significant effect of time or dose.

(>20% reduction in mean arterial pressure from baseline), and given the known hypotensive effect of oxytocin, it was considered that this was possibly due to study drug. Ephedrine 5 mg was administered intravenously, and blood pressure increased 5 min thereafter to 96/47 mmHg and 15 min thereafter to 111/71 mmHg, with no recurrent episodes of hypotension. On further questioning, she noted that she had experienced similar feelings of clamminess associated with times of anxiety.

Approximately 20 min after injection, the same volunteer who experienced hypotension after oxytocin injection noted numbness in buttocks and left third to fifth toes. She was still in the right lateral decubitus position, and she moved to the supine position. On physical examination, there were no motor deficits including foot plantar flexion, deep tendon reflexes were normal and unchanged from baseline, and there were no sensory deficits to light touch in lower extremities or on buttocks. No sensory abnormalities were noted on testing of the foot (sensory threshold to von Frey filament application or light stroking with a cotton swab). After repositioning, over the next 10 min, she noted expansion of a tingling/numbness sensation extending from the buttocks to the perineum. She was asked to perform a pelvic floor exercise (Kegel) and she reported this as normal. This altered sensation began to resolve 60 min after injection and was completely resolved 90 min after injection. She urinated before leaving the General Clinical Research Center and reported no difficulties with urination or ambulation. Follow-up at 12 and 24 h as well as prespecified follow-up intervals to 6 months after study were normal. Her demographic measures, CSF oxytocin concentrations, pain scores, and resting hemodynamic values were within the 25th to 75th percentile range of the subject population.

This episode was reported within 24 h to the institutional review board, the Food and Drug Administration, and the data safety monitoring committee. The data safety monitoring committee considered that the timing and characteristics of the initial hypotension after spinal needle insertion were consistent with a vaso-vagal episode although it was possible

that the lingering and less severe hypotension 15 min after injection were due to systemic absorption of oxytocin and its action on peripheral blood vessels. This hypotension clearly and rapidly responded to ephedrine. The cause of the subjective negative sensory symptoms was unclear. The study was placed on hold for 30 days, and the protocol revised for more frequent blood pressure monitoring in the first 10 min after spinal injection. None of the subsequent four individuals who received 150 μ g oxytocin experienced hypotension (fig. 1C), bradycardia, or altered sensation.

Cerebrospinal fluid oxytocin concentrations were 9.5 ± 3.1 pg/ml before injection and increased in a dose-dependent manner 60 min after 5, 15, 50, and 150 μ g oxytocin injection to 26 [22 to 28], 154 [126 to 170], 313 [266 to 379], and 1,200 [1,187 to 1,448] ng/ml, respectively. The subject with the serious adverse event had a CSF oxytocin concentration of 1,448 ng/ml.

Efficacy Measures

Average pain intensity report for the 49° and 51°C combined before spinal injection was 3.7 ± 2.2 cm in the leg and 3.6 ± 2.3 cm in the arm. In the primary analysis, oxytocin did not affect this measure of pain intensity reporting in the leg or arm (fig. 3, A and B, $P = 0.11$ for leg and $P = 0.22$ for arm). Similarly, oxytocin did not affect pain unpleasantness reporting to the two highest temperature stimuli (data not shown).

Full factorial modeling of time, dose, site, and temperature revealed highly significant four-way interactions and for each of the three-way combinations of both pain and unpleasantness ($P < 0.0001$). Collapsing across time, there was a highly significant three-way combination for site, dose, and temperature ($P < 0.0001$), and separate analysis for site revealed a significant interaction between temperature and dose ($P < 0.0001$). The thermal stimulus response for pain differed by dose in both the arm and the leg, and there was a nonlinear relationship between dose and pain report. There was not a sex difference in pain report when this variable was added to the full factorial analysis.

As regards temporal summation, only five subjects rated the first mechanical stimulus as painful, making it infeasible to examine the ratio of the 10th to the 1st stimulus as previously described.²⁰ Overall, only 103 of 320 pain ratings were greater than 0, with an average collapsed across time of 0.4 ± 0.8 on the 1st stimulus and 0.8 ± 1.4 on the 10th stimulus. There was no effect of time or dose on the difference between the 10th and the 1st stimulus.

Discussion

By their nature, first-in-human safety trials expose only a small number of subjects to drug and use a wide dose range, further limiting the ability to observe serious safety signals. For example, with only five subjects per dose, there is only a 50% chance of observing an adverse event with a true incidence as great as 60%. As such, the conclusion from these trials is

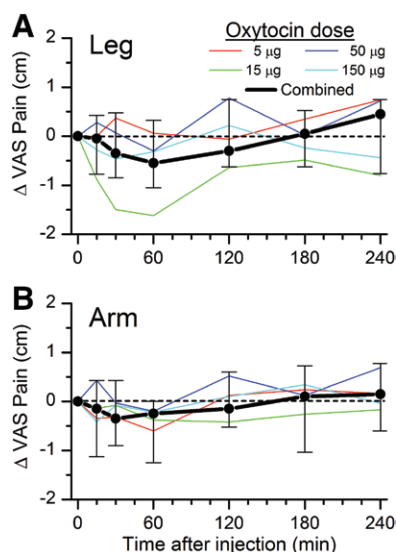


Fig. 3. Change in average of the pain intensity report on a 10-cm visual analog scale (VAS) to 5-s stimuli at 49° and 51°C on the (A) leg or (B) arm before and after spinal injections of different doses of oxytocin. Thin lines represent the median of five individuals, and the thick line represents the median \pm interquartile range of the population. No significant effect of time or dose.

either that a drug is unsafe or that it is reasonable to proceed cautiously with continued investigation rather than that the drug is safe. These data agree with preclinical observations of safety and suggest that it is reasonable to proceed cautiously with continued investigation of intrathecal oxytocin.

Interpretation of the adverse event in the subject receiving 150 μ g oxytocin is complicated by the onset of symptoms just before injection and the presentation of symptoms (clamminess or pallor) and signs (hypotension, bradycardia, or narrow complex rhythm in the absence of P waves) consistent with vaso-vagal near syncope. It is conceivable that accidental intravenous injection of oxytocin could cause acute hypotension, but this is highly unlikely because this hypotension is typically associated with tachycardia rather than bradycardia and because CSF concentrations of oxytocin 60 min after injection were consistent with intrathecal injection. Although none of the other four volunteers receiving this dose of oxytocin exhibited hypotension, the presence of these symptoms in one individual suggests that future studies should include monitoring of blood pressure and heart rate after injection.

The presence of subjective tingling and numbness in the same volunteer who experienced hypotension is consistent with a drug effect, as it was restricted to sacral dermatomes (perhaps extending to L5), predominantly on the left side while the subject was in the right lateral decubitus position for several minutes after injection. We did not measure baricity of the oxytocin solution, but the diluent, normal saline, would be expected to be hypobaric compared with CSF and drug exposure should be greater to left nerve roots and spinal cord when the subject is in the right lateral decubitus

position. The lack of objective signs of altered sensation or objective or subjective weakness, including pelvic floor muscle contraction, lack of alteration of deep tendon reflexes, and rapid resolution of the symptoms, is reassuring as is the lack of similar subjective sensations in other volunteers receiving this dose. Nonetheless, we believe that future investigations of intrathecal oxytocin should include systematic questioning and physical examination for focal neurologic signs and symptoms and extended follow-up of all subjects exposed to this treatment.

Aside from this one individual, intrathecal oxytocin produced mild or no side effects. We note that only gross neurologic effects were examined in the current study, and that oxytocin-induced subtle effects on modality-specific sensory thresholds could have occurred without detection. Blood pressure increased by a small amount 60 min after injection. Although we did not measure oxytocin in the systemic circulation in the current study, time of peak absorption after intrathecal injection is approximately 60 min for bupivacaine and morphine,^{21,22} and it is conceivable that this increase could reflect actions of oxytocin on vascular arginine vasopressin V1a receptors. Arguing against this is the lack of dose dependency in this effect in dogs¹³ or humans in the current study. Bradycardia was noted in dogs receiving 550 μ g intrathecal oxytocin, but aside from the one episode of symptomatic bradycardia and hypotension, we did not note bradycardia in this clinical study. The increase in heart rate observed 3 and 4 h after injection was small (<10%) and dose independent. These data are consistent with a review of 1,529 subjects receiving 18 to 72 μ g intranasal oxytocin without the evidence of toxicity.²³

Three special concerns with oxytocin in the nonpregnant patients are effects on QT interval, serum sodium, and, after intrathecal administration, itching. We observed neither a change in QTc in this small safety study nor did any of the 20 individuals show prolonged QTc after drug administration. Similarly, the only abnormal serum sodium in this study was very mild hypernatremia in one individual, and water intoxication from oxytocin has only been observed in cases with prolonged administration.¹² Scratching behavior in rodents after intrathecal oxytocin is directed to the dermatomes near the injection site, consistent with a pruritic effect or potentially hypesthesia.¹⁴ This does not occur in dogs,¹³ and no subject in the current study reported itching or hypesthesia, so it is likely that there is a species-dependent effect with rodents being susceptible.

Studies in animals conflict on whether intrathecal oxytocin produces antinociception to acute stimuli in normal individuals. Some studies demonstrate antinociception to thermal,¹⁵ chemical,¹⁶ and mechanical¹⁵ stimuli although it is unclear whether scratching behaviors elicited by oxytocin in these rodent studies interfered with measurements. Other studies demonstrate an effect only in hypersensitivity states.¹⁷ Our exploratory results do not support for an analgesic effect of intrathecal oxytocin to acute noxious heat stimuli in normal humans although the study was not placebo controlled

or adequately powered to observe a subtle effect, and further studies are necessary to definitively test this hypothesis. We were unable to replicate the temporal summation protocol previously described,²⁰ perhaps due to the use of the von Frey filament, which has a larger surface area of point of contact than the custom-designed metal filaments used in that study, so could not examine the effects of intrathecal oxytocin on experimentally induced hypersensitivity. A study in progress will examine this effect in a controlled manner.

In summary, these data suggest that intrathecal oxytocin after a single bolus over a dose range of 15 to 150 µg does not cause a high incidence of effects on blood pressure, heart rate, QT interval, serum sodium, or neurologic symptoms and does not produce analgesia to acute noxious heat stimuli in normal individuals. One subject did experience transient cardiovascular depression and focal neurologic symptoms, so future studies should carefully assess these systems.

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Competing Interests

Dr. Eisenach has received fees for consultation to Aerial Biopharma (Morrisville, North Carolina) and Adynxx (San Francisco, California) on topics unrelated to this article. The other authors declare no competing interests.

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