Evidence for Zolpidem efficacy in brain damage

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Abstract

Previous reports have shown that zolpidem could reverse semi-coma and improve cerebral perfusion after brain injury. Studies in animals have implicated omega 1 GABAergic action as reason for this improvement. Evidence for the efficacy of zolpidem in a wide range of brain pathology is reviewed here and the mechanism of zolpidem in brain injury is considered from the perspective of diaschisis and neurological dormancy after brain injury.

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Introduction

Over the past years we have observed clinical and scintigraphic improvement in brain injured patients after administration of 10 mg zolpidem. Zolpidem is a non-benzodiazepine drug belonging to the imidazopiridine class, chemically distinct from sedatives such as barbiturates, antihistamines, benzodiazepines and cyclopyrrolones. It has 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 oxidised and hydroxylated by the liver to inactive metabolites that are eliminated primarily through renal excretion.[1] GABA systems involve various receptors and receptor subtypes. The GABA (A) receptor chloride channel macromolecular complex 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.[2]

Our interest in Zolpidem was spurred by the accidental discovery of its effect on a patient who had been in semi - coma for more than three years. The patient woke up from his semi-coma after receiving zolpidem and could recognize and greet his mother for the first time since losing consciousness years earlier.[3] The astounding findings in this patient, such as the return to his semi-comatose state after the lapse of drug action and the subsequent re-awakening from semi-coma after renewed drug application, and also the findings of improved perfusion in previously supposed dead 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.[4]

Current findings

So far, most of our studies show improved perfusion after zolpidem at the brain injury site on ^{99m}Tc HMPAO *(hexa-methyl-propylene amine oxime)* Brain SPECT *(Single Photon Emission Computed Tomography)* imaging, and sometimes at other brain sites such as physiologically suppressed cerebellum (cerebellar diaschisis). ^{99m}Tc HMPAO Brain SPECT maps blood flow changes in the brain and can determine if areas of the brain are functioning properly or not. This is in contrast this to MRI and CT scans that typically show only structural brain abnormalities such as tumours or necrotic lesions. Changes on ^{99m}Tc HMPAO Brain SPECT after zolpidem are often accompanied by improving clinical states in brain damaged patients, such as awakening from semi-coma, relief from brain injury symptoms and improvement in sleep abnormality.

Figure 1 shows a section of damaged brain on ^{99m} Tc HMPAO SPECT imaging in the left fronto-parietal hemi-cortex of a long distance walker before and after

Figure 1: 99mTc HMPAO Brain SPECT slices showing the left fronto-parietal cortex of a long distance walker five years after his motor vehicle accident, (a) before and (b) after zolpidem.

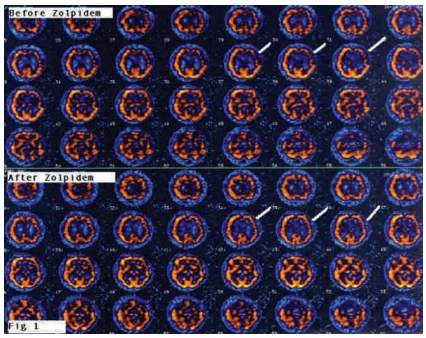


Figure 2: 99mTc HMPAO Brain SPECT images showing reversal of crossed cerebellar diashisis in a stroke patient. Image (a) shows decreased tracer uptake in the right cerebral hemisphere (stroke) and left cerebellum (crossed cerebellar diaschisis) before zolpidem. Image (b) shows improved left cerebellar uptake (reversal of diaschisis) after zolpidem but no change in the right cerebral hemisphere uptake.

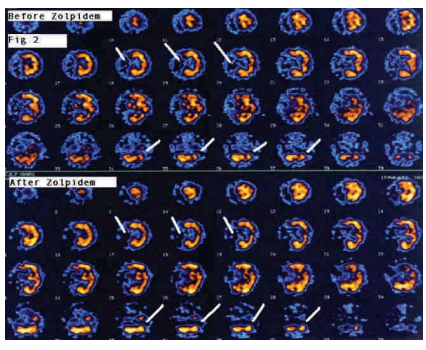
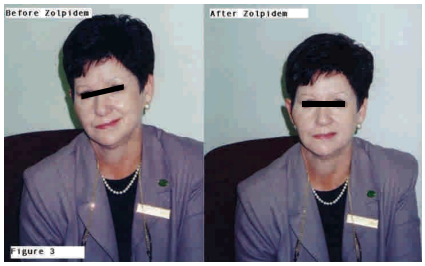


Figure 3: Bell's palsy in a patient (a) before and (b) after zolpidem



zolpidem. This victim of a motor vehicle accident five years prior to the scan, experienced right sided weakness and could not walk effectively without the drug. Figure 2 shows improved symmetry of a crossed cerebellar diaschisis in a stroke patient, using the drug for insomnia. This patient had a left hemiplegia but, in addition could not use his right hand due to insufficient coordination, although it was not paralyzed. After zolpidem, the left hemiplegia remained but the patient was able to use his right hand normally again. Figure 3 shows a patient with Bell's Palsy as complication after removal of an acoustic neuroma more than a decade prior to zolpidem treatment. After zolpidem, the Bell's Palsy improved and nerve conduction studies showed a decreased latency from 4.9 ms to 4.45 ms. In a family of patients suffering from spinocerebellar ataxia type II, four out of five patients showed improvement in their clinical features after zolpidem application. [5]

There are further reports of the efficacy of zolpidem in brain pathology by other authors. In 1997 Thomas *et al* reported the recovery from catatonia in patients after zolpidem.[6] The drug was also reported to have a beneficial effect in certain Parkinson's disease patients and in Progressive Supranuclear Palsy.[7, 8] In a recent case report, a patient with aphasia after stroke managed to speak normally again for the duration of drug action after ingesting 10 mg zolpidem. [9] This transient effect could be repeated on a daily base, much as was observed in our own patients. Further recent reports have shown that the drug is effective in relieving symptoms in long standing brain anoxia and in blefarospasm.[10, 11]

When investigating the phenomena in baboons, we could reproduce and quantify the effect of zolpidem in a brain injured baboon. The injured, poorly perfused brain region improved after zolpidem.[12] When exploring the site of drug action by blocking omega receptors with flumazenil, it could be shown that observed effects are due to omega binding.[13]

Discussion

The above evidence indicates a role for GABA and GABA-dependent systems in brain injury and ultimately coma. When zolpidem is applied some time after brain injury, there is an improvement in the clinical features caused by the brain injury. Concurrent changes in brain perfusion and metabolism are usually detected on ^{99m}Tc HMPAO Brain SPECT. The action is highly specific and it involves in particular omega 1 GABA systems. For instance, when the semi-comatose patient received the non-selective benzodiazepine diazepam instead of zolpidem for imaging studies, he was not awakened. It appears that the majority of brain injuries or brain pathologies are associated with a neurodormancy or diaschisis that probably has its roots in a neuroprotective reaction of the brain during brain damage. Dormancy results in a clinical presentation that is actually worse than would be expected from the lesion alone (i.e. the brain lesion without the associated dormancy).

Dormancy or hibernation of myocardium after an ischeamic 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.[14, 15] Similar to myocardial tissue, brain dormancy appears to occur with most forms of ischeamic brain injury or other forms of brain damage. Its reversal 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. Brain dormancy is most likely concurrent with a structural change or folding of the complex GABA receptor molecule. This state can be at least partially reversed by selective GABAergic stimulation of in particular the omega 1 receptors by zolpidem. [16]

The benefit of zolpidem in brain injured patients is transient and it occurs for the duration of drug action only. However, after first application and proof of efficacy in a controlled environment, it can be used daily for many years in brain injured patients, without adverse effects in our experience. Dosages can be reduced without compromising the effect of the drug on brain damage.[10] The drug remains potent after a once off brain injury, even after many years of constant treatment. In progressive disease however, as in progressive supranuclear palsy, effects may wane.[8] This is probably due to the progressive nature of the disease with less and less dormant tissue available for reversal as the disease progresses. Zolpidem reverses symptoms due to brain dormancy but does not change those due to necrotic or scarred brain tissue. Hence the clinical effect that can be expected from the drug depends on the size and location of the brain dormancy area that can be reversed, and not the size of the actual brain lesion itself. A lesion on CT with a disproportionate clinical incapacitation may respond well to Zolpidem while a lesion with a small dormancy component or one where the dormancy is located in an insignificant brain location, may show no clinical response.

Conclusion

There is increasing evidence for an important role of zolpidem in the treatment of the sequelae of a wide range of brain pathology, based on its reversal of dormant neural tissue after brain damage. A number of brain injured patients may benefit from this treatment, especially those with features of neurodormancy as proven by ^{99m}Tc HMPAO Brain SPECT, or a clinical picture that is disproportionate or incongruent to the one that is expected from radiological CT findings.

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