COVER SHEET

Name: The impact of ramelteon on sleep and delirium in patients who undergo pulmonary thromboendarterectomy (PTE) surgery

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

The impact of Ramelteon on sleep and delirium in patients who undergo Pulmonary Thromboendarterectomy (PTE) surgery

2. PRINCIPAL INVESTIGATOR

Robert L. Owens, MD
Assistant Professor of Medicine
Department of Medicine, Division of Pulmonary and Critical Care

3. FACILITIES

UCSD Hospitals specifically Sulpizio Cardiovascular Center and Thornton Hospitals, and associated outpatient clinics

4. ESTIMATED DURATION OF THE STUDY

24 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Sleep deprivation is known to affect brain function but is often ignored in the sickest patients including those in the intensive care unit after major surgery. In these patients, the levels of melatonin can also be altered.

Melatonin is a hormone secreted in the brain that maintains the body's sleep-wake, or circadian, cycle. We want to test whether improving sleep quality affects the risk of developing confusion (delirium) in patients having clot removed from their lung (open heart surgery). In order to improve sleep quality, we will conduct a study of Ramelteon, a medication that mimics the activity of melatonin and measure its effects on levels of melatonin and monitor sleep.

6. SPECIFIC AIMS

1. To measure duration (total sleep time) and pattern (sleep fragmentation) of sleep after PTE surgery, and its relationship with post-operative delirium
2. To measure levels of melatonin after PTE surgery, and their relationship with post-operative delirium
3. To evaluate the effects of Ramelteon (a melatonin receptor agonist) on sleep, melatonin levels and delirium after PTE surgery

7. BACKGROUND AND SIGNIFICANCE

Most patients, and most physicians, think that a "good night's sleep" is crucial for most medical and psychiatric illnesses. Adequate sleep can promote attention, vigilance and a sense of well-being. Conversely, sleep deprivation can lead to decreased neurocognitive performance and alertness, and disorganized thinking. Although the science is still emerging, sleep appears to be crucial for maintaining homeostasis and immune function, with decreased sleep associated with insulin resistance, risk of myocardial infarction, and increased infection risk. Despite these known or suspected benefits, sleep is not prioritized in most intensive care units (ICUs). As a result, ICU patients are denied sufficient sleep by a host of potentially modifiable environmental and pharmacological factors, with a median sleep time of just 3 minutes!

Of particular interest is the role of sleep deprivation as a contributor to ICU delirium, a form of acute brain dysfunction common in critically ill patients. Delirium independently predicts a 3-fold increase in one year mortality, is associated with prolonged hospital stays, markedly increased costs of care, and long-term cognitive impairment. The role of sleep deprivation and/or sleep fragmentation in the pathogenesis of ICU delirium is not known.

Sleep in the ICU has been difficult to study for a variety of reasons: the wide variety of ICU patients and medications used that affect standard sleep staging criteria, the inability to monitor sleep before critical illness, and the difficulty in continuously objectively measuring sleep using EEG in critically ill patients.

The University of California San Diego (UCSD) is the world leader in the surgical treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH). More than 170 patients from around the world are admitted for pulmonary endarterectomy (PEA). Of the patients carefully screened for cardiopulmonary bypass surgery and deep hypothermic cardiac arrest (DHCA), nearly 20% develop post-operative ICU delirium. This cohort has several unique advantages, especially as related to the study of sleep and its contribution to ICU delirium. Patients are much more homogenous than a general ICU population, and have a defined "start" to their critical illness. Post-operative care is also relatively standardized. With such a patient group, many of the difficulties previously encountered in understanding how sleep impacts ICU delirium can be overcome. There have also been some reports of "temporary neurological dysfunction" including delirium occurring in patients after DHCA.

Melatonin and Ramelteon, a melatonin receptor agonist have been reported, inconsistently, to reduce the rates of ICU delirium. However, if this effect is real, the mechanism is not known. These medications may work by improving sleep, regulating the endogenous circadian rhythm, or through other effects.

8. PROGRESS REPORT

Not Applicable (initial submission)

9. RESEARCH DESIGN AND METHODS

Design: The project will be a single-center, randomized, double blinded, placebo-controlled trial with an intention-to-treat analysis. Subjects will be recruited amongst patients with CTEPH who are planned to undergo PTE surgery at UCSD and will be recruited during already scheduled clinic visits (details below). During this clinic appointment, potential participants will meet with study personnel who will provide information about the study.

Intervention: Patients who meet the inclusion criteria and who provide consent for the study will be randomized by a concealed computer-generated number assignment to either receive placebo (Placebo group) or Ramelteon 8mg by mouth (Treatment group). Both groups will receive study drug by mouth the night prior to the surgery (if already admitted to the hospital) at 9 pm and continuing for a total of 7 days or until their transfer out of the Intensive Care Unit (ICU), whichever comes first. The medication or placebo will be dispensed by a Research Pharmacist and will be administered by the patient's nurse in a blinded-fashion. If the patient is unable to take the drug orally, such as when intubated, the drug will be administered via the nasogastric or orogastric tube.

Monitoring and Measurements: On arrival to the ICU after surgery, two EEG sensors will be applied only to the patient's forehead (not a full EEG montage) after surgery. These EEG sensors will be used to record sleep and will remain in place for the first 72 hours after surgery, or until ICU discharge, whichever comes first. We will also monitor sound and light levels using commercially available meters during this time to help understand causes of arousal from sleep.

A member of the study team will obtain a 10mL urine sample from the patient every six hours for the first 48 hours after the surgery from the patient's existing urinary catheter. Samples will be stored in a freezer until analysis of the Melatonin levels can be conducted using commercially available ELISA kit by the Clinical and Translational Research Institute (CTRI) at UCSD. Samples will be batched to run all at the same time at the end of the study. The urinary samples will not be stored for any other biomarker studies. We will not be obtaining any blood samples.

Patients will be assessed by members of the research team twice daily (once in the morning, once in the afternoon, at least 6 hours apart) for delirium using the Confusion Assessment Method or CAM-ICU. This is a brief (usually <2 minute) interview that is sensitive and specific for ICU delirium that is used clinically and is standard of care. These assessments will occur for 7 days after surgery. If a patient develops delirium, it will be treated as per the treating physician's discretion using other methods. There will be no impact on the standard of care in the postoperative period.

Outcomes: The primary endpoint of the study is Total Sleep Time (TST) as measured by EEG. The secondary endpoints of the study will be incident delirium (as measured by the Confusion Assessment Method or CAM-ICU) during the 7 days, average daily pain score, measures of sleep hygiene such as the light and sound quality, length of ICU stay and length of hospital stay. We will also collect other data from the patient's medical record including the patient demographics, detailed information regarding the surgery and postoperative course, choice of sedation and other medications used in the postoperative period. This information will be used later for subgroup analysis.

Analysis: The data will be analyzed using SPSS, SAS or an equivalent statistical software. Comparative statistics will be used to determine differences in delirium between the two groups and a multivariate analysis will be performed to identify contributing factors. Based on a 80% power to detect a 20% improvement in incidence of delirium, we plan to enroll 60 patients in each group to allow for multiple subgroups to be analyzed.

10. HUMAN SUBJECTS

We will recruit a total of 120 subjects (60 patients in the Placebo group and 60 patients in the Treatment group) amongst patients with CTEPH who are admitted to UCSD for the planned PTE surgery. Adult subjects who are at least 18 years of age will be recruited without regards to race, gender or ethnicity.

Inclusion Criteria:
1. Patients with CTEPH who are admitted to UCSD for a planned PTE surgery.
2. Age > 18 years

Exclusion Criteria:
1. Pregnancy
2. Cirrhosis of any etiology
3. Current use of any atypical antipsychotic including Fluvoxamine (contra-indicated with Ramelteon)
4. Any contraindication to EEG/Sleep recording
5. Non-English speaking (who are unable to complete delirium questionnaires)

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

All patients referred to UCSD CTEPH clinic will be recruited. No private or protected health information will be required for recruitment; no procedures preparatory to research will be undertaken. An investigator or study staff will speak with patients who meet inclusion criteria either at the end of their clinic visit or prior to their scheduled surgery after they are admitted.

12. INFORMED CONSENT

Consent will be obtained by the investigator or research staff. All research staff are certified in clinical research by CITI and have thorough knowledge of the study to be able to answer any questions regarding the study. Consent will be obtained during the initial clinic visit or on the day prior to their scheduled surgery in a private room in the UCSD medical center. We will not enroll non-English speaking patients given the inability to complete all subject assessments, some of which use questionnaires only available or validated in English only. Consent will be documented in hardcopy and stored securely in the research master file. No research or screening procedures will be performed prior to obtaining consent. The subject will be apprised that the consent process will not waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the University or its agents from liability for negligence.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participation in this study is to not participate. Declining participation in the study will not affect ongoing evaluation and treatment. Ramelteon is FDA-approved for the treatment of insomnia, characterized by difficulty with sleep-onset, and will be available for use by the patient for this indication if needed.

14. POTENTIAL RISKS

There are a few risks associated with participation in the study.
1. Risks of the drug. Ramelteon has been associated with some mild side effects (in less than 5% of the cases) including dizziness, somnolence, fatigue, worsened insomnia, depression, nausea, taste perversion, myalgias and arthralgias. Rarely (in less than 1% of the cases) decrease in serum testosterone levels, increase in serum prolactin levels, complex sleep-related behaviors (sleep-driving, cooking or eating food, making phone calls) as well as severe anaphylactic reactions have been reported. Of note, these risks are generally associated with much longer use than we propose in the current study.
2. EEG monitoring involve the application of sensors with adhesive to the skin, which could result in a minor skin reaction. Although unlikely this potentially could require medical attention, however this has never occurred in many hundreds of prior studies. The EEG devices may constrict movement, which could result in poor sleep However, the EEG device has been specifically designed to be minimally invasive and not interfere with patient's movements.
3. Every effort will be made to maintain patient confidentiality in accordance with HIPAA and UCSD IRB guidelines. Despite this, breaches in confidentially of medical information can occur, and carry associated risks to employability, insurability, reputation, ability to adopt and other social risks.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Subjects, or their surrogates, may withdraw their consent at any time. An investigator or study personnel will be available to answer questions or concerns at any time. One of the investigators is a research fellow with protected full time for research. Dr. Owens, the PI of the study, is available at any time by page. Additional study staff in the division will be available for assistance.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Recruitment and consent will take place within an enclosed examination room to maintain privacy. We will make every effort to maintain patient privacy and confidentiality both during and following the study.
Electronic study data will be de-identified by substitution of codes for names and hospital identifiers and will be stored in an online secure (password protected) database (REDCap) for access by Investigator and study staff only and a hard copy will be stored in a locked cabinet. This study does not involve the collection of sensitive personal information from subjects. Data will be stored only at UCSD sites and will be confined to that specified in this protocol and its approved amendments. It is not anticipated that reportable information will be obtained for this study.
The only biological materials collected in the study will be urine samples. These will also be stored in de-identified fashion in the UCSD CTRI, which is a locked facility.

17. POTENTIAL BENEFITS

The study will provide valuable insights into the understanding of development of delirium in post-pulmonary thromboendarterectomy patients and in post-surgical and critically ill patients in general. We will be able to better define the relationship of delirium and sleep in critically ill patients, which can lead to better outcomes and less length of stay for the patients in the future.
Patients may benefit from participation in the study in that they will have neurological status checked by study staff twice daily. The results of this testing will be made available to the clinical team. If delirium is noted, it may be discovered sooner than expected during normal clinical care, and appropriate actions can be undertaken by the clinical team.

18. RISK/BENEFIT RATIO

This study has few risks with no serious risks. Patients in the study will be carefully monitored for brain dysfunction in the study, which may alert clinicians to changes as well as minimize other therapies that can contribute to ICU delirium. Therefore, we feel the overall benefits outweigh the risks.

19. EXPENSE TO PARTICIPANT

There will be no expense to participants in this study.

20. COMPENSATION FOR PARTICIPATION

There will be no compensation, financial or otherwise, to participants in this study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Atul Malhotra M.D. is the Chief of the Division of Pulmonary and Critical Care Medicine and Director of Sleep Medicine at UCSD
Michael Madani M.D. is the Chief of the Division of Cardiovascular and Thoracic Surgery at UCSD
Robert Owens M.D. is an Assistant Professor in the Division of Pulmonary and Critical Care Medicine
Anuja Vyas M.D. is a Fellow in Division of Pulmonary and Critical Care Medicine
William Auger M.D. is a Professor of Clinical Medicine in the Division of Pulmonary and Critical Care Medicine
Jeremy Orr M.D. is a Clinical Instructor in the Division of Pulmonary and Critical Care Medicine

22. BIBLIOGRAPHY

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5. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA psychiatry. 2014;71(4):397-403. doi:10.1001/jamapsychiatry.2013.3320.

23. FUNDING SUPPORT FOR THIS STUDY

The project is funded via the Division of Pulmonary and Critical Care. The light and sound recording devices are owned by Dr. Owens. Protected research time through the Fellowship in Pulmonary and Critical Care Medicine will be used by Dr. Vyas.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

The protocol does not involve transfer of any human tissue or biological fluid to another institution.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not Applicable. Ramelteon has been FDA-Approved for use in Insomnia.
We confirm that all six of the following conditions are met:
1. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2. it is not intended to support a significant change in the advertising for the product;
3. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
6. it does not intend to invoke 21 CFR 50.24.

26. IMPACT ON STAFF

A research pharmacist will be involved in dispensing the medication. Bedside nurses will administer this medication or placebo once per night – thus, the impact on clinical staff will be minimal. Otherwise, there will be no change in the usual care burden on non-study physicians and other clinicians.

27. CONFLICT OF INTEREST

The investigators and study staff have no relevant conflicts of interest for this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

No other approvals are required for this study.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

We will be obtaining informed consent from patients who have already been deemed to have capacity in order to consent to their Pulmonary Thromboendarterectomy Surgery. Patients without decisional capacity to provide consent will not be offered surgery and therefore will not be enrolled in this study.