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

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

BACKGROUND
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 acute mild TBI patients showed increased metabolism in medial frontal cortex, thalami and posterior thalamic regions after zolpidem. 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.²

METHODS
- Single subject, unblinded study
- Subject admitted to inpatient neurology unit
- Maintained home zolpidem dosage
- 3½ hours elapsed
- FDG-PET OFF and ON zolpidem

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

Coherence (Day 2)

Findings

OFF Zolpidem
Dysfunctional communication and motor control, with:
- Global hypometabolism (L-HR) on 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 deactivation.

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 incorporation of frontal systems mediating executive and pre-motor function, via release of thalamocortical output.

As a GABA-A agonist, zolpidem may inhibit the GABA-sensitive neurons of the globus pallidus internus (GPI), thus removing their tonic inhibition of the thalamus and potentially cortical-cortical-pallido-thalamo-cortical networks (see figure).²³ A direct effect on cortical inhibitory thalamocortical 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 basal ganglia and suggests other potential targets for therapeutic intervention, which have had empirical success:
- Dopaminergic agents support the function of striatal medium spiny neurons.
- Thalamic DBS directly activates thalamostriatal and thalamocortical output.²²

REFERENCES