Impact of Oxytocin on Obstructive Sleep Apnea Induced Changes in Sleep

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Protocol Version: December 14th, 2017

Background:

One major, yet poorly understood cardiovascular health risk that occurs in as many as 24% of males and 9% of females within the US population is obstructive sleep apnea (OSA). Severe OSA increases cardiovascular mortality 4 fold, and even when corrected for other risk factors increases cardiovascular mortality 3 fold. OSA can participate in both the initiation and progression of several cardiovascular diseases including sudden death, hypertension, arrhythmias, myocardial ischemia and stroke. Treatment of OSA is primarily continuous positive airway pressure (CPAP).

Diminished cardiac vagal activity is thought to be associated with many of the adverse cardiovascular consequences of OSA. Heart rate is dominated by cardioinhibitory parasympathetic activity. Parasympathetic cardiac vagal activity is typically cardioprotective and there is a high tonic level of parasympathetic and little sympathetic cardiac activity at rest. Re-establishment of cardiac vagal activity prevents arrhythmias, decreases risk of sudden death, and protects against ischemial/reperfusion injury, suggesting that restoring parasympathetic cardiac activity could be an effective therapeutic target to decrease mortality and morbidity associated with OSA.

In human volunteers intranasal administration of oxytocin significantly increases parasympathetic and decreases sympathetic cardiac control. In addition to the classic effects of oxytocin on uterine contraction and milk ejection, recent work indicates oxytocin is present in both males and females and has an important role in both behavior and cardiovascular homeostasis, particularly during anxiety and stress.

There are no clinical guidelines for the use of intranasal oxytocin in the treatment of sleep apnea but we propose that it may have a positive impact on the outcome of patients with sleep apnea, however, this research is not intended to change any clinical guidelines.

This project's specific aim will test the following hypothesis:
Intranasal oxytocin administration will blunt the deleterious hypoxia/hypercapnia induced changes in heart rate that occur during apnea in patients with OSA.

Study Proposal:

This proposal, based on the above detailed role of oxytocin in increasing parasympathetic and decreasing sympathetic cardiac control, will test if oxytocin administration blunts the deleterious hypoxia/hypercapnia induced changes in heart rate that occur during apnea in patients with OSA. This project will lay the groundwork and provide preliminary data to obtain NM funding to test this hypothesis more thoroughly and in larger clinical trials.

Study Objectives:

Primary Objective: This study will explore if intranasal oxytocin has any positive impact on blunting the deleterious hypoxia/hypercapnia induced changes in heart rate that occur during apnea in patients with OSA.

Protocol Outline:

To test this specific aim we will examine the changes in heart rate in a group of patients that have recently been diagnosed with OSA. The following approach will be taken for the two study cohorts listed below:

Cohort A: 10 Subjects

1. 10 subjects that have recently undergone a standard "in the sleep-lab" diagnostic polysomnography (per standard of care medical guidelines, and not for research purposes) and have been diagnosed with OSA will be recruited into the research study to assess the beneficial effects of oxytocin treatment.
2. For research: These 10 subjects will undergo another "in the sleep-lab" diagnostic polysomnography that is identical to the one that they had for standard of care to diagnose OSA. This polysomnography that is performed for research will be funded externally by the investigating group.

If subjects are female and of child bearing potential, then their birth control method for the duration of the study will be recorded, and a urine pregnancy test will be performed prior to the PSG.

3. Within one hour prior to the research polysomnography the subjects will be given oxytocin 40 International Units, (IU) intranasally.
4. The following 4 outcome measurements will be compared between the two sequential diagnostic polysomnographies (initial without, and second with oxytocin) in the same subjects:
    i. basal heart rate before sleep (primary outcome)
    ii. mean changes in heart rate with apneic and hypopneic events (primary outcome)
    iii. apnea-hypopnea index (secondary outcome)
    iv. percentage of time spent by the patient with oxygen saturations: > 90%, > 80% but < 90%, and < 80% (secondary outcome)

The intranasal oxytocin dose is 40 IU. The drug will be stored in the Investigational Drug Pharmacy according to the vendor's recommendations.

Polysomnography (PSG) is a comprehensive recording of the biophysiological changes that occur during sleep. It is usually performed at night, when most people sleep, though some labs can accommodate shift workers and people with circadian rhythm sleep disorders and do the test at other times of the day. The PSG monitors many body functions including brain (EEG), eye movements (EOG), muscle activity or skeletal muscle activation (EMG) and heart rhythm (ECG) during sleep. After the identification of the sleep disorder sleep apnea in the 1970s, respiratory airflow and respiratory effort indicators were added, along with peripheral pulse oximetry.

Cohort B: 40 Subjects

Once enrollment in Cohort A is complete, then enrollment into Cohort B will begin.

1. 40 Subjects that have recently undergone either a standard "in the sleep-lab" diagnostic polysomnography (per standard of care medical guidelines, and not for research purposes) or an "at home" PSG test and have been diagnosed with OSA will be recruited into the research study where we will assess the beneficial effects of oxytocin treatment.
2. For research: These 40 subjects will undergo an "in the sleep-lab" diagnostic polysomnography that would be identical to the one they had for standard of care medical guidelines if they were diagnosed with OSA "in the sleep-lab". This research

polysomnography should be performed within 4 weeks of their OSA diagnosis PSG. This PSG that is being performed for research will be funded externally by the investigating group.

If subjects are female and of child bearing potential, then their birth control method for the duration of the study will be recorded, and a urine pregnancy test will be performed prior to the PSG.

3. Subjects will be randomized by the Investigational Drug Services Pharmacy of the MFA to be administered either Oxytocin (40 IU) or placebo within one hour prior to beginning the study polysomnography.
    a. Both the polysomnography technician, the patient, and all research staff will be blinded to this randomization. The only un-blinded personnel will be the IDS pharmacy staff.
4. Subjects will then return within **4 weeks** to have a **second research study** polysomnography performed by the sleep-lab. This polysomnography that is being performed for research will be funded externally by the investigating group.
5. Subjects will be administered the intervention that ***they did not received*** during the first research PSG study within one hour prior to beginning the second polysomnography. Either Oxytocin (40 IU) or placebo.
    a. Both the polysomnography technician, the patient, and all research staff will be blinded to this randomization. The only un-blinded personnel will be the IDS pharmacy staff.

    For example: If at study polysomnography 1 a subject is randomized to receive placebo 1 hour prior to the start of the polysomnography, then at study polysomnography 2 the subject will be administered oxytocin (40 IU) 1 hour prior to the start of the polysomnography.
6. The following 4 outcome measurements will be compared between the two sequential diagnostic PSGs (initial standard of care without oxytocin, and second for research with oxytocin) in the same subjects:
    i. basal heart rate before sleep (primary outcome)
    ii. mean changes in heart rate with apneic and hypopneic events (primary outcome)
    iii. apnea-hypopnea index (secondary outcome)
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Inclusion Criteria:

- Men or women 18 years old or older of any ethnic background

- Subjects that have recently undergone a standard "in the sleep-lab" diagnostic polysomnography (per standard of care medical guidelines), or the "at home" diagnostic test for cohort B, and have been diagnosed with OSA will be recruited into a follow-up study to assess the beneficial effects of oxytocin treatment.

Exclusion Criteria:

- Pregnant or nursing women.
- Women at any child bearing age who are not willing to undergo pregnancy tests, and stable and reliable methods to prevent pregnancy
    - A female subject of childbearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oopherectomy, or medically documented ovarian failure. Menopause can be assumed to have occurred in a woman when there is either:
        1. Appropriate medical documentation of prior complete bilateral oophorectomy OR
        2. Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency. Ovarian hormonal deficiency is documented by serum follicle stimulating hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed.
           OR
        3. Menopause is defined as occurring 12 months after your last menstrual period and marks the end of menstrual cycles
- Subjects who are on medications that affect cardiac autonomic function (eg. Beta blockers)
- Smokers
- Subjects who are unable to read or answer questions in the English language

The following information will be recorded on each patient before and after the use of intranasal oxytocin:

- Clinical data:
    1. Demographics — Age, gender, ethnicity, weight, BMI.
    2. Physiological data to be acquired:
        a. Basal heart rate before sleep
        b. Apnea-hypopnea index
        c. Mean changes in heart rate with apneic and hypopneic events
        d. Percentage of time spent by the patient with oxygen saturations: > 90%, > 80% but < 90%, and < 80%.
    3. Medical History Information: Current and past medical conditions, to be investigated for correlations to sleep.
    4. Standard of care sleep study data:
- The Polysomnography (PSG) monitors many body functions during sleep, including brain (EEG), eye movements (EGG), muscle activity or skeletal muscle activation (EMG), heart rhythm (ECG), respiratory airflow, thoracic and abdominal respiratory effort, body position, limb movement, and oxygen saturation using pulse oximetry. Recording and scoring is done per the standards set by the American Academy of Sleep Medicine.

All these data will be stored in a secured cabinet in the division of Pulmonary, Critical Care and Sleep Disorders offices. The primary investigator and study staff only will have access to these data. These data will lack any information that may lead to identifying any subject in the research.

Study Treatment:

The study medication, oxytocin, and its matching placebo will be purchased from Victoria Pharmacy in Switzerland and shipped to the MFA Investigational Drug Pharmacy via DHL Express or another express transportation service. Victoria Pharmacy will handle the packaging and shipping in accordance with the appropriate method required for the drug. The study medication will be received by and stored in the Investigational Drug Pharmacy and dispensing of study medication will be performed by a pharmacist in the Investigational Drug Pharmacy. The study is operating under FDA approved IND#120989. Patients will be administered oxytocin, 40 IU, or placebo (also a spray to be administered intranasal) within 1 hour prior to sleeping during the second sleep study. The PI will instruct the patient on how to use the spray, including how to prime the spray, and how to administer it.

Benefits/Risks:

There are no social/cultural, financial or legal risks to the subjects from participation in this study. No additional costs will be incurred to the patient or the institution as a result of this study. Oxytocin nasal spray is relatively safe when used as directed. Side effects are extremely rare. The intranasal oxytocin dose is 40 IU. The oxytocin and placebo sprays will be compounded by Foer's Pharmacy in Bethesda, Maryland, and then shipped to our research pharmacy, Investigational Drug Services (IDS) Pharmacy, when it is prepared. IDS will store the oxytocin and placebo sprays according to the vendor's recommendations.

Some minor side effects may include: nasal irritation, runny nose, or tearing of the eyes, nausea and vomiting and an irregular heartbeat. Intranasal oxytocin is not FDA approved. Women of childbearing age who are not on a stable, reliable form of birth control will be excluded from the study.

It is acknowledged that there may be slight emotional discomfort associated with completing the consent form and participating in the research, but subjects are always free to drop out of the study if they encounter emotional discomfort.

In animal models of social stressors oxytocin has been shown to be protective against behavioral and cardiac dysfunction. For example social isolation, which increases heart rate, diminishes HR variability and vagal regulation of the heart, was prevented with oxytocin administration. Most pertinent to the hypotheses put forth in this proposal, the stress and increased anxiety in response to inhalation of 7.5% CO2 in healthy volunteers was prevented by intranasally administered oxytocin.

In addition, in human subjects, the evidence shows that intranasal oxytocin: (1) produces no detectable subjective changes in recipients, (2) produces no reliable side-effects, and (3) is not associated with adverse outcomes when delivered in doses of 18-40 IU for short term use in controlled research settings [ref 1]

Any data containing patient identifiers will be kept in separate files from the clinical data collected and will be stored in a secure location in the Division of Pulmonary, Critical Care and Sleep Medicine.

In order to make the oxytocin and placebo nasal sprays, Foer's Pharmacy needs to be provided with subject's personal information. **We will need to provide the following to Foer's Pharmacy in order for subjects to participate in the study: Name, Date of Birth, Address, Phone Number and Drug Allergies.** This information will only be used for purposes of making the drug, and it will not be released to any other parties, or to the subject's insurance company.

Confidentiality:

Individual research records will be stored securely in locked offices in the MFA Div. of Pulmonary, Critical Care and Sleep Medicine. They will be available only to study personnel. Individual records may be made available to personnel from The George Washington University Institutional Review Board for inspection purposes only. With this exception, individual records will be kept strictly confidential. The data will be stored until it has been analyzed and potentially used for publication purposes. Any publication of these data will not include personal identifiers.

As data is collected, subjects will be assigned a study identification number. Code break information (subject initials and subject medical identification number) will be stored in a separate file. Data files and the code break file will be password protected and files which contain any patient identifiers will be kept separate from the main data set.

Costs to Subjects:

There will be no additional costs to the subjects to participate in this protocol. The routine medical care for all tests and medications associated with the diagnosis and treatment of sleep apnea will be the responsibility of the patient.

Subject Compensation:

Subjects involved in this study will not receive any compensation.

Statistical Considerations:

ANOVA and Fisher's Exact Test will be done to compare multiple means from repeated measures. A consultation with an expert statistician will also be considered for data analysis.

Consent:

Recruitment will occur through patient visits to the MFA, or through referrals from Walter Reed National Military Medical Center and DC Veterans Affairs providers. Introduction to the study will occur by face-to-face conversations with the subjects. The full study will be reviewed with a trained member of the research team in a private room. Subjects will be given the opportunity to ask questions and opt-out from the study during this conversation. If possible, written consent will be obtained then, but in order to avoid pressure or coercion, subjects will be provided the option to take the ICF home with them. If the subjects decide to participate they can either fax or scan and email a signed copy of the ICF to a member of the research staff. Then, either bring the wet-ink version, or wet-ink sign the ICF when they come in for their visit 1. The ICF needs to be signed prior to visit 1, as it is required for filling out the research drug prescription. During the subject's participation and during all collection and analysis activities, data will be assigned a unique study number and subsequently de-identified. No personal or demographic information

other than that specified in the study protocol will be acquired nor stored. A copy of the signed consent form will be will be provided to the patient

Conflicts of Interests:
None

References:

1) Psychoneuroendocrinology 2011 Sep;36(8):1114-26