The Unusual Story of Zolpidem
Treating Traumatic Brain Injuries

• Chapter 1, Page 1 of every textbook, guideline or critical pathway regarding the treatment of acquired brain injury in a rehab setting is;

"Wean sedating medications as soon as possible."

• In the past few years this tenet has been challenged.
Zolpidem as Treatment for TBI?

- In 2000, there was a case report in the *South African Medical Journal* describing the wakening of a young man described as being in a vegetative state for 3 years following a TBI. His arousal occurred within 30 minutes of a 10 mg dose of Zolpidem (given to treat agitation) and was characterized by:
  - Greeting his mother
  - Answering questions about himself and his environment
  - SPECT scan showed increased activity in the thalamus, lentiform and caudate nuclei
  - Peak response was noted approximately 1 hour after administration of Zolpidem and lasted for a maximum of 4 hrs before the patient settled back into his vegetative state.
Zolpidem as Treatment for TBI?

• In 2001 a 2 year update was provided about this same patient in the same journal. With continuous treatment of Zolpidem 10 mg daily, he had improved cognition and memory. The duration of his clinical response had increased from 3-4 hrs to 6 hrs.

• A case report in 2008 of an Israeli women was similar, with improved functioning 30 minutes after a dose of 10 mg of Zolpidem with the effect lasting approximately 3 hours.
Zolpidem as Treatment for TBI?

- Another 2008 case report described a male patient in a minimally conscious state, who had failed to respond to methylphenidate, levodopa/carbidopa and antidepressants but responded to 10 mg of Zolpidem with the ability to:
  - Follow directions
  - Speak
  - Socialize with family
  - Eat independently
Zolpidem in PVS and MRS

- **Persistent Vegetative State (PVS)**
  - “wakefulness without responsiveness”. A patient in a PVS has sleep wake cycles but displays no awareness of themselves or their surroundings.

- **Minimally Responsive State (MRS)**
  - wakefulness with inconsistent but reproducible awareness of the environment (such a patient will occasionally but inconsistently follow simple commands).
Case History #2

• MK is a 17 year old young man who had a spontaneous rupture of an arteriovenous malformation (AVM) at the age of 10 years. By history, he completely recovered from this episode but, as a result of diagnostic studies at the time, was found to have a second AVM in the right thalamus. This AVM could not be reached by any means.

• The second AVM was followed with annual CT scans which, ironically, was found to be unchanged on 7/8/11, the same day it ruptured.
Case History #2

- He was initially intubated and hyperventilated, placed on mannitol and had a right decompressive craniotomy with externalized ventricular shunts
- Placed on prophylactic Keppra (no seizures observed)
- VP shunt placed 8/1/11
- Bone flap replaced 8/5/11
- Thalamic storming controlled with propranolol
Case History #2

• He was admitted to our rehab unit Mid-August 2011 (6 weeks after the AVM rupture)

• His admission physical exam was notable for;
  – Spontaneous eye opening but no visual tracking
  – Withdrawal from noxious stimuli bilaterally
  – No response to non-noxious stimuli (voice, visual, etc.)
  – No communication, no vocalizations
  – Right sided spasticity, left sided dystonia
  – Non-purposeful movement of the right side
  – Would inconsistently follow simple commands (Minimally Responsive State)
Case History #2

Admission medications included:
- Modafinil (Provigil) 100 mg daily
- Clonidine (Catapres) Patch 0.2 mg/day
- Levetiracetam (Keppra) 500 mg every 12 hours
- Baclofen (Lioresal) 10 mg every 8 hours
- Propranolol (Inderal) 10 mg every 12 hours
- Docusate (Colace) 100 mg 3 times a day
- Senna 15 mls twice daily
- Heparin 5,000 units s.q. every 8 hours for DVT prophylaxis
Case History #2

- During his rehab admission he had had the following acute medical interventions/problems;
  - Shunt malfunction and revision, September 2011
  - Diagnosed with Supraventricular Tachycardia, October 2011
  - Intrathecal Baclofen Pump Placement, November 2011

- 7 months after AVM rupture MK remained in a Minimally Responsive State despite the use of Amantadine and Aricept.
Case History #2

• At that point, at the family’s request, 10 mg of Zolpidem was administered.

• Medications at this time were Ferrous sulfate, Famotidine, Atenolol, Amantadine, Aricept, Intrathecal Baclofen (500 mcg/day, simple continuous infusion), Zoloft and Cholecalciferol.
Case History #2

• 20 minutes after Zolpidem, MK had increased alertness, increased responsiveness, spontaneous smile, began to consistently follow commands (turn his head, snap his fingers, wave, etc.). This effect lasted 3-4 hours then MK returned to a minimally responsive state.

• Upon repeat dosing the next day MK wrote “Hi” on a white board. He was able to use a buzzer with his right hand to correctly identify visitors present in the room, identify pictures of family/friends and perform simple math problems.

(More on this case later)
Zolpidem in PVS and MRS

- John Whyte, MD, PhD and Robin Myers, PT, NCS of the Moss Rehabilitation Research Institute in Philadelphia studied the responsiveness of patients in PVS and MRS to Zolpidem.
- They published a preliminary version of their work in the American Journal of Physical Medicine and Rehabilitation, Vol 88, No 5, May 2009 and a more extensive study in the same journal in February.
Moss Rehab Research Institute Data

- 84 Patients in a PVS or MRS naive to Zolpidem, 1 month or more after brain injury (range 1 mo. to 23 years), were recruited for a 2 Phase study;

**Phase I**
- the percentage that would respond to Zolpidem
- the degree of response (if any)
- the presence and frequency of any adverse effects

**Phase II**
- the clinical characteristics of responders

- Phase I of the study was double blind, placebo controlled, cross-over design and used the Coma Recovery Scale – Revised (CRS-R) to measure response.
In Phase I, 5% of the patients responded to Zolpidem with:

- Clinically significant improvement in CRS-R within 30 minutes of administration of 10 mg of Zolpidem.
- Patients had improvements such as:
  - increased movement
  - social interaction
  - consistently following simple commands
  - attempts at communication
  - functional object use
- Effect wore off in 1-2 hours and sometimes ended with increased somnolence
- Adverse events were mostly rated as “mild”
• The 4 responders from Phase I of the study were supplemented with 4 other known responders for Phase II of the study.
  • 7 of the 8 responders were from a slightly higher level of function pre-treatment (MRS vs. PVS) raising the possibility that Zolpidem responders are more likely to have a slightly level of consciousness.
  • Responders were clinically indistinguishable from non-responders on the basis of location of injury in the CNS, etiology of injury, etc.
  • The shortest onset of action was 10 minutes, the longest 1 hour.
  • Mechanism of action of Zolpidem in these patients is unknown
Zolpidem Responders

- It has been suggested that there are 3 types of Zolpidem responders;
  - About 70% respond consistently to each dose but cannot take doses more frequently than every few days without degradation of their response.
  - About 30% respond consistently to a dose taken daily but not to repetitive doses the same day.
  - A very small percentage of responders may have incremental improvement of their baseline function (level of function between doses) with regular daily dosing.
165 patients less than 60 years of age, in a vegetative state for at least 1 month (GCS 3-8) were enrolled in this study. Population was divided into 4 groups by mechanism of injury and location:
- 42 Countercoup injury
- 38 Primary brain stem injury
- 40 Space-occupying lesion / Brain Compression type injury
- 45 Secondary brain stem injury

Average age of patients was 38
Mean duration of vegetative state was >60 days
All patients were given 10 mg of Zolpidem via NG tube daily at 8 p.m. for 1 week.

Before and 1 hour after dosing patients had a SPECT scan and a Cerebral State Monitor (hand-held EEG).

The Cerebral State Monitor (CSM) was used to measure:

- “Cerebral State Index” – linear scale from 0 to 100 corresponding to higher levels of consciousness.
- Burst suppression
- EMG
Shenzhen People’s Hospital Data

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Zolpidem’s Other Uses?

- Case report in NEJM in 2004, a 52 year old woman S/P CVA with chronic aphasia and insomnia had dramatic improvement in her speech following Zolpidem.
- Case report in NEJM in 2004, 5 family members with cerebral ataxia, 4 had clinical improvement in ataxia, handwriting, tremor and titubation (the act of staggering or reeling) 20 minutes after Zolpidem.
Action of Zolpidem

- Zolpidem (Ambien) binds to the omega 1 subunit of the GABA (gamma aminobutyric acid) receptor and acts as an agonist.
- Since GABA is an inhibitory neurotransmitter this tends to suppress neural function and results in sleep – in most circumstances.
- Several investigators have tried to define the paradoxical action of Zolpidem in patients in VS and MRS.
Actions of Zolpidem in VS and MRS

- SPECT scans, fMRI’s, proton magnetic resonance spectroscopy (Proton-MRS), PET scans and EEG’s have been used to explore the possible mechanism of action of Zolpidem in brain injured patients versus controls.

- Observations include:
  - Changes in metabolites in damaged areas of the brain
  - Increased blood flow in damaged areas of the brain
  - Improvements in patient’s EEG’s.
Case History #2 (Conclusion)

• MK was discharged on Zolpidem 10 mg via GT daily nearly 3 months after the initial dose.
• MK’s baseline level of functioning between doses of Zolpidem had risen so that he was now following simple instructions consistently and operating a communication device.
• At discharge Zolpidem continued to be beneficial as it increased alertness and improved his response time for 3 – 4 hours after a dose.
• 3 weeks following discharge MK had a generalized seizure and was placed on levetiracetam (Keppra) and clonazepam (Klonopin).

• His baseline level of functioning remained unchanged but Zolpidem now resulted in somnolence.

  *Clonazepam acts by enhancing the effect of GABA in the CNS*

• Zolpidem was subsequently discontinued without a change in his neurologic status.
• Conclusions:
  – Zolpidem is a neuroactive substance which occasionally has a paradoxical response in patients with brain injury (and possibly a variety of brain dysfunctions).
  – The mechanism of action in these cases is undefined.
  – Its most common adverse effect is somnolence.
  – Effectiveness, when present, is apparent within minutes.
  – Further research is needed.
Thank You
Case History #1 (RS)

- Surgeries included craniotomy, terminal ileocecal resection, ORIF of tibia, tracheostomy (subsequently decannulated), gastrostomy.
- CT scan 48 days post-injury revealed dilated ventricles and a VP shunt was placed.
- Upon admission to rehab had GCS of 7, Severe TBI, Possibly in a Minimally Responsive State.
- Her only admission medication was lansoprazole.
Case History #1 (RS)

- After a few months of neurosensory stimulation there is no change in RS’s status. She is admitted to our facility for discharge planning 5 months post-injury.

- What would you do next?

- We started amantadine 100 mg via GT daily in the a.m.
  - After 3 weeks (now 6 months post-injury) RS had increased spontaneous eye opening with some visual fixation and a question of visual tracking.
Case History #1 (RS)

• What would you do next?

• We started donepezil (Aricept) 5 mg via GT qhs.
  – Within 2 weeks RS begins to turn to voice and seemed more alert.
  – In 6 weeks (now 7 ½ months post-injury) RS is clearly more alert, visually tracking, consistently responding to simple commands, identifying pictures (e.g. cat vs. dog) with eye gaze, begins to take small amounts p.o.
  – In 3 months (9 months post-injury), RS is moving her arms and left leg purposefully, signaling “yes” and “no”, sequencing pictures into stories, recalling info from 24 hours previously.
  – She has poor endurance.
Case History #1 (RS)

• What would you do next?

• We started modafinil (Provigil) 100 mg via GT in a.m. to try to improve endurance.
  
  – Caused severe insomnia and dose was decreased to 50 mg daily

  – 1 week later RS had improved endurance w/o insomnia and was spelling on a spelling board, using a keyboard (haltingly), began communicating with friends via facebook.

  – Psychological assessment for possible mood disorder, 9 and ½ months post-injury. Expressive aphasia, memory impairment, possible depressed mood
Case History #1 (RS)

- What would you do next?

- We started sertraline (Zoloft) 50 mg qhs eventually increased to 100 mg. Discharged prior to potential impact of this change.

  – Phone follow-up nearly 2 years later.
    - Mother states RS “is there”, going to school, keeping up academically, physical disabilities still significant.
    - Donepezil (Aricept) used for a total of 6 months then discontinued without clinical consequence.


References


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