Agitation Management of the Traumatic Brain Injury Patient

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Disclosures

• None
Outline

- Definitions of post-traumatic agitation
- Pathophysiology
- Differential diagnosis/confounding factors
- Monitoring
- Treatment
  - Environmental
  - Pharmacologic
- Treatment overview
Rancho Los Amigos Levels of Cognitive Function

- I – No response
- II – Generalized response to stimulation
- III – Localized response to stimuli
- **IV – Confused and agitated**
- V – Confused and inappropriate (not agitated)
- VI – Confused and appropriate
- VII – Autonomic and appropriate
- VIII – Purposeful and appropriate
Is it required for recovery?

• Galaski et al (1994) studied 28 persons admitted to a brain injury unit with a primary diagnosis of stroke, trauma or anoxia
  – 39 % demonstrated aggressive behaviors in the first week of admission
  – Correlation between aggression, disorientation and severity of injury
Is it required for recovery?

• Brooke et al (1992): prospective study of 100 consecutive severe TBI admissions to rehabilitation
  – Only 11 of 100 demonstrated agitation by their definition
  – Most agitated patients’ behavior resolved in a week
  – 35 were found to be restless
Is it required for recovery?

• Kadyan et al (2004) studied 158 persons with TBI in an inpatient rehab setting
  – 50 % experienced agitation
  – Typically lasted <10 days
What is it?

• Hard to define but:
  “I know it when I see it”
  » Justice Potter Stewart, 1964
Survey of AAPM&R Brain Injury Special Interest Group (Fugate et al 1997)

- Physical aggression
- Explosive anger
- Increased psychomotor activity
- Impulsivity
- Verbal aggression
- Disorganized thinking
- Perceptual disturbances
- Reduced ability to maintain or shift attention
Akathisia

- Constant sense of inner restlessness
- Has been described in other populations:
  - Extrapyramidal side effect
- Does not require aggression
A definition

• Suggested definition of post traumatic agitation:

  “We suggest that post traumatic agitation be defined as a state of aggression during post-traumatic amnesia. This state occurs in the absence of other physical, medical or psychiatric causes. It can be manifested by intermittent or continuous verbal or physical behaviors....”

  -Lombard and Zafonte (2005)
Differential diagnosis or augmenting factors

• Drug/alcohol withdrawal
  – Alcohol w/d can occur 72 h after last drink
    • Hypertension, tachycardia, disorientation, tremors, agitation
  – Heroin w/d peaks at 24-48 h
    • Restlessness, abdominal pain, yawning
  – Benzodiazepine w/d in 2-7 d, may last weeks
    • Hypertension, tachycardia, diaphoresis, tremors, hyperthermia, seizures
Differential diagnosis or augmenting factors

- Seizures
- Hypoxia
- Hypoglycemia
- Infection/fever
- Sundowning
Measuring agitation

• Scales can be used to objectify agitation, monitor success [or failure] of interventions, monitor patterns of agitation

• Less than half of brain injury specialists use objective measurements of agitation (Fugate 1997)

• Angelino et al (2002) followed Agitated Behavior Scores (ABS) of a 16 yo from coma to wakefulness
  – ABS correlated appropriately both with behavior and with cognitive recovery
Agitated Behavior Scale

- Components each scored from 1 (behavior is absent) to 4 (present to an extreme degree)
- Score ranges from 14-56
- Score ≥ 21 defined to be agitated
- Has been shown to have good inter- and intra-rater reliability
Environmental issues

• Sleep
  – In the intensive care setting, constant stimulation may lead to day/night confusion
  – 50 % of persons admitted to TBI rehabilitation unit report difficulty sleeping (Clinchot et al 1998)
  – Suggest close monitoring of sleep cycles, quiet nighttime environment, breaks during the day, sleeping medications when necessary
Environmental issues

• Pain
  – Has been shown as a cause of agitation in demented elderly persons (Zieber et al, 2005)
  – Many different potential pain generators: other injuries (occult or otherwise), spasticity, heterotopic bone, tracheostomies, gastrostomy tubes, etc.
Environmental Issues

• Pain
  – If pain is an issue, consider using analgesic medications (maybe scheduled?) and monitor agitation
  – Reduction of unnecessary medical devices
Nonpharmacological management

• Overstimulation
  – Persons with TBI often become overwhelmed in distracting environments
    • Education of staff and families is key!!!!
    • Limit television use
    • Limiting number of visitors
    • Limiting visitors’ cell phone use
    • Quiet, isolated treatment areas - “Low-stim gym”
Nonpharmacological management

• Restraints
  – Minimally invasive: avoid direct-contact restraints (ie wrist restraints, vest restraints)
Nonpharmacological management

• Try to cover necessary tubing
  – “Out of sight, out of mind”

Abdominal binder to cover up PEG tubes

Sleeve to cover IV lines
Nonpharmacological management

• **1:1 Coach (not sitter) Criteria**
  – Harmful to self: pulling vital tubes, suicidal
  – Disruptive to other patients
  – Does not follow weight bearing, helmet precautions
  – Not manageable with enclosure bed
  – High elopement risk, unable to care for self
Aggression Management

Written behavioral plan: staff/family agreement

• Quantify acceptable and problematic behaviors
• Environment: special beds, time out, control stimuli
• Redirect behavior: physical activity with coach
• Minimize sedation
• Observe for complex seizures: stereotypic outbursts, large fluctuations in level of consciousness
• Co-Treat for protection
Pharmacological Treatment of Agitation
Pharmacological Treatment of Agitation

- Anticonvulsants
- Antidepressants
- Antipsychotics
- Benzodiazepines
- Beta-Blockers
- Lithium
- Neurostimulants
- Others
Anticonvulsants

• Valproic Acid
  – Used for mania in bipolar disorder
  – Dementia related agitation
    • Limited by side effect profile in Cochrane database review
Anticonvulsants: Valproic acid

• Case report of successful use in 16 year old with rapidly cycling affective disorder and a history of TBI at 4 years old (Monji et al 1999)
• Significantly reduced negative behaviors in 1-2 days in 5 persons with TBI related agitation that had not been controlled with other measures (Wroblewski et al 1997)
• Of 29 persons with TBI related agitation, 90 % responded with decreased agitation after valproic acid within 7 days of treatment (Chatham-Showalter et al, 2000)
Anticonvulsants: Valproic acid

• The good:
  – Rapid load of 10-20 mg/kg/day
  – Fast onset

• The bad:
  – Hepatotoxicity, thrombocytopenia, elevated ammonia levels
  – TBI patients metabolize faster, may need larger doses (Anderson et al, 1998)
Anticonvulsants: Valproic acid

• The questionable:
  – Previous evidence of neurocognitive slowing in epileptics and normal controls
  – No effects on neurocognitive testing seen in a double blinded study of 279 TBI patients who were given valproic acid for post-traumatic seizures
Anticonvulsants: Carbamazepine

• Successful use in a case series of 7 TBI rehabilitation inpatients with combativeness (Chatham-Showalter et al 1996)

• Open label study in 10 TBI patients with agitation (Azouvi et al 1999)
  – Measured ABS scores and MMSE
  – Good improvement in 5, modest in 3, none in 2
  – No decrease in mental status
  – Improved irritability and disinhibition
Anticonvulsants: Carbamazepine

• The bad:
  – Hyponatremia, renal failure, aplastic anemia
  – Slower titration than valproic acid
Anticonvulsants: Others

• Gabapentin reported to be helpful for dementia-related agitation
  – Case series reported paradoxical effects in 2 patients with TBI

• Lamotrigine and levetiracetam have been suggested
  – No studies at present
  – No blood levels to check
Antidepressants: Tricyclics

- Two groups:
  - More noradrenergic (protriptyline and desipramine) for hypoarousal
  - More serotonergic (amitriptyline and imipramine) more sedative

- Significant side effect profile:
  - Cardiac, lowered seizure threshold, significant sedation
Antidepressants: Tricyclics

• Success with amitriptyline in a patient with significant frontal lobe damage and aggression (Jackson et al, 1985)

• 12 out of 17 TBI patients responded well to amitriptyline (Mysiw et al 1988)
  – Worked best with those still in PTA
Antidepressants: SSRI

• SSRI used for several other symptoms in TBI patients:
  – Depression
  – Emotional lability
  – Hypoarousal (but questionable results)

• Less seizure and cardiac risk than tricyclics
Antidepressants: Sertraline

- Case series with Huntington’s disease showed decreased irritability and aggressive behaviors with sertraline (Ranen et al 1996)
- Open-label trial in 13 persons with TBI for 8 weeks resulted in reduced irritability and aggression, but no reduction in depression (Kant et al 1998)
- Fann et al (2007) found sertraline reduced depression and aggression in 15 outpatients with severe depression
Antidepressants: SSRI

• Timing to efficacy?
  – In depression, takes as long as 2 weeks for effect
  – Unclear timing for agitation treatment
Typical Antipsychotics

- Classified by predominant D2 receptor activity
- Longstanding use for immediate control of agitation due to psychiatric disturbance, sundowning, delirium, and brain injury related aggression
- Haloperidol has been commonly used
  - Rapid onset
  - IM, IV, PO administration
Typical Antipsychotics

• Stanislav and Childs (2000)
  – Prospective evaluation of 27 persons with TBI related agitation
  – Episodes treated with intramuscular droperidol
  – Time to achieve calming was shorter with droperidol than with haloperidol, lorazepam, and diphenhydramine
Typical Antipsychotics

- Maryniak et al. 2001
- Retrospective chart review of 120 persons with TBI in an inpatient rehabilitation unit
- 48% were treated with methotrimeprazine
- 2 had developed extrapyramidal symptoms
Typical Antipsychotics

• Patients treated with methotrimeprazine had
  – Longer lengths of stay
  – Longer time in PTA
• Sampling issue?
Antipsychotic concerns

- Animal study by Feeney et al found slowed motor recovery in an animal model of TBI
Antipsychotic concerns

• Stanislav (1997)
• Neuropsychological testing improved significantly 1 and 3 weeks after discontinuation of antipsychotics in subjects with TBI
• Effect was greatest in those taking thioridazine
Antipsychotics

Typical Antipsychotic

Atypical Antipsychotic
Atypical Antipsychotics

- Kim and Bijlani 2006
- Treatment of 7 subjects with aggression after sustaining a TBI with quetiapine in dosages ranging from 25 mg to 300 mg daily
- Overt Aggression Scale scores significantly decreased
- Noted improvement in cognitive functioning
Atypical Antipsychotics

• Noë et al. 2007
• Ziprasidone used in 5 persons with severe TBI and agitation
• Followed Agitated Behavior Scores
• Within 2 weeks ABS decreased from 27.2 to 18
• Treatment range of 35-68 days
• No side effects noted
Atypical Antipsychotics

• Silver et al. 2003
• Case report of an adolescent with anoxic brain injury and burns due to lightning strike
• Risperidone, in addition to amantidine and methylphenidate allowed for decreased restlessness and improved wound healing
Antipsychotic concerns

• Reports of neuroleptic malignant syndrome in persons with TBI:
  – Kadyan et al. 2003
  – Wilkinson et al. 1999
  – Vincent et al. 1986
Typical versus Atypical

- Groups were given daily injections of haloperidol, olanzapine, or vehicle and tested 11-15 days after injury
- Group treated with haloperidol performed significantly worse than vehicle-treated rats
- Olanzapine group did not show the decrement in performance seen in haloperidol group
Typical versus Atypical

• Kline et al 2007:
• Induced TBI in rats, who were then treated with either single doses or chronic treatment with haloperidol, risperidone or vehicle
• Single doses of either agent did not depress performance in beam walking or Morris water maze
• Daily doses of either risperidone or haloperidol did significantly reduce performance
• Deficits still present after a 3 day washout period
Benzodiazepines

• General indications
  – Sedation in intensive care unit
  – Sedation for surgical procedures (amnestic effect)
  – Alcohol or drug withdrawal
  – Acute mania
  – Treatment of neuroleptic-induced akathisia
  – Spasticity management
  – Acute seizures
Benzodiazepines

• Early and daily administration of diazepam impaired motor recovery in rats with cortical lesions (Schallert et al, 1986)

• Case series of 8 persons with a distant history of stroke given light sedation with midazolam had transient reappearance of neurologic symptoms (Lazar et al, 2002)
Benzodiazepines

- Elderly who take benzodiazepines regularly have a lower functional status (Reid et al 1998)
- Paradoxical agitation can be seen with administration
- Naturally cause an amnestic effect
Benzodiazepines

- Potential utility in TBI population
  - Alcohol withdrawal
  - Sedation for procedures
  - Emergency/rescue medication
- Other indications:
  - Alcohol withdrawal
  - Hyperadrenergic state
  - Neuroleptic induced akathisia
Beta blockers

• Low dose propranolol decreased agitation, aggression and wandering in demented patients (Shankle et al 1995)

• Lipophilic agents (propranolol, metoprolol) might be more centrally acting
Beta blockers

• Pindolol reduced violent behaviors in 8 out of 13 TBI patients in a placebo controlled trial (Greendyke et al 1989)
  – Reduced care needs in some due to improved behavior

• Cochrane database review cited beta blockers as having the best evidence for treatment of TBI related agitation (Fleminger et al 2003)
Lithium

• One of the oldest treatments for bipolar disorder
• Method of action is unclear
  – Alters sodium transport
  – Increases intracellular metabolism of catecholamines
  – Questionable DA blocking effects
Lithium

• Case report of 12 year old with agitation and hypomania treated with 6 month course of Lithium (Cohn et al 1977)

• 2 adults with severe post TBI agitation in state psychiatric facilities experienced a reduction of outbursts and need for other medications (Bellus et al, 1996)
Lithium

- 10 inpatient TBI rehabilitation patients were given lithium for severe aggression
  - 5 experienced a significant improvement with increased participation in rehabilitation
  - 3 had such significant side effects that they needed to discontinue it

Glenn et al. 1989
Lithium

• Side effects include:
  – Movement disorders, seizures, hypothyroidism, bradycardia, vomiting

• Toxicity level (>1.4 mEq/L) is very close to therapeutic range (0.6-1.2 mEq/L)

• Patients need close monitoring by practitioners experienced in titrating this medication
Neurostimulants

- Agents for enhancing awareness and cognition
- Perhaps helping focus and decreasing confusion leads to less agitation?
- Potential for overstimulation
- Caution for sleep disregulation with more activating agents
Neurostimulants

- Bromocriptine was shown to be helpful in the treatment of TBI associated akathisia in two case reports (Powell et al, 1996; Steward 1989)
  - Movement disorder as side effect
- The TBI related anger of 38 persons was significantly reduced with 30 mg methylphenidate daily (Mooney and Haas, 1993)
Neurostimulants: Amantadine

• Reduced agitation in 7 of 19 persons with dementia (Muller et al, 1979)
  – Significant side effects including overactivity, anxiety and visual hallucinations were seen in 8 of the subjects
• Several small case series in persons with TBI showed amantadine reduced agitation (Rosati 2002; Chandler et al 1988; Nickels et al 1994)
• In early survey of TBI specialists in the AAPM&R, amantadine was found to be the preferred agent for agitation in patients with TBI (Fugate et al, 1997)
Electroconvulsive therapy

• Case report of TBI patient with agitation unresponsive to pharmacological treatment
• Course of 6 brief-pulse treatments
• Improved participation in self care skills and response to medication
  – Kant et al 1995
Magnesium

- Suggested treatment for acute mania in bipolar disorder
  - Studies using IV drip
- Potential neuroprotective effects in animal models
- Issues with IV administration, side effects of bradycardia
ICU vs Rehab unit

• Goals of treatment of agitation in the ICU very different:
  – Protection of unstable fracture/spine/ET tube
  – ICP management
  – Pain can be a major factor
  – Confounding factors of withdrawal symptoms
  – Control often more important than alertness
    • Propofol
    • Short-acting benzodiazepines
    • Beta blockers
Identification of undesirable behaviors

Consideration of possible differential diagnosis:
- Drug withdrawal
- Infection
- Pain
- Hypoxia
- Seizure disorder

Assure good sleep cycle regulation

Consideration of environmental issues
- Low-stimulation environment
- Reduction of physical discomfort
- Reduction of lines/physical restraints
- Reorientation

Medication management
- Minimizing benzodiazepines and typical antipsychotic agents as possible
  - Anticonvulsants
    - Valproic acid (monitor liver function)
    - Tegretol (monitor Na levels)
  - Neurostimulants (i.e. amantadine)
  - Beta-blocker, especially if hyperadrenergic

And/or

Reassessment with objective measures
- Consider use of secondary agents
  - Atypical antipsychotics
  - SSRI
  - Lithium