Polysomnographic Study Comparing the Use of Dexmedetomidine and Zolpidem to Induce Natural Sleep

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BACKGROUND AND SIGNIFICANCE

Sleep is a natural human behavioral state of decreased arousal, crucial for survival, maintenance of health and consolidation of newly learned information.[1,2,3,4] Population-based studies estimate that 25 to 35% of American adults suffer from transient insomnia, 10% to 15% from chronic insomnia, with 2 to 6% of the population taking medications to promote sleep.[5,6] Sleep disturbance directly results in poor memory, impaired work performance, reduced concentration, and increased risk of accidents.[7,8,9] Symptoms of insomnia that lead to these clinically significant functional impairments include difficulty in initiating and maintaining sleep.

Insomnia treatments have generally involved behavioral changes and pharmacotherapy with sedating antidepressants, antihistamines, anti-cholinergics, melatonin receptor agonists, benzodiazepines, and non-benzodiazepine hypnotics.[10,11] The benzodiazepines and the newer sedative hypnotics zolpidem (Ambien CR), zaleplon (Sonata), zopiclone (Imovane), and eszopiclone (Lunesta) form the mainstay of current treatment.[10,11] These drugs modulate the activity of the γ-Amino butyric acid A receptor causing a generalized state of sedation with alteration of normal sleep electrophysiology. Additionally, they pose the added risk of tolerance and dependence.[10,11]

The architecture of natural sleep consists of regular cycling at approximately 90-minute intervals between non rapid eye movement (nREM) and rapid eye movement (REM) sleep. Since these drugs do not provide for natural non REM-REM cycling, they lead to disruption in awake-performance and create what many patients report as a state of grogginess.[11] Consequently, these medications do not provide the restorative benefits of natural sleep. Furthermore, consistency in sleep maintenance by these drugs has not been clearly demonstrated.[10] Hence, the beneficial effects from effective sleep therapies that maximize the benefits of restorative sleep cannot be understated.

With this in mind, we are proposing to uncover the benefits of the medication, dexmedetomidine, for inducing physiologically natural sleep in insomniacs. The FDA approved dexmedetomidine in 1999 for short-term sedation by intravenous administration in the intensive care unit.[12] Its indication was recently expanded to include non-intubated patients requiring sedation for surgery or procedures.[12] The neurophysiological and behavioral characteristics of the sedative state induced by dexmedetomidine closely resembles non REM sleep.[13, 14, 15] This is because dexmedetomidine binds to alpha$_2$ receptors on neurons in the locus ceruleus (LC), causing an inhibition of the LC with the downstream effect of VLPO activation via direct neuronal projections. The active VLPO facilitates $GABA_A$ and galanin mediated inhibition of the midbrain, hypothalamic, and pontine arousal nuclei, promoting non REM sleep. [16,17,18,19] Damage to the VLPO bilaterally attenuates the sedative response to dexmedetomidine[20.] Additionally dexmedetomidine has been confirmed to decrease expression of c-Fos in the LC and tuberomammillary nucleus, with increased expression in the VLPO.[26] In essence, dexmedetomidine converges on endogenous sleep pathways to exert its effect. Since this drug is an intravenous agent, it has not been immediately apparent that it might be useful as a therapeutic agent for sleep therapy.

We propose to undertake a study to characterize the benefits of dexmedetomidine for inducing a natural, restful night's sleep in insomniacs. Intravenous dexmedetomidine will be administered to promote sleep in healthy volunteers and patients with insomnia, comparing its effects to the

FDA-approved medication zolpidem. The benefits of dexmedetomidine will be demonstrated electrophysiologically by characterizing the sedative state induced by dexmedetomidine and also by assessing the impact of treating insomnia with dexmedetomidine on sleep quality, awake performance and cognition relative to zolpidem. This project is based upon the mechanistic understanding of how dexmedetomidine works, clinical experience with the sedative state induced by dexmedetomidine, electroencephalogram (EEG) patterns that are consistent with natural sleep in recent medical literature and on the SEDLine™ Brain-Function Monitoring System utilized in the MGH operating rooms.

In contrast to existing sleep medications, which are non-specific sedatives, we believe that dexmedetomidine is biochemically well suited to engage the natural mechanisms that drive sleep. This study would help demonstrate that dexmedetomidine can be used to induce normal physiological sleep in humans suffering from insomnia, providing a new approach to the treatment of this debilitating disorder by strongly suggesting a new class of medications to be developed as a sleeping aid. In addition to this, a novel neurophysiological description of the state of the brain under this new and important drug will be accomplished.

SPECIFIC AIMS:

The specific aims of this research project will test our hypotheses that dexmedetomidine exhibits neurophysiological and behavioral characteristics that closely resemble normal sleep in humans.

Hypothesis 1: Intravenous therapy with dexmedetomidine will induce a sedative state whose architecture closely resembles the architecture of natural sleep

Hypothesis 2: The architecture of the sedative state induced by dexmedetomidine will be closer in nature to the architecture of natural sleep than the sedative architecture induced by zolpidem

Hypothesis 3: Dexmedetomidine will have minimal to no effect on the sleep architecture of healthy subjects

Hypothesis 4: Dexmedetomidine will be objectively and subjectively more restful than zolpidem.

Hypothesis 5: Compared to zolpidem, next day cognitive and psychomotor function will be improved

SUBJECT SELECTION AND ENROLLMENT

We will select 30 male and female volunteers for this study, comprised of 15 healthy controls and 15 patients with insomnia between the ages of 18 and 35.

The subjects will be recruited using:

1. An announcement of the study distributed through the Partners Public Affairs distribution list.
2. MGH Research Study Volunteer Program.
3. Through the Division of Sleep Medicine at Massachusetts General Hospital where physicians will identify insomnia patients. Patients found suitable will be given information about the study. This will include a clear statement that decision to forego or participate in the study will have no impact on their ongoing medical treatment.

All subjects will be fit and healthy, meeting the American Society of Anesthesiologists (ASA) physical status classification P1 (normal healthy patient) or P2 (stable chronic problem) and of normal body habitus. A complete medical history will be taken in addition to performing a complete physical examination in order to rule out active and chronic medical problems.

Medical History. Chronic health conditions that will exclude subjects from the study include but are not limited to:

Cardiovascular:	hypertension, myocardial infarction, coronary artery disease, peripheral vascular disease, arrhythmia, congestive heart failure, valvular disease, resting heart rate less than 55 beats per minute**,** cardiac electrophysiological abnormalities ascertained from the screening ECG (i.e. but not limited to second and third degree heart block in the absence of a pace maker, supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, junctional heart rhythms.)
Respiratory:	asthma, sleep apnea, bronchitis, chronic obstructive pulmonary disease, smoking, shortness of breath
Hepatic:	hepatitis, jaundice, Child-Pugh Class C liver disease, generalized anasarca, ascites, encephalopathy and caput medusa
Neurologic:	seizure, stroke, positive neurologic findings on neurologic examination, multiple sclerosis, Meniere's disease, Parkinson's disease
Gastrointestinal:	esophageal reflux, hiatal hernia, ulcer
Endocrine:	diabetes, thyroid disease
Hematologic:	blood dyscrasias, anemia, coagulopathies
Musculoskeletal:	prior surgery or trauma to head neck or face, arthritis, personal or family history of malignant hyperthermia.
Psychiatric:	history or treatment for an active psychiatric problem, including, but not limited to: Attention Deficit Hyperactivity Disorder, depression, bipolar disorder, and schizophrenia.
Reproductive:	pregnancy, breast-feeding.
Medications:	regular use of prescription and non-prescription medications expected to affect central nervous system function or sleep.
Allergies:	dexmedetomidine or zolpidem

Physical Examination. The subject will be given a standard pre-anesthetic physical examination. Abnormal findings on physical examination will provide reason for exclusion from the study. Abnormal finding(s) will be reported to the affected subject and recommendation(s) for medical follow-up will be given as needed.

Screening Tests. A complete blood count, blood glucose level, liver function test (LFT), blood urea nitrogen (BUN), and creatinine (Cr) level will be obtained at the initial screening visit. For inclusion into the study protocol, each subject will be required to have a platelet count, blood glucose, BUN and Cr levels in the normal range. LFT's for inclusion will be required to be within 1.5 times the upper limit of normal. Additionally, white blood cell count, hemoglobin, and differential will be required to range within 15% normal values in order to be included in the study. Each subject will provide a urine specimen for a toxic substance screen both at the initial

examination and on each active study day. Each female subject will be administered a pregnancy test at the initial examination and each active study day. Positive toxicity screening and/or positive results on the pregnancy test will prompt exclusion from the study. A 5-lead electrocardiogram will be performed on all study subjects at the initial screening visit to identify any pre-existing cardiac issues. On active study nights, a five lead electrocardiogram will be applied to continuously monitor cardiac electrophysiological status.

If a subject in the insomnia group is already taking prescription medications for sleep, he/she will not be eligible for the study. We will only be recruiting insomnia subjects who are undergoing behavioral therapy or are not being pharmacologically treated for insomnia.

Primary **Exclusion** Criteria for "Healthy" control subjects:

1. Abnormal sleep habits (This will be objectively assessed by wrist actigraphy measured for one week prior to the first study night).
    a. Sleeping less than 5 hours each night
    b. Going to sleep before 9:00 PM or after 2:00 AM on a regular basis
    c. Waking up before 5:00 AM or after 10:00 AM on a regular basis.
2. Sleep latency greater than 60 minutes, or greater than 3 awakenings per night. (This will also be objectively assessed by wrist actigraphy.)
3. A score greater than or equal to 10 on the Epworth Sleepiness Scale.
4. Takes medication that alters sleep, cognitive function, or both.
5. Has a history of a known neurological or psychiatric problem.
6. Younger than 18 or older than 35 years of age.
7. Known or suspected sleep disorder(s).

Primary **Inclusion** Criteria for "Insomniac" subjects*:*
Subjects will be deemed "Insomniacs" if they suffer from any of the following:

1. Subject will be required to meet the criteria for insomnia, set by the International Classification of Sleep Disorders, which requires that a patient have difficulty initiating or maintaining sleep that is not accounted for by another sleep disorder, neurologic or psychiatric disorder or substance or medication.
2. Subjects are required **not** be on any current pharmacological sleep disorder treatment.
3. Between the ages of 18 and 35.
4. Not taking any prescription medications that alter sleep, cognitive functions, or both.

MRI Reasons for **Exclusion**
High magnetic fields may pose a serious health hazard to subjects with implanted ferromagnetic objects. Every participant in this study will be screened for implanted ferromagnetic objects before they are enrolled and will provide written responses to a questionnaire to screen for implanted ferromagnetic objects before entering the high magnetic field shielded room. Subjects with the following conditions/diseases will be excluded from the study:

a) History of head trauma
b) Surgical aneurysm clips
c) Cardiac pacemaker
d) Prosthetic heart valve

e) Neurostimulator
f) Implanted pumps
g) Cochlear implants
h) Metal rods, plates
i) Screws
j) Intrauterine device
k) Hearing aid
l) Dentures (which might create artifacts)
m) Metal injury to eyes
n) Metallic tattoos anywhere on the body or tattoos near the eye

Remuneration
Prior to the study, each subject will sign witnessed, informed consent for anesthesia, EEG, MRI, and other physiological measures. For successful completion of this protocol, subject remuneration will be $500. If the study subject is unable to complete the entire protocol, the proration will be as follows:

1. Study subjects who complete the medical evaluation will receive $25.
2. Study subjects who complete only one sleep study night will receive $100.
3. Study subjects who complete only two sleep study nights will receive $200.
4. Study subjects who complete only three sleep study nights will receive $300.
5. Study subjects who complete all four sleep study night will receive $400.
6. Study subjects who complete the optional fifth day-time sleep visit will receive $150.
7. Study subjects who complete the MRI visit will receive $100.
8. Study subject who complete all 4 sleep visits and the MRI visit will receive $500.
9. Study subjects who complete all 4 sleep visits, the optional day-time visit, and the MRI visit will receive $650
10. If the study must be stopped due to concerns for the study subject's medical safety, subjects will receive remuneration commensurate with their time given to the study as listed above.

Parking vouchers will be provided.

STUDY PROCEDURES
This study will follow a 3 part randomized design. Upon study enrollment, each subject will be assigned to receive each treatment: intravenous dexmedetomidine, zolpidem, and regular sleep (X, Y, or Z) in a random order.

Study Design Schematic

Screening Visit	Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4	Study Visit 5 (optional)	fMRI Visit
Consent, Labs, etc	Acclimation Night	X, Y, or Z	X, Y, or Z	X, Y, or Z	Day time visit with Dexmedetomidine	fMRI scan

Active study nights will not occur back-to-back ensuring that there are no residual effects or interactions with the drugs being studied (i.e., a 48 hour washout period,). Visit 1 is intended for the subject to acclimate to the recording equipment. The second, third and fourth nights will be designated as an active study night where the subject will receive dexmedetomidine, zolpidem or regular sleep. The subject will be aware of the treatment assignment.

Since the order in which these treatments are given is randomized at study enrollment, the active pill day (zolpidem administration) will never coincide with the active intravenous day (dexmedetomidine administration). Each subject will only receive dexmedetomidine or zolpidem once**.**

Initial Screening Visit:
Prior to the beginning of the study, the study subject will sign informed consent. Next, the subject will undergo an initial pre-anesthetic exam and toxicology screening to assess exclusionary criteria. A pregnancy test will be administered to female subjects. A electrocardiogram will be performed on all study subjects at the initial screening visit to identify any pre-existing cardiac issues. Subject will also complete a questionnaire concerning his/her sleep habits. This questionnaire is in clinical use by the Massachusetts General Hospital sleep laboratory. Afterward, the subject may be outfitted with an Actiwatch actigraphy monitor, similar to a regular wrist watch, to track their activity levels prior to the first study day. Every subject will be required to maintain a sleep log from the week prior to the first study night, until the last study night.

Study Visit 1: Subject will arrive at the study site. Actigraphy and the sleep log will be checked to ensure that the subject has kept a consistent schedule, in keeping with the screening criteria defined above. A toxicology screen will be administered to exclude the use of prohibited substances, and female subject will again be required to undergo a pregnancy test.

High-density EEG will be collected using a flexible cap with embedded electrodes that fits over the subject's head and fastens beneath the chin. Physiological measures may also include 2 electrooculogram (EOG) channels, 2 chin electromyogram (EMG) channels, a 5 lead electrocardiogram (ECG), saturated oxygen levels, heart rate, non-invasive blood pressure cuff**,** end-tidal CO_2, and audio/video data. All of the leads and sensors used are removed easily and comfortably following the sleep study.

The EEG cap will be placed on the subject to enable acclimation to the device. ECG, EOG and EMG channels will be attached, and a mock (non-invasive) intravenous line will be attached so that the subject can acclimate to the sensation of contact at these points. The purpose of the first study night is for the subject to become acclimated to the study site and recording equipment, as well as to obtain a baseline reading of their brain activity during sleep.

Just before bed the subject will participate in a 10 minute Psychomotor Vigilance Test (PVT), as well as the Motor Sequence Task (MST) and then be instructed to try to sleep for 8-hours. If he/she wakes up before the designated time, he/she will be instructed to stay in bed and try to go back to sleep. After the sleep period, has concluded the subject will then again participate in a 10 minute Psychomotor Vigilance Test (PVT) and the Motor Sequence Task (MST). Upon conclusion of testing a member of the study staff will remove the physiological monitors and the subject will be permitted to shower and eat breakfast and will then be permitted to resume his/her day as normally would.

A trained technician will be with the subject all night, monitoring the subject's room with audio and video equipment. An on-call physician is available, at all times, in the event of an unforeseen problem.

Study Visit 2: Subject will return to the study site. A toxicology screen will be administered to exclude the use of prohibited substances. Electrodes on the EEG cap will be fixed in place with conductive paste, and ECG, EOG and EMG channels will be attached per standard procedure. The subject will then participate in a 10 minute Psychomotor Vigilance Test (PVT) and complete the Motor Sequence Task (MST). If indicated according to the randomization schedule, a peripheral intravenous line will be placed for administration of dexmedetomidine. We will then follow the "DEXMEDETOMIDINE DOSING PROCEDURES" listed below.

The subject will be instructed to try to sleep for 8-hours. If he/she wakes up before the designated time, he/she will be instructed to stay in bed and try to go back to sleep. After 8-hours have elapsed the subject will then again participate in a 10 minute Psychomotor Vigilance Test (PVT) and the Motor Sequence Task (MST). Upon the conclusion of testing a member of the study staff will remove the physiological monitors, and the subject will be permitted to shower. Prior to leaving the study site, each subject will complete a brief post-sleep questionnaire. This will also include some questions about dreams. In addition, the subject will respond to a questionnaire regarding time estimation – not only of his/her sleep patterns from the prior night, but also of the time required to perform the various cognitive and other testing components described above. The will help address the issue of sleep misperception which is common in the insomnia population (likely multi-factorial, and one of the potential contributors is misperception of elapsed time).

Each subject may be fitted with an Actiwatch actigraphy monitor prior to leaving the study site to monitor his/her sleep cycle until the following study visit. Subjects will then resume his/her normal workday.

Study Visit 3: The subject will repeat the protocol as specified in Study Visit 2. However, it will be the second of the randomized treatments; he/she will receive zolpidem, dexmedetomidine or regular sleep.

Study Visit 4: The subject will repeat the protocol as specified in Study Visit 2. However, it will be the third of the randomized treatments; he/she will receive zolpidem, dexmedetomidine or regular sleep.

Study Visit 5 (optional): The subject will repeat the protocol as specified in Study Visit 2. However, this study visit will not be randomized; he/she will receive dexmedetomidine during an active study day instead of night. This will enable us to study the effect of the human circadian rhythm on sleep induction with dexmedetomidine.

Dexmedetomidine Dosing Procedures

Dexmedetomidine will be administered by one of the study anesthesiologists through a peripheral 18 or 20 gauge intravenous line. The study anesthesiologist will initiate and terminate the dexmedetomidine infusion using the following dosing scheme: Subjects will be randomized by block design to receive dexmedetomidine at 1.0mcg/kg over 10 minutes or 0.5 mcg/kg over 10 minutes. 1.0 mcg/kg is the standard specification for the loading dose for procedural sedation.[12]

The study anesthesiologist will monitor the patient continuously for the duration of the infusion, a research technician will also be present to ensure that standard of care is maintained at an

optimum. At the conclusion of infusion, the infusion pump will be turned off and the syringe containing dexmedetomidine will be removed to prevent inadvertent drug administration. Reflecting standard of post procedure monitoring, the study anesthesiologist will monitor the patient for one hour after the infusion has been stopped to ensure normal physiology. All aspects of the sleep study will also be attended during the night by a technologist to assure that the subject's safety and comfort needs are met.

On the active dexmedetomidine study night, discharge home will be based on criteria established by the MGH Department of Anesthesia practices for discharge from the hospital following ambulatory surgery. The subject must have stable vital signs, i.e., within 20% of pre-study values, be able to respond appropriately to normal commands, be pain free, be free from any nausea and vomiting, and have no bleeding from the intravenous insertion site. Subjects will be advised not to drive or operate heavy equipment for 24 hours.

Cognitive Testing
The subject will undergo the Motor Sequence Task (MST) and the PVT before and after sleep of each visit.

Motor Sequence Task: Participants will be trained on a motor sequence task (MST), a well-established probe of sleep-dependent memory consolidation, on a laptop prior to the onset of sleep and then tested 8 hours later. The MST involves pressing four keys with the fingers of the left hand, repeating a five digit sequence (*e.g.*, 4-1-3-2-4) "as quickly and accurately as possible" for 30 seconds. During both the training (night time) and test sessions (morning), participants will perform twelve 30-second tapping trials each of which is followed by a 30 second break. During tapping trials, the computer screen will be green with the numeric sequence displayed at the top, and dots appearing from left to right beneath the sequence with each keystroke. During the breaks, the display will be red, and instead of showing the sequence, numbers (displayed as words) counted down the seconds until the next trial. Three seconds before the display turns green, the words will be replaced by flashing dots to alert the participant. We will measure the number of correct sequences per 30 second tapping trial, which reflects the speed and accuracy of performance. Any unfinished sequence at the end of a trial will be added to the total, as a fraction of a correct sequence. Next-day improvement will be calculated as the percent increase in correct sequences from the last three training trials to the first three test trials. Learning during training will be calculated as the percent increase in correct sequences from the first training trial to the average of the last three training trials. Participants will be paid a bonus of $0.05 for every correct sequence.

Psychomotor Vigilance Task (PVT): is a highly sensitive assay of vigilant attention used commonly in the study of sleep disruption after each night of sleep. [21]

While seated at a laptop computer, the subject will be asked to attend to an area enclosed by a small green rectangle against a black screen. After a variable delay (chosen randomly to last between 2 to 10 seconds) a digital millisecond counter will begin inside the rectangle.
The subject will be asked to stop the timer as quickly as they can by pressing the space bar. At this time, the subject can view his/her reaction time, which serves as feedback for that trial.

Instruction is given to avoid premature button presses during the variable inter-stimulus interval. If such a false start occurs, the subject will be asked to wait for the timer to begin before pressing the space bar and a new trial will commence. Trials of this nature repeat throughout a 10 minute session.

The following instructions will be presented to the subject:

Welcome. In this task, a rectangle will appear in the center of the screen. After a delay of variable duration, a counter will begin inside this rectangle. Your job is to press the SPACEBAR as rapidly as possible once this timer begins. Hitting the spacebar will stop the timer; you will then have a chance to view your speed. Aim for low numbers, but be sure not to press the spacebar before the timer starts! The task will continue for 10 minutes, and the computer will let you know when you have finished.

From this task we will analyze outcome measures such as the median reaction time, the variability of these reaction times, the occurrence of "lapses," (response times over 500 ms) errors of commission ("false-starts"), and a measure of performance degradation through time. The subject will perform this test before and after sleep on each study day.

fMRI Visit: This visit may occur at any time during the course of the study. Concomitant to the registration of the EEG, subjects will participate in an fMRI scan to aid in source localization for data analysis. The study subject will arrive at the Martinos Center for Biological Imaging and a urine sample will be obtained for a toxic substance screen and for female study subjects a urine pregnancy test. The subjects will undergo approximately 45-60 minutes of MR imaging. No drugs will be administered at this visit.

The study subject will be able to verbally communicate with the investigators during the structural MRI portion. MR images of the brain will be acquired using the Siemens 3 Tesla Tim Trio scanner or the Siemens 3 Tesla Biograph mMR scanner. Head motion will be minimized during the image acquisition by use of a foam head holder. When applicable, the study subjects will be instructed to lie still during the imaging protocol.

Inter-modality coordinate system co-registration*:* The structural MRI will be registered with the locations of the EEG sensors using a Polhemus FASTRAK digitizing system. Using this digitizing system fiducial landmarks (periauricular points, nasion), EEG electrode locations, and the head outline are digitized in 3D space, and then registered with the study subject's structural MRI in order to construct an anatomically accurate EEG forward model (Hari and Lounasmaa, 1989).

BIOSTATISTICAL ANALYSIS

Neurophysiological endpoint: Using an endpoint of total sleep time to guide sample size calculations. Our null hypothesis is the average within subject difference in total sleep time for dexmedetomidine compared with zolpidem is zero. Alternative hypothesis is the average within subject difference in total sleep time for dexmedetomidine compared with zolpidem is 1.5 hours. Assuming that the variance in total sleep time is 2.75 hours^2, a type I error of 0.05 and minimum power of 0.80 and 0.90 for a one-sided z-test, the sample size determinations for our study are 8 and 11 respectively. Therefore, we should detect a clinically relevant improvement in total sleep time if we successfully enroll only 8 insomnia patients.

Behavioral endpoint: Using an endpoint of performance score on the word-pair task word-pair task (a cognitive exercise that tests the interaction of sleep and interference learning on long-term memory consolidation) to guide sample size determination. Our null hypothesis is the average within subject difference in performance score for dexmedetomidine compared with zolpidem is zero. Our alternative hypothesis is the average within subject difference in performance score for dexmedetomidine compared with zolpidem is 3. If we assume that the variance in performance score is 9, a type I error of 0.05 and a minimum power of 0.80 or 0.90 for a one-sided z-test, the sample size determinations for our study are 7 and 9 respectively.

Therefore, we should detect a clinically relevant improvement in performance score if we successfully enroll only 7 insomnia patients

RISK AND DISCOMFORT

Dexmedetomidine Risks: The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in patients with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. As such, study subject hemodynamic parameters will be continuously monitored to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes.

Zolpidem Risks: The most common side effects associated with the administration of zolpidem are dizziness, headache, and drowsiness. Actual frequency of these effects may be dosage form, dose, and/or age dependent.

Polysomnography risks: Electrodes placed on the scalp may cause temporary redness.

MRI risks: Risks already established for MRI include claustrophobia due to confinement of the patient in the system, malfunction of electromagnetic implants caused by interaction with the magnetic fields, projectiles and tissue burns caused by metallic tattoos or implants, risks to the fetus of a pregnant patient, surface burns due to interaction of metallic system components or surface adhesives with the patients skin, slight hearing impairment due to high acoustic noise levels generated by the system, and slight neuromuscular twitching (for the higher field strength systems). However, system safeguards have been designed and operating guidelines have been provided to minimize any of the aforementioned risks.

POTENTIAL BENEFITS

There are no direct benefits to the individual subjects involved in this study. The potential benefits of this study to society are a clearer understanding of the potential benefit of dexmedetomidine as a therapy for insomnia compared with the established therapy zolpidem. We hope to also gain insight into the extent of which dexmedetomidine affects the sleep architecture of healthy subjects. If successful, this study may lead to the identification of a new class of medications for sleep therapy.

MONITORING AND QUALITY ASSURANCE

All EEG data will be stored for later off-line analysis. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines.

An anesthesiologist will monitor the study subject throughout the time he/she is receiving intravenous drug infusions (dexmedetomidine), and for one hour thereafter. This is in accordance with MGH Department of Anesthesia, Critical Care, and Pain Medicine (DACCPM) standards for monitoring during procedural sedation at an out-of-operating room location and the standards for monitoring in the post-anesthesia care unit. A DACCPM provided emergency airway bag and supplemental oxygen tanks will be made available on all active study nights, as well as an MGH pharmacy emergency medicine kit containing glycopyrrolate, atropine, and epinephrine. Study personnel will also be required to perform mock emergency drills on all study nights.

The Siemens system has a built in self-monitoring system that automatically shuts off if parameters exceed safe levels. For backup protection, the study stuff will constantly be in contact with the subject during the scan. Subject monitoring will be performed using the 2-way intercom system between the scanner operator and subject and by visual monitoring of the subject through the window into the scan room or monitoring cameras (the subject is visible to the operator at all times). Quality assurance of the scanner's performance is obtained by a daily quality assurance protocol. More extensive quality assurance protocols are performed monthly under the commercial service contract with Siemens Healthcare.

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