Zolpidem's Paradoxical Arousing Effect in Unresponsive Wakefulness Syndrome and Minimally Conscious State Patients

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Abstract

Several reports have been published over recent years about Zolpidem's paradoxical arousing effect in unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) patients. During Zolpidem pharmacological intervention, we emphasized the importance of using the heart rate variability (HRV) methodology to assess the autonomic system by the HRV methodology, comparing UWS vs. MCS patients. This study included five UWS, five MCS patients, and twenty healthy voluntary subjects, matched by age and gender as a control group. The most striking finding was the significant decrement of A-PSD in the HF band in the UWS group, demonstrating a vagolitic effect of Zolpidem. This group also had a significant increment of slow frequencies (VLF and LF), mainly for VLF. The MCS group showed an early increment of AP for all bands after Zolpidem intake. Later, A-PSD in the frequency band significantly decreased, and A-PSD of LF and VLF tended to increase significantly. In the control group, the Zolpidem effect was characterized by early oscillations in AP values, with a posterior progressive increment of AP indices. In the MCS group of patients, the vagolitic effect and the increment of VLF and LF absolute powers were not so pronounced after Zolpidem intake compared with the UWS cases. We discussed the possible pathophysiological mechanisms to explain these findings in UWS and MCS patients.

Keywords: zolpidem; heart rate variability; zolpidem's paradoxical arousing effect; unresponsive wakefulness syndrome (UWS); minimally conscious state (MCS)

1 Introduction

Several reports have been published over recent years about the paradoxical arousing effect of Zolpidem, a highly selective nonbenzodiazepine gamma-aminobutyric acid (GABA) agonist acting on the [omega]-1 site of the GABAA receptor, in unresponsive wakefulness syndrome (UWS), in minimally conscious state (MCS) patients, ischemic stroke cases, after brain injury, and in patients suffering hypoxic encephalopathy. We have published several papers on Zolpidem's paradoxical arousing effect in disorders of consciousness (DoCs).[1-18] During Zolpidem pharmacological intervention, we emphasized the importance of using the heart rate variability (HRV) methodology to assess the autonomic system in a UWS patient. Cardiovascular autonomic regulation initially showed a significant parasympathetic predominance during the first ten minutes of the post-administration period, followed by an ulterior ostensible vagolytic effect and significant sympathetic activation, which provoked a reduction of the overall HRV with peaks after Zolpidem, clearly coinciding with yawns and increased sympathetic predominance.[12-15]
This paper will compare Zolpidem's paradoxical arousing effect on the autonomic system by the HRV methodology, comparing UWS vs. MCS patients.

2 Methods

2.1 Subjects

This study included five UWS, five MCS patients, and twenty healthy voluntary subjects, matched by age and gender, as a control group. Inclusion criteria for the patients, regardless of etiology, for UWS patients were: eye movements with lack of fixation, no evidence of awareness of self or environment, lack of interaction with others, and no comprehension or expression of language. Often, stimuli resulted in massive stretching or startled reactions, sometimes showing massive flexing responses without proper habituation. Occasionally grimacing occurred after stimulation. Nonetheless, external stimuli did not evoke purposeful or sustained and reproducible voluntary behavioral responses.[19-26]

We selected the MCS cases according to Giacino et al.[22,27] Patients with limited but discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis by one or more of the following behaviors: Following simple commands; Gestural or verbal yes/no responses (regardless of accuracy); Intelligible verbalization; Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity.

After a detailed neurological examination, the diagnosis was primarily based on the clinical history and caregiver interview and confirmed on the first day of testing by two experienced neurologists. Patients were evaluated by the JFK Coma Recovery Scale-Revised (CRS-R).[28,29] Normal subjects, matched in sex and age with patients, did not have a history of any neurological or other chronic diseases, and they were not under any medication.

Participants were excluded if they were at this time under Zolpidem or a related benzodiazepine medication or if their clinical status impeded participation in the protocol.

Normative data from our Lab for HRV data, calculated from 371 healthy normal subjects from 12 to 65 years old, were used to obtain the corresponding multiple regression equations (MRE) for each VFC index. The Experimental Protocol was submitted and approved by the Scientific Committee of the National Institute of Neurology and Neurosurgery and the Ethics Committee of this same institution. After meeting with the principal investigator, informed consent was obtained from each participant's proxy and the normal subjects.

2.2 Experimental design

Every member of the experimental groups: UWS, MCS, and controls received Zolpidem. The drug consisted of a 10 mg dose of Zolpidem tablets, which were cracked and duly dissolved in 30 ml saline solution was, both for the patients and the control group.

2.3 Description of experimental sessions.

Patients and normal subjects arrived at our Lab at 9:00 am and were placed in a quiet room with dim light and a controlled temperature of 25° Celsius, where only one examiner from our staff and one patient's relative were allowed to stay. They stayed resting in this room for at least 15 minutes before starting the experimental session. All recordings were performed with the subjects lying in a recumbent position. After testing the recording conditions of the different signals, the experimental recording session began. The first 30 minutes were considered the basal record. Then the pharmacist brought the test tubes containing the placebo-Zolpidem solution and was administered using a syringe to patients through gastrostomy and orally to normal subjects. Product administration took 1 minute. Then, the experimental recordings continued for at least 90 minutes. After this time, clinical inspection continued until 4 hours after Zolpidem intake.

2.4 Electrocardiograms (ECG) recording

Electrocardiograms (ECG) were recorded simultaneously with the MEDICID-05 (Neuronic, S. A.) with disposable electrodes placed on the chest in positions CM2 and V4, using a sampling frequency of 200 Hz. Filters were set for a band spectrum of 0.1-50 Hz. ECG digital data was exported offline to a custom-tailored software tool developed by our staff to inspect and detect the "R" wave peaks visually. Accurate "R" peak detections were visually controlled and properly corrected when it was necessary.

Bipolar ECG recordings were exported offline as ASCII files to a software tool developed by our staff designed in Delphi version 7.0 (MultiTools version 3.1.2, 2009-2011) for visual inspection, detection of the "R" wave peaks, and enabling manual editing. Accurate "R" peak automatic detections obtained with the software's algorithms were always visually checked and adequately corrected, when it was necessary, by a member of the staff. In order to transform the sequential R-R interval (RRI) series into proper temporal series, the original RRI sequences were interpolated using the piecewise cubic Hermite interpolation method using a sampling frequency of 6.83 Hz. The entire consecutive sequences of RRI obtained using this procedure were stored digitally for further instrumental analysis.

2.5 HRV spectral analysis

HRV indices were obtained from 300 seconds of RRI sequences free of artifacts. The absolute power spectral density (A-P SD) estimation and time-domain indices were calculated for every window using an FFT-based windowed periodogram method (Hann's window and 2048 samples). Absolute and relative powers were calculated for the very-low-frequency (VLF) band in limits from 0.02 to 0.04 Hz, the low-frequency band (LF) from 0.04-0.15 Hz, the high-frequency band (HF) from 0.15-0.4 Hz, and the total spectral power band (Tot) from 0.02-0.4 Hz. Zeta values were calculated for all time, and spectral-domain indices considered control values obtained during the pre-administration phase.

2.6 Statistical analysis

The normal distribution of the different time and frequency indices was achieved by transformations on the original values, when necessary before any parametric comparative test was performed. HRV values of every patient calculated in the time and frequency domains for RRI sequences of 5-minutes were compared with the standard normative values used in our Laboratory and assessed as Z-scores. HRV data from 371 healthy normal subjects from 12 to 65 years old were used to obtain the corresponding multiple regression equations (MRE) for each VFC index, considering the independent factors age (A), gender (G), and the interaction "age x gender," and the standard error of the estimations (SEE). For statistical assessment of observed differences between EEG and HRV analysis spectral indexes, we applied the Student "t" test for dependent samples using the software Statistica 10.0. Other details of the methods and the statistical analysis can be found elsewhere. Technical details are published elsewhere.[12-15,17,30-32]

3 Results

Figure 1 shows the A-PSD of all HRV bands for the UWS and MCS groups. When comparing both groups, the most outstanding finding was the Zolpidem vagolitic effect (decrement A-PSD in the HF band) in the UWS patients. The time elapsed for the first abnormal A-PSD in the HF band showed significant decrement of value after Zolpidem intake (Z-scores under 2.0) varied among the UWS patients. Still, all cases showed a significant reduction of this variable. The MCS group showed oscillations of A-PSD values for the different frequency bands; a significant increment of A-PSD in the HF band occurred in two cases.
Figure 1 shows the A-PSD of all HRV bands for the UWS and MCS groups. When comparing both groups, the most outstanding finding was the Zolpidem vagolitic effect (decrement A-PSD in the HF band) in the UWS patients. The MCS group showed oscillations of A-PSD values for the different frequency bands.

Figure 2 compares the Grand average of A-PSD of all frequency bands for the control, UWS, and MCS groups. Again, the most striking difference was the significant decrement of A-PSD in the HF band in the UWS group, demonstrating a vagolitic effect of Zolpidem. This group also significantly increased slow frequencies (VLF and LF), mainly for VLF. The MCS group showed an early increment of A-PSD for all bands after Zolpidem intake. Later, A-PSD in the HF band significantly decreased, and A-PSD of LF and VLF increased significantly. In the control group, the Zolpidem effect was characterized by early oscillations in A-PSD values, with a posterior progressive increment of A-PSD indices.

Discussion

Our most striking finding was the vagolitic effect of Zolpidem in UWS and MCS patients, although, in the MCS group, this effect was less pronounced.

Zolpidem’s paradoxical arousing effect in UWS and MCS patients is not well understood. A comparable phenomenon, known as paradoxical excitation, occurs in anesthesiology when low doses of anesthetics induce excitation rather than sedation.[2]
Zolpidem is a nonbenzodiazepine sedative-hypnotic, of the imidazopyridine class. It works by enhancing the activity of the brain's inhibitory chemical transmitter, GABA. GABA is the primary inhibitory neurotransmitter within the mammalian central nervous system. Inhibitory effects of GABA are exerted via the type GABA_A receptor, a ligand-gated chloride channel containing at least five different subunits in different orders or sequences that conform to the channel for Cl⁻ or HCO₃⁻. These subunits have been studied and classified, receiving names with Greek letters. There are no fewer than 20 subunits: α1-6, β1-4, γ1-3, δ, ζ, π, p1-3, and 0-1. [33-42]

A hypothesis for Zolpidem's paradoxical arousing effect must not only be associated with sleep centers. Still, it should have more widespread effects knowing the broad expression of α-1, α-2, and α-3 subunits in the CNS. GABA_A receptors that contain subunits α1β2γ2 are the most extended in the brain (~ 60%) and have been identified in the cerebral cortex (layers I-VI), olfactory bulb, hippocampus, pallidum, striatum, thalamic relay nuclei, cerebellum, amygdala, basal forebrain, substantia nigra reticulata and compacta substantia nigra, inferior colliculus, and brainstem. These receptors show a high affinity for Zolpidem. The GABA_A receptors with a combination of subunits α2β2γ2 comprise 15-20% of them and show an intermediate affinity for Zolpidem and high affinity for classical benzodiazepines.[2,43-48]

Clauss et al. have explained Zolpidem’s paradoxical arousing effect on the so-called dormancy theory. This theory emphasizes that excitatory and inhibitory neurotransmitters, mostly Glutamate and GABA, increase after brain injury. Although Glutamate's excitatory action induces apoptosis in brain cells to absorb toxic metabolites stabilizing the ischemic microenvironment, after brain damage, GABA's inhibitory effect predominates, suppressing cellular metabolism, which protects cells from unfavorable environments leading to loss of consciousness. After some time, GABA content lessens due to increased usage and escape from the brain into the blood. GABA cannot be refurbished adequately after brain injury due to low energy metabolism, impairs enzyme mechanisms involved in GABA production and activates secondary protective response, making GABA receptors hypersensitive to GABA. This phenomenon is called up-regulation, so that decreased GABA levels can maintain their suppressive effect, and promote a tendency of synchronized slow-wave activity in the brain, termed neurodormant state.[6,7,49-53] Dormancy or hibernation of the myocardium after an ischemic insult has been described in cardiology; it is applied to the brain is recognized as neurodormancy.[12,15,54,55]

Nonetheless, in our opinion, neurodormancy does not wholly support Zolpidem’s paradoxical arousing effect in UWS cases because the pathological patterns of UWS cases are diverse, and the location of lesions, either focal in different brain regions or widespread brain injury, should be taken into consideration.[56]

Schiff and Posner offered a persuasive hypothesis to explain Zolpidem’s paradoxical arousing effect.[57,58] This was based partly on results from imaging studies, which showed that brain regions, including the frontal cortex and the thalamus, were highly active when the patient was on Zolpidem and highly inactive when she was not.[59] Based on the “mesocircuit” hypothesis, these authors have recently explained the Zolpidem effect in UWS cases. Different brain injuries generate a global decrement of excitatory neurotransmission producing overall changes in cerebral background activity levels, producing a pattern of marked cortical and thalamic hypometabolism. Extensive damage to the cortex can lead to the loss of pathways between cortical regions and cortical and subcortical areas. This pathway consists of excitatory projections from the cortex to the striatum (subcortical structure), which sends inhibitory projections to the globus pallidus. When not inhibited by the striatum, the globus pallidus inhibits the thalamus. The net effect is that loss of excitatory projections from the cortex after a severe brain injury can indirectly inhibit the thalamus. Removing this inhibition is critical for restoring normal brain function because the thalamus is a significant source of arousal inputs to the cortex. Zolpidem is known to be selective for a particular subtype of GABA receptors (GABA_A). The striatum's medium spiny neurons (MSNs) have a crucial role in maintaining the anterior forebrain's inhibitory projections to the globus pallidus interna, inhibiting the central thalamus. Therefore, central thalamic activity is reduced when MSN activity diminishes due to brain injury. These authors proposed that Zolpidem blocks the inhibitory inputs from this structure to the thalamus, thus allowing the thalamus to excite the cortex and help restore cognitive and motor functions. [58]

Nonetheless, the “mesocircuit” hypothesis [57,58] cannot explain Zolpidem’s paradoxical arousing effect when there is massive destruction of both thalami, as in YOR patients, who, on the contrary, showed a significant autonomic and cortical activation after Zolpidem intake. Therefore, it is necessary to discuss other possible targets to explain this drug effect.[12]

GABAergic ascending neurons in the basal forebrain project to the cortex and might act in synergy with the cholinergic neurons in cortical activation, likely by ascending disinhibition, since they largely innervate inhibitory cortical neurons. Thus, there is little doubt that the substantia innominata and the adjacent basal forebrain as a whole, including cholinergic, GABAergic, and perhaps further, non-identified neurons, play an essential role in cortical activation, during waking and paradoxical sleep, and in the modulation of different cortical rhythmic activities. Recent studies indicate that the basolateral amygdala, the neocortex, and the hippocampus, receive GABAergic inputs from the basal forebrain, in addition to the well-established cholinergic inputs. These results suggest that GABAergic neurons of the basal forebrain provide indirect disinhibition of cortical neurons. Hence, Zolpidem might activate GABAergic neurons of the basal forebrain, which provide disinhibition (activation) of cortical neurons. [1,2,12,13,60,61]

Another possible target of Zolpidem action is the mesopontine GABAergic column (MPGC). It is a GABAergic neuronal population, appearing as a column of cells, with a long-axis in the sagittal plane, extending through the midbrain andpons. The contiguous, columnar, anatomical distribution suggests operation as a functional neural system, influencing REM sleep and wake expression. Microinjecting the GABA_A receptor agonist muscimol into the pontine reticular formation increases wakefulness, suggesting that GABAergic neurotransmission promotes wakefulness in the pontine reticular formation. Hence, GABAergic transmission in the pontine reticular formation suppresses sleep and promotes wakefulness.[12,13,62]

Therefore, in a global decrement of excitatory neurotransmission after brain injury, Zolpidem might activate GABAergic neurons inducing disinhibition (activation) of different brain structures, such as the central thalamus. According to the mesocircuit theory, those GABAergic neurons of the basal forebrain provide the disinhibition (activation) of cortical neurons at the mesopontine GABAergic column and in other brain structures. [12,13]

In our cases, it is also essential to discuss the Zolpidem effect on the autonomic function. Parasympathetic neural control of the heart rate is directly related to neurons located in the dorsal nucleus of the vagus nerve (VDN) and the nucleus ambiguous (NA). The so-called Polyvagal theory.[63-66] and other evidence point to a predominance of the neurons in the NA as the primary source of the chronotropic cardiac activity.[67-72]

The VLF band in the range 0.0033–0.04 Hz is related to the thermoregulatory mechanisms, the renin-angiotensin system, and the vasomotor limb of the sympathetic branch of the ANS. The LF band covers the range from 0.04 to 0.085 Hz and is related to the sympathetic influences. The HF band covers from 0.15 to 0.4 Hz and is mainly related to the vagal influences on respiration and chronotropic activity.[12,13,31,32,56,73-76]

Cardiac vagal neurons possess gabazine-sensitive GABA_A receptors (mediating phasic synaptic current) and gabazine-insensitive but
picrotoxin-sensitive receptors (mediating extrasynaptic tonic current). Benzodiazepines recruit a third type of GABA<sub>3</sub> receptor that is gabazine-sensitive. From neurons located within the nucleus tractus solitarius, cardiac neurons receive excitatory glutamate-mediated influence and GABAergic-mediated influences. Many other central nervous system structures send excitatory or inhibitory effects to the cardiac vagal neurons. Only to mention some of them: from the hypothalamic paraventricular nucleus arise direct glutamatergic projections; synaptic terminals of neurons containing hypocretin with a selective enhancement of inhibitory character project to the lateral hypothalamus; It is also essential to know that in the cardiac neurons in the VDN and the NA different subtypes of serotonin, adrenergic β-2 receptors, have also been identified that play an essential role in different autonomic reflexes integrated at the brainstem level. Recently, clonidine, an α-2 receptor agonist, has been shown to diminish neurotransmission of cardiac vagal neurons in the NA.[77-88]

From neurons located within the nucleus tractus solitarius, cardiac neurons receive excitatory glutamate-mediated influence and GABAergic-mediated influences. Therefore, after brain injury characterized by a condition of global decrement of excitatory neurotransmission, Zolpidem might activate GABAergic neurons at the NA, which induce inhibition of preganglionic vagal neurons, with a subsequent a vagolitic effect, and a sympathetic predominance, expressed by an increment of LF absolute power, as occurred in our UWS cases.[4,6,7,49,50,61,86,89-93] Since there are many excitatory and inhibitory connections in the medulla, other brainstem regions also play a relevant role in the Zolpidem effect on parasympathetic and sympathetic outflows.[56]

Studies have proposed that the ventrolateral region of the medulla oblongata is an important site of synaptic interaction between respiratory and sympathetic neurons. However, other brainstem regions also play a relevant role in patterning respiratory and sympathetic motor outputs. Recent findings suggest that the neurons of the nucleus of the solitary tract (NTS) in the dorsal medulla are essential for the processing and coordinating of respiratory and sympathetic responses to hypoxia.[94-98]

Regarding the VLF band, there are still discussions about its origin. The VLF power influences the heart, such as the renin-angiotensin system, thermoregulation, and sympathetic vasomotor activity; other authors consider that the VLF band indicates sympathetic-vagal function.[31,32,99-101]

We have recently discussed that there is an essential sympathetic contribution to the VLF band.[56] Several authors have suggested that VLF frequencies originate in supraspinal vasomotor centers.[56,102] Kuo and Yang have demonstrated that the VLF power of arterial pressure variability is related to vasomotor reactivity in response to control signals from the rostral ventrolateral medulla via the sympathetic system in the rat. [102] Hence, the sympathetic predominance after Zolpidem intake might explain the increment of VLF absolute power in our UWS patients.[56]

In the MCS group of patients, the vagolitic effect and the increment of VLF and LF absolute powers were not so pronounced after Zolpidem intake compared with the UWS cases. Although the pathophysiological mechanisms might be similar to those in the UWS patients, it is essential to consider that the cortex has a more functional state in MCS cases.[103-105]

**Conclusion**

Although a drawback of our study might be the relatively reduced number of cases, we consistently found in all cases a Zolpidem's paradoxical arousing effect on the autonomic nervous system (chronotropic effect without a vasomotor influence).

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