Quantitative neurophysiologic characterization of a paradoxical response to zolpidem in a severely brain-injured human subject

541.6

S. T. Williams[1], M. M. Conte[1], E. J. Kobylarz[1], J. E. Hersh[2], J. D. Victor[1], N. D. Schiff[1]

[1]Department of Neurology and Neuroscience and [2]Department of Public Health, Weill Cornell Medical College, New York, NY

PURPOSE

To explore the spectral and coherence characteristics of the paradoxical arousal response to zolpidem after severe brain injury.

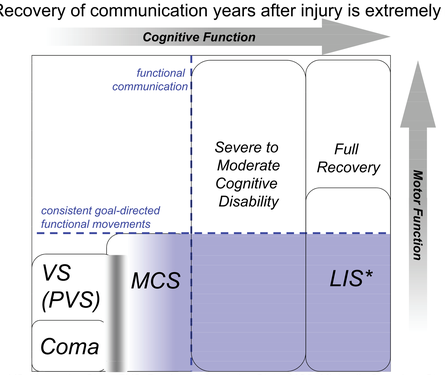
BACKGROUND

Overview:

- Zolpidem is commonly used to induce sleep in healthy adults.
- Paradoxical arousal response observed in some brain-injured patients, the physiological basis for which is unknown.
- Prior study in akinetic mute patient shows increased metabolism in medial frontal cortex, thalami and postrolandic regions after zolpidem[1]
- No study to date compares EEG & PET characteristics of the arousal response to zolpidem in severe brain injury in humans.

About Brain Injury:

- Over 1.4 million cases annually.[2]
- Etiologies: head trauma, cerebrovascular events, seizure, cardiopulmonary insufficiency, intracranial masses, infectious or inflammatory diseases, metabolic disorders, toxic ingestions.
- Recovery of communication years after injury is extremely rare.[3]



VS: Vegetative State. PVS: Persistent Vegetative State. MCS: Minimally Conscious State.
LIS: Locked-In Syndrome (*not a disorder of consciousness). Adapted from Schiff, 2004[4]

About Zolpidem:

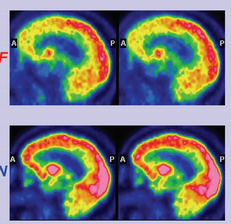
- Imidazopyridine GABA-A1α receptor agonist
- Trade names: Ambien®, Stilnoct®, Myslee®, Noctidem and others
- Maximum plasma concentration 1.6 hours after administration
- Half life = 2.4 hours (in healthy subjects)[5]

About EEG Power & Coherence Spectra:

- Power spectra used to estimate the relative contributions of each frequency to overall composition of a time-varying EEG signal
- Power content of each frequency band changes with arousal state
- Coherence between regions suggests correlated activity
- May be used to establish prognosis after severe brain injury[6]

PET Images OFF and ON Zolpidem

Global metabolism increased ~2 fold.

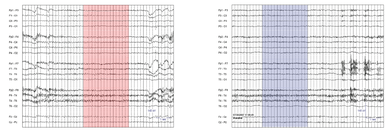


Region	% Change in Mean SUV* Left	Right
Mesial frontal	139%	146%
Lateral frontal	166%	183%
Calcarine	145%	153%
Striatum	156%	156%
Thalamus	148%	127%

*SUV = Standardized Uptake Value

Data Collection & Analysis

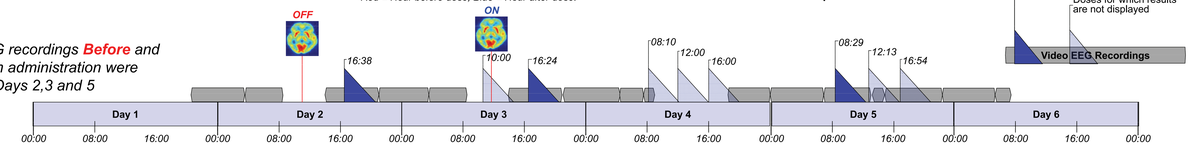
- Single subject, unblinded study
- Subject admitted to inpatient neurology unit
- Maintained home zolpidem dose
  - 10mg crushed, in solution by mouth via syringe
  - Every 3-5 hours during day
- ^{18}FDG-PET OFF and ON zolpidem



Sample EEG Segments Selected for Analysis.
Red = Hour before dose, Blue = Hour after dose.

Timeline

*Adequate EEG recordings **Before** and **After** zolpidem administration were available for Days 2,3 and 5*



METHODS

- 24 hr continuous video EEG
  - 200Hz sampling rate
  - Longitudinal bipolar montage (International 10-20 system)
  - XLTEK data acquisition system (XLTEK, Ontario)
- Two- and three-second EEG segments with minimal artifact identified
- Power & coherence spectra estimated using five Slepian functions as tapers[7]

Subject

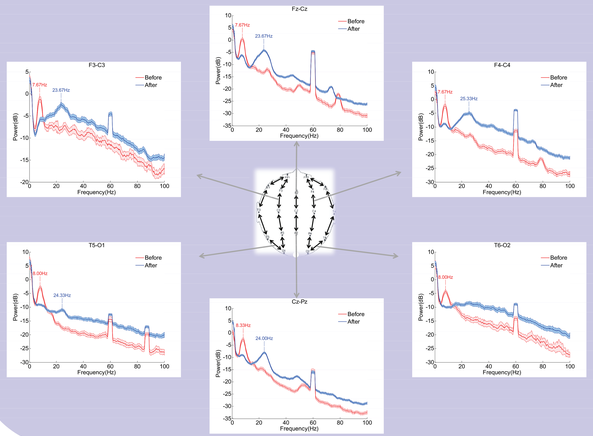
- 32 year old male, near drowning 9 years prior
- Severe hypoxic brain injury; MCS for >2 years
- MRI: Left thalamic lesion
- Arousal response to zolpidem discovered incidentally by mother

Observed Behavior

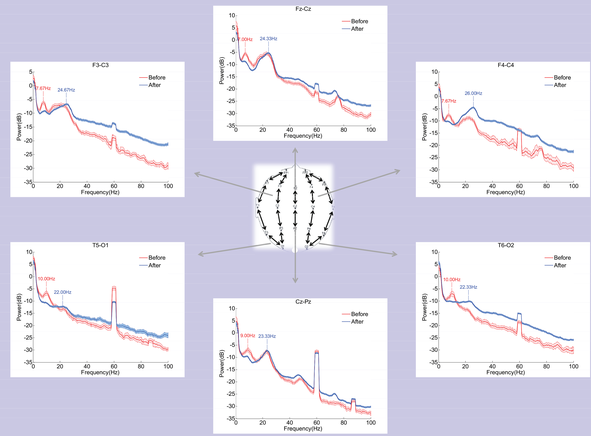
OFF Zolpidem	ON Zolpidem
AOx2 (self, location)	Improved verbal fluency & articulation
Dysarthria	Shortened latency of motor responses
Dysphagia	**Able to feed orally**
L hemiparesis, spasticity	Reduced spasticity
LUE: flexor posturing	**Smooth, goal-directed movements**
RUE: 1-1.5Hz resting tremor	Elimination of resting tremor
LLE & RLE: extensor posturing	Object manipulation (pen, spoon, baseball)

RESULTS

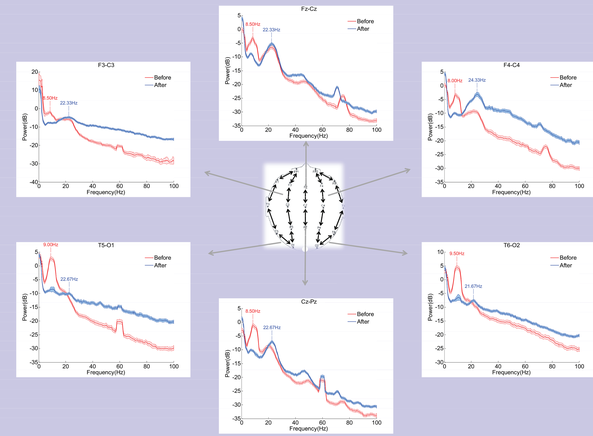
Power Spectra: Before & After Zolpidem (Day 2, Afternoon Dose)



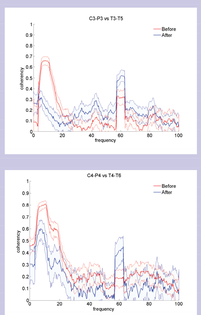
Power Spectra: Before & After Zolpidem (Day 3, Afternoon Dose)



Power Spectra: Before & After Zolpidem (Day 5, Morning Dose)



Coherence (Day 2)



Peaks in short-range coherence noted in 5-15Hz frequency range, which are reduced after zolpidem administration.

Findings

OFF Zolpidem:

Dysfunctional communication and motor control, with:

- Global hypometabolism (L>R) on ^{18}FDG-PET
- Narrow, aberrant EEG spectral peaks in 7-11Hz range globally
- Intermittent spectral peaks at 70-80Hz
- Peak in local coherence in 5-15Hz range

➢ The OFF state low frequency peak (at 7-11Hz) may correlate to pathologic conditions: hypoxic-ischemic encephalopathy, alpha coma, thalamic deafferentation.

ON Zolpidem:

Improved communication and motor control, with:

- Increases in regional & global metabolism
- Loss of aberrant spectral peaks in 7-11Hz range
- Downward shifting of 70-80Hz peaks
- Reduction in local coherence in 5-15Hz range

➢ The ON state behaviors reflected normalization of integrative function that is dependent on circuit-level mechanisms.

DISCUSSION

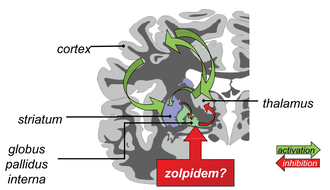
Possible Mechanisms

A possible physiological basis for the change in EEG power spectra is increased activation of frontal systems mediating executive and pre-motor function, via release of thalamocortical outflow.

As a GABA-A1α agonist, zolpidem may inhibit the GABA-sensitive neurons of the globus pallidus interna (GPi), thus removing their tonic inhibition of the thalamus and upregulating cortico-striato-pallido-thalamo-cortical networks (see figure).[8-10] A direct effect on cortical inhibitory interneuronal networks likely also contributes to the observed effects.[11]

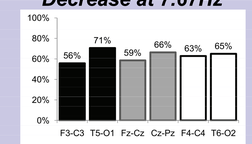
This model predicts increased metabolism in the thalamus, striatum and frontal cortex and decreased metabolism in the GPi and suggests other potential targets for therapeutic intervention, which have had empiric success:

- Dopaminergic agents support the function of striatal medium spiny neurons.
- Thalamic DBS directly activates thalamostriatal and thalamocortical outflow.[12]



Adapted from Schiff (2009)[13]

Average % Power Decrease at 7.67Hz



The bars represent the mean percent decrease in power at 7.67Hz, averaged over the 3 doses in the panels above. Black = Left hemisphere, White = Right hemisphere, Gray = Midline.

REFERENCES

1. Brefel-Courbon C, Payoux P, Ory F, Sommet A, Slaoui T, Raboyeau G, Lemesle B, Puel M, Montastruc JL, Demonet JF, Cardebat D. Clinical and Imaging Evidence of Zolpidem Effect in Hypoxic Encephalopathy. Ann Neurol 2007; 62: 102-105.
2. Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta (GA): Centers for Disease Control and Prevention, Nation Center for Injury Prevention and Control; 2006.
3. Schiff ND. Modeling the minimally conscious state: measurements of brain function and therapeutic possibilities. Progress in Brain Research 2005;150:477-497.
4. Schiff ND. The neurology of impaired consciousness: challenges for cognitive neuroscience. In: Gazzaniga MS ed. The Cognitive Neurosciences, 3rd ed. Boston: MIT Press; 2004.
5. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. Drugs. 2000;59:865-889.
6. Davey MP, Victor JD, Schiff ND. Power spectra and coherence in the EEG of a vegetative patient with severe asymmetric brain damage. Clin Neurophys 2000;111:1949-1954.
7. Mitra PP, Pesaran B. Analysis of dynamic brain imaging data. Biophysical Journal 1999; 76: 691-708.
8. Schiff, ND, Ribary, U, Moreno, D, Beattie, B, Kronberg, E, Blasberg, R, Giacino, J, McCagg, C, Fins, JJ, Llinas, R and Plum, F. Residual cerebral activity and behavioral fragments in the persistent vegetative state. Brain 2002;125, 1210-1234.
9. Schiff ND, Rodriguez-Moreno D, Kamal A, Petrovich N, Giacino J, Plum F and Hirsch J. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 2005;64:514-523.
10. Schiff ND, Posner JB. Another "Awakenings". Ann Neurol. 2007;62:5-7.
11. McCarthy MM, Brown EN, Kopell N. Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol –induced paradoxical excitation. J Neurosci. 2008;28:13488-13504.
12. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007; 448: 600-603.
13. Schiff ND. An integrative research paradigm for the cognitive neuroscience of consciousness. In: Gazzaniga MS ed. The Cognitive Neurosciences, 4th ed. Boston: MIT Press; 2009.

Support: The Rockefeller University Clinical and Translational Science Center, Clinical Scholars Program (STW), The Charles A. Dana Foundation (NDS), The James S. McDonnell Foundation (NDS), and NIH HD 91512 (NDS). We thank Bradley Beattie for quantitative analysis of the PET images. Please direct correspondence to ***shawniqua.williams@gmail.com****.*