

Drug induced arousal from the permanent vegetative state

Ralf Clauss^{a,*} and Wally Nel^b

^a*Nuclear Medicine Department, Royal Surrey County Hospital, Guildford, UK*

^b*Family Practice, Pollack Park, Springs, South Africa*

Abstract. *Background:* Zolpidem is an omega 1 specific indirect GABA agonist that is used for insomnia, but may have efficacy in brain damage. The long term efficacy of zolpidem in the permanent vegetative state is described in three patients.

Method: Two motor vehicle accident patients and one near drowning patient, all of them in the permanent vegetative state for at least three years, were rated according to the Glasgow Coma and Rancho Los Amigos scale before and after zolpidem application. Long term response to daily application of this drug was monitored for 3–6 years.

Results: All patients were aroused transiently every morning after zolpidem. Glasgow Coma Scale scores ranged from 6–9/15 before to 10–15/15 after zolpidem. Rancho Los Amigos Cognitive scores ranged from I–II before to V–VII afterward. Drug efficacy did not decrease and there were no long term side effects after 3–6 years daily use.

Conclusion: Zolpidem appears an effective drug to restore brain function to some patients in the permanent vegetative state.

Keywords: Diaschisis, GABA, dormancy, brain injury, permanent vegetative state

1. Introduction

Over the past years, clinical and scintigraphic improvements have been observed after Zolpidem in patients with brain damage [6,7,10]. The effect of Zolpidem in traumatic brain injury was first described after the accidental discovery of its effect on a patient who had been in the permanent vegetative state for more than three years following a motor vehicle accident. The patient awoke from his permanent vegetative state after receiving Zolpidem and could recognize and greet his mother for the first time since losing consciousness years earlier [6]. The astounding findings in this patient, such as the return to his vegetative state after lapse of drug action and the subsequent re-awakening from his vegetative state after renewed drug application, and also the findings of improved perfusion in hypoperfused brain tissue, led to further exploration of

this phenomenon in animal studies and later in brain-injured patients who received the drug for treatment of insomnia [9]. In a family of 5 spinocerebellar ataxia patients, 4 of the patients had symptom improvement after Zolpidem [8]. In another recent case report, a patient with aphasia after stroke managed to speak normally again for the duration of drug action [10]. Further recent reports have shown that the drug is effective in relieving symptoms after long standing brain anoxia and in blephorospasm [13,30].

Zolpidem is a non-benzodiazepine drug belonging to the imidazopyridine class, chemically distinct from sedatives such as barbiturates, antihistamines, benzodiazepines and cyclopyrrolones. Zolpidem has a selectivity for stimulating the effect of gamma aminobutyric acid (GABA) and is used for the therapy of insomnia. It has a short half life of 2.4 hours with no active metabolite and does not accumulate with repeated administrations. The drug is oxydised and hydroxylated by the liver to inactive metabolites that are eliminated primarily through renal excretion [27]. GABA systems involve various receptors and receptor subtypes. It is the GABA(A) receptor chloride channel macro-

* Address for correspondence: R.P. Clauss, Nuclear Medicine Department, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey, GU2 7XX, UK. Tel.: +44 1483 571122; Fax: +44 1483 406702; E-mail: rclauss@royalsurrey.nhs.uk.

Table 1
Zolpidem efficacy in the permanent vegetative state as measured by Glasgow Coma Scale and Rancho Los Amigos Cognitive scores

Patient	Age	Tveg.	RLA Scale		GC Scale		Tzolp
			BZ	AZ	BZ	AZ	
L (m)	31	3 years	I–II	VI–VII	9	15	6 years
N (m)	31	3 years	II	V	6	10	5 years
G (m)	29	5 years	II	VI–VII	9	14	3 years

Tveg.: Time in permanent vegetative state before start of Zolpidem therapy.

RLA Scale: Rancho Los Amigos Scale.

GC Scale: Glasgow Coma Scale.

Tzolp.: Time on daily Zolpidem.

BZ: Before Zolpidem.

AZ: After Zolpidem.

(m): male.

molecular complex that is implicated in sedative, anticonvulsant, anxiolytic and myorelaxant drug properties. Its major modulating site is located on the alpha sub-unit, referred to as the benzodiazepine (omega) receptor. There are at least three omega receptor subtypes. Benzodiazepines bind non-selectively to these while Zolpidem binds preferentially to omega 1 receptors [28].

In view of the previous evidence for the efficacy of Zolpidem in patients with brain damage, the effect of the drug was documented in patients L, N and G who were categorized to the permanent vegetative state. The long term daily use of the drug is described in these patients.

2. Method and results

After extensive counselling and advice to their families, a 10 mg dose of Zolpidem was prescribed to patients L, N and G. All patients were scored on the Glasgow coma scale and on the Rancho Los Amigos cognitive scale, before and one hour after Zolpidem application. The results are summarized in Table 1.

Patient L was a 31 year old male patient in a nursing home who had been in the permanent vegetative state for 3 years following a motor vehicle accident. He had right sided hemiplegia and left sided muscle spasm and contractures. He had no coordinated reaction to pain or touch and did not respond to any commands. Although he had a regular sleep/wake cycle, he had no meaningful response to visual, auditory or physical stimuli by staff or visiting family. There was no evidence of language comprehension and there was no sphincter control. The patient did not receive any short or long term medication in his vegetative state. After Zolpidem, the patient could meaningfully inter-

act with staff, family, friends and strangers. There was a sustained purposeful and voluntary behavioural response to visual, auditory and physical stimuli and he could speak and engage in meaningful conversation. For example, when questioned who his favourite rugby player was, he answered appropriately. He could make simple calculations when asked to do so and his emotional response was appropriate. He could take food and put it into his mouth and swallow it. He could also have a meaningful conversation on the telephone and could make jokes. Maximum arousal was 1 hour after Zolpidem application although there was already some limited response to commands after 20–30 minutes. The effect lasted for approximately four hours. The Glasgow coma scale score improved from 9 to 15 after Zolpidem and the Rancho Los Amigos score from I–II to VI–VII. Though impaired to begin with, his short and long term memory continues to improve after the start of his daily Zolpidem therapy 6 years ago, but he cannot remember anything that happened to him in his vegetative state.

Patient N was a 31 year old male with quadriplegia who was nursed by his family and who had been in the permanent vegetative state for 3 years following a motor vehicle accident. The patient received no short or long term medication in his vegetative state. He had no coordinated response to visual, auditory or physical stimuli. He did not interact with his family or visitors. For example he did not respond to commands and he appeared permanently distressed and was constantly uttering random screams. However, he had a regular sleep/wake cycle. There was no evidence of language comprehension and there was no sphincter control. After Zolpidem, the patient stopped screaming and there was a limited but appropriate response to visual and auditory stimuli. He started watching television and he appeared to react appropriately to the scenes on the tele-

vision screen. For example, he laughed at funny scenes and was quiet with other ones. There was also a meaningful response to commands and there was meaningful reaction to family and carers. Although he struggled, he could state his name and age when asked to do so. Maximum arousal was 1 hour after Zolpidem application and the effect lasted for approximately four hours. The Glasgow coma scale score improved from 6 to 10 after Zolpidem and the Rancho Los Amigos score from II to V. The ^{99m}Tc HMPAO Brain SPECT of patient N showed marked improvement in the frontal regions bilaterally and reversal of left sided cerebellar diaschisis after Zolpidem. N has been treated daily now for five years.

Patient G was a 29 year old male patient who was nursed by his family and who had been in the permanent vegetative state for 5 years before Zolpidem therapy, following a near drowning after a motor vehicle accident. He had left sided hemiplegia and right sided muscle spasm. At the time of his accident, he was submerged for approximately 8 minutes before rescue. He did not interact meaningfully with staff or family that came to visit him. He had a regular sleep/wake cycle but no sustained, reproducible or purposeful response to visual or physical stimuli and there was no sphincter control. There was no meaningful response to commands or requests by his mother or carers. He received no short or long term medication in his vegetative state although he received two courses of hyperbaric oxygen therapy since starting his Zolpidem therapy. After Zolpidem, the patient could meaningfully interact with his family and friends. There was a sustained behavioural response to visual, auditory and physical stimuli and he could engage in limited meaningful conversation. For example when he was asked to lift his hand or smile or count to five he did so. He could also answer simple questions and could even catch a baseball. From no response before Zolpidem application, there was a limited response to commands at 20–30 minutes after Zolpidem and maximum arousal was 1 hour after application. The effect lasted for approximately four hours. The Glasgow coma scale score improved from 9 to 14 after zolpidem and the Rancho Los Amigos score from II to VI–VII. G has been treated now on daily zolpidem for three years.

3. Discussion

The categorization of the above patients to the permanent vegetative state was based on the criteria of the

Multi Society Task Force on the Persistent Vegetative State [21].

All of the above patients were aroused from their permanent vegetative state on first application of Zolpidem and repeatedly on a daily base since then. Their physical disabilities remain but L and G have a marked decrease in spasticity of their non hemiplegic side while on Zolpidem. Although the patients return repeatedly to the vegetative state after four hours when drug action subsides, they are repeatedly aroused from this state on a daily base with renewed drug application.

The action of Zolpidem is highly specific and it involves in particular omega 1 GABA(A) binding. For instance, when L received the non-selective benzodiazepine diazepam instead of Zolpidem for imaging studies, he was not awakened. N showed normalisation of a left sided cerebellar diaschisis, a phenomenon that has been reported previously after Zolpidem application [7].

Zolpidem is not approved for long term use, however it is a safe drug with relatively few side effects. The above patients were all exposed to the long term use of this drug. There was no evidence of tolerance to the drug and it remains as effective after years of treatment. Regular full blood count, renal and liver function tests remain within normal limits in all patients.

Dormancy or hibernation of myocardium after an ischaemic insult is a well-known phenomenon in the heart. Hibernating myocardium is non-functional but fully viable. When blood supply is re-instated after bypass surgery, hibernating myocardium becomes functional again [1,14]. It has been proposed that the reversal of diaschisis and neurodormancy explains the wide efficacy of Zolpidem in unrelated brain injuries, from genetic disorders such as spinocerebellar ataxia type II, to stroke and traumatic brain injury [7]. When investigating diaschisis and neurodormancy in animals, the injured, poorly perfused dormant brain region improved after Zolpidem [5]. When exploring the site of drug action by blocking omega receptors with Flumazenil, it could be shown that the effects of Zolpidem are due to omega binding [4].

There are many studies investigating the effect of brain injury and anoxia in the vertebrate brain. It is known that in the first hours after brain injury, there is a neuroprotective surge in GABA levels to suppress brain activity [16,25,31]. In contrast, late after brain injury and in chronic brain pathologies GABA levels become normal or subnormal [11,15]. Brain suppression and dormancy can remain however.

Anoxic brain survival strategies have been shown before in animals such as fresh water turtles [2,15,19].

These animals can survive experimental anoxic submergences up to 5 months at 3 degrees Celsius. They do this by a reduction in their energy metabolism to approximately 10% of the normoxic rate. This is concurrent with reduced ATP production and ATP consuming pathways, and by a shift to anaerobic glycolysis and anaerobic metabolic pathways. In fact, the anoxic turtle suppresses brain activity to such a degree that it becomes virtually comatose. The underlying mechanism of this has been ascribed to the closing down of cellular ion conductance and the release of GABA and Adenosine [24]. A similar observation has been reported in lesioned unconscious rat brains. In these animals, there was a marked reduction in ATP levels in regions such as the hippocampus ipsilateral to the brain lesion and there was also a reduction in the ATP levels in the hypothalamus, hippocampus and striatum of the opposite side, ascribed to possible diaschisis [35]. This may be evidence for the existence of an anaerobic brain metabolism in association with dormancy and diaschisis that occurs in anoxic mammalian brains. Moreover, there is evidence for a metabolic shift in human brains and increasing brain lactate concentrations that occur in these anoxic brains [3,26,29,33].

GABA(A) receptors are ligand operated ion channels that control cellular ion conductance [18,32]. It is postulated that modified GABA(A) receptors modulate cell metabolism and ion exchange after anoxic stimulation in brain injury, and that neurodormancy is the manifestation of this remodulated cell metabolism.

In anoxia tolerant vertebrates, there are several metabolic changes that occur with brain ischaemia. They include amongst others ion channel shutdown and reduction in cellular metabolism [24]. The aim of these changes is to reduce ATP consumption and prevent calcium influx into cells. Initially the reduction in ion exchange is started by markedly increased levels of the inhibitory neurotransmitter GABA, while excitatory neurotransmitters such as glutamate and other neurotransmitters are only moderately raised [33,34]. In contrast, anoxia intolerant vertebrates have marked increases in GABA as well as in excitatory neurotransmitters such as glutamate [26,33,35]. Such high glutamate levels promote calcium influx into cells and are ultimately responsible for apoptosis and cell death. This phenomenon is called excitotoxicity [22].

It seems that in anoxia intolerant brains, parallel to excitotoxicity and dying cells, there are some cells that survive and achieve a state of dormancy after hypoxia. This is most likely due to a GABA receptor modification with supersensitivity to the inhibitory neurotransmitter GABA.

GABA resources in ischaemic brains are intracellular stores of GABA. In addition, GABA is synthesized by the decarboxylation of glutamate, which is the forerunner of GABA [12]. Glutamate on the other hand is replenished from intracellular stores and de novo production from two sources, by an ATP consuming pathway from glutamine and an ATP conserving pathway from glycogen. The ATP conserving pathway branches from the glycolytic cycle by conversion of α -Ketoglutarate to glutamate [12]. During brain anoxia, glutamate sourcing and ultimately GABA sourcing would be from the glycogen stores within the brain. When local glycogen stores in the brain become depleted, particularly in the area of brain damage, the brain saves its glycogen and neuroprotective GABA resources by supersensitising its GABA receptors to GABA. Minimal GABA levels then continue suppressing cellular metabolism in the anoxic brain.

Prolonged diaschisis or neurodormancy are manifestations of this remodulated, GABA receptor induced, downregulated cellular metabolism. A previous study has, in fact, shown that diaschisis is associated with an altered composition of GABA(A) receptor subunits [34]. In another study, diaschisis was associated with reorganisation of GABA mediation [23].

It is suggested that two cellular pathways are initiated during brain injury. The first utilises glutamate and is an excitotoxic pathway that results in apoptosis and death of neural cells with consequent non reversible damage [22]. Parallel to this there is a neurodormancy pathway that is GABA induced and that ultimately results in areas of cellular survival [7].

When Zolpidem attaches to the modified GABA receptors of the neurodormant cells, the modified receptor structure is distorted and the promulgation of the abnormal cell metabolism ceases. As a consequence, the dormancy is switched off. If dormancy affects large or important brain areas, then clinical changes that occur after dormancy switch-off by Zolpidem, can be dramatic, such as arousal from the permanent vegetative state.

4. Conclusion

A repeated drug induced arousal from the permanent vegetative state has been possible on Zolpidem in the above patients for several years. It appears that Zolpidem may have a broad application in patients with brain injury. Its mode of action may be due to a GABA receptor based re-activation of dormant neural tissue of

injured brain. Further tests are now planned to evaluate the effect of Zolpidem on neurodormancy in larger groups of patients with brain damage.

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Interest statement

The Authors have applied for a usage patent of Zolpidem in brain damage.

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