Cognitive Effects of Opioid Therapy

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Cognitive Function
- Brain’s acquisition
- Information system
  - Processing
  - Storage
  - Retrieval
- Includes: dementia, delirium
- Not synonymous with level of consciousness

Prevalence
- Which population?
- How is it defined?
- Hospitalized oncology patients
  - 14-77%
- Palliative Care patients
  - 20-44%
  - Average 6-16 days before death

Significance of Cognitive Effects
- Quality of Life
  - Physical
  - Psychological
  - Sociological
  - Spiritual
- Fear
  - Opiophobia
  - Impact on prescribing behaviors
- Lack of Subjective Assessment

Delirium (DSM IV)
- A disturbance in consciousness and alertness with associated disturbance in the sleep wake cycle
  - Changes in cognition
  - Altered psychomotor activity
  - Emotional liability
  - Fluctuates during the day
  - Usually attributed to > 1 etiology
Dementia v Delirium

<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Course</td>
<td>Fluctuating</td>
<td>Steadily progressive</td>
</tr>
<tr>
<td>Consciousness &amp; orientation</td>
<td>Clouded, disoriented</td>
<td>Clear until late stages</td>
</tr>
<tr>
<td>Attention &amp; memory</td>
<td>Poor short term memory, inattention</td>
<td>Poor short term Memory without marked inattention</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Common</td>
<td>Less common</td>
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</tbody>
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Risk Factors for Delirium

- Diagnosis of dementia
- Advanced age
- Infection/sepsis
- Hospitalization
- Isolation/unfamiliar surroundings
- Surgery/post op status
- MI, CHF
- Acute blood loss
- Subcortical CVA
- Fluid / electrolytes
- Azotemia
- Constipation or diarrhea
- Fracture
- Sleep deprivation
- Malignancy
- ETCH/substance abuse
- Medications
- Unrelied pain

ACUTE CHANGE IN MS

- Antiparkinsonian drugs
- Corticosteroids
- Urinary incontinence drugs
- Theophylline
- Emptying drugs
- CV drugs
- H₂-blockers
- Antimicrobials
- NSAIDS
- Geropsychiatric drugs
- ENT drugs
- Insomnia drugs
- Narcotics
- Muscle relaxants
- Seizure drugs

Types of Delirium

- Hypoactive
  - Sedative, subtle
  - Associated with opioid initiation, dehydration
- Hyperactive
  - Agitation, neurotoxicity association (myoclonus, hyperalgesia, allodynia, perceptual disturbances)
  - Associated with chronic opioid use, metabolite accumulation

Pathophysiology

- Biochemical changes caused by the opioid
  - Alterations in neurotransmitters
- Opioid metabolites
- Renal impairment
- Lack of tolerance
- Hepatic impairment?

Assessment of Opioid-Induced Cognitive Effects
“One of the main reasons for missing the diagnosis of cognitive impairment or delirium is the failure to regularly conduct an objective cognitive assessment.”


Cognitive Assessment Scales

- Mini-mental State Examination
  - 11 questions
  - Orientation, Memory registration, Attention and Concentration, Memory recall, Language
- Confusion Assessment Method
  - 9 questions for the nurse to ponder
  - Diagnostic Algorithm: Acute Onset and Fluctuating Course, Inattention, Disorganized Thinking, Altered Level of Consciousness

Cognitive Assessment

- Mini-mental State Examination
  - Detection of cognitive deficits
- Confusion Assessment Method (CAM)
  - Brief assessment tool
- Memorial Delirium Assessment Scale (MDAS)
  - Measures the severity of delirium
- Delirium Rating Scale (DRS)
  - Severity scale


Driving Issues

- Quality of life issue
- N=24 cancer patients on stable doses of morphine and 25 pain free patients
- Morphine group performed more poorly
- No significant differences between two groups


Assessment Domains

- Awareness and interaction
- Cognitive capacity
- Thoughts and speech
- Perception
- Psychomotor activity
- Delusions
- Sleep pattern
- Emotional
- Temporality


Preventing Opioid-Related Cognitive Effects

- Quality of life issue
- N=24 cancer patients on stable doses of morphine and 25 pain free patients
- Morphine group performed more poorly
- No significant differences between two groups

Steps for Prevention

1. Ongoing cognitive assessment.
2. Start low and go slow.
3. Use benzodiazepines and psychotropic agents with caution.
4. Maintain adequate hydration if possible.
5. Choose opioids wisely!
6. Use adjuvants to decrease opioid requirements and provide better pain control.

Opioids – Impact on Cognitive Function

- Avoid the obvious
  - Meperidine, propoxyphene
- Morphine – metabolites M3G and M6G
- Hydromorphone – metabolite H3G ? role
- Fentanyl – case reports
- Methadone
  - Cumulative effect with protein binding may contribute to cognitive effects
  - Case reports of cognitive impairment

Morphine Metabolites

- Morphine-3-glucuronide (M3G)
  - conjugation accounts for over 50%
  - antagonizes analgesic effect of morphine and M6G
  - ? neurotoxic side effects
- Morphine-6-glucuronide (M6G)
  - conjugation accounts for over 5%
  - more potent analgesic activity than morphine
  - contributes to overall analgesic effect
- Higher concentrations of M3G and M6G after development of delirium

Morphine Metabolites

- Variable with route of administration
  - 1st pass hepatic glucuronidation higher M3G and M6G/morphine plasma concentration ratio
  - potentially more side effects with oral route
- Variable with repeated administration
  - results in accumulation of M6G and greater contribution to the analgesic effect and potentially more sedative side effects

Influence of Renal Impairment on Cognitive Function

- Role of renal excretion
  - elimination of active drugs and metabolites
- Morphine
  - elimination of morphine unimpaired
  - accumulation of M3G and M6G - related to creatinine clearance
- Contribution to cognitive impairment and overall side effects

Be Careful with Duragesic

- Advantages: easy route, ? constipation
- 25 mcg Duragesic = approximately 75 mg oral morphine
- Do not use on opioid naive patients!
- Elderly have higher fat: muscle ratio that can prolong the half-life of lipophilic drugs
- Naloxone drip needed for overdose
Methadone Advantages

- No known active metabolites
- Most of drug is protein bound resulting in a slow release - long duration of action
- NMDA activity may be beneficial to decrease tolerance – less drug titration and inhibit neuropathic pain
- Lack of known neurotoxic metabolites
- Cost effective


Methadone Disadvantages

- Large inter-individual variations
- Variations in individual patients from day to day and week to week!
- Methadone bound to Alpha 1-acid glycoprotein (AAG)
  - Can be displaced from AAG binding sites by propanolol, chlorpromazine, prochlorperazine, thioridazine, and imipramine enhance methadone effectiveness

Opioid Dosing and Titration

- Start low and go slow – especially in the elderly
- Perform titration after reaching steady state
  - Average 4-5 half-lives for IR opioids
  - Average 2-3 days for CR opioids (or >)
- Titrate 24 hour dose by 25-33%
- Keep breakthrough dose at approximately 10-20% - higher with severe incident pain
- Consider dose reduction for cross tolerance
  - 50-75% with good pain control
  - 0-25% with poor pain control


Management of Opioid-Related Cognitive Effects

Managing Hypoactive Delirium

- Use of psychostimulants
  - Methylphenidate
    - 2.5-5 mg doses upon initiation, especially elderly
  - Dextroamphetamine
  - Pemoline
  - Chewable tablets available, risk of hepatotoxicity
  - Modafinil
- Side effects: agitation, aggravation of perceptual disturbance

Managing Hyperactive Delirium

- Discontinue medications thought to exacerbate delirium
- Pharmacologic management
- Opioid rotation
- Route rotation
- Nursing interventions
- Family support

Pharmacologic Management

- Haloperidol
- Chlorpromazine
- Lorazepam
- Methotrimeprazine
- Midazolam
- Risperidone
- Olanzapine

Opioid Rotation

- Consider change in opioid if analgesia is ineffective after aggressive titration
- Consider change in opioid for deleterious side effects
  - Cognitive impairment
  - Nausea and vomiting
  - Constipation? – treat with softener/stimulant
  - Other

Morphine to Oxycodone

- Two randomized, double blind, crossover studies
- Improvement in mental state, sedation with oxycodone
- Less perceptual disturbance with oxycodone

Route and Cognitive Function

- 1st pass effect leads to greater accumulation of opioid metabolites
- As the route is closer to the opioid receptors, the dose decreases
  - Oral morphine 30 mg
  - Parenteral morphine 10 mg
  - Epidural morphine 1 mg
  - Intrathecal morphine 0.1 mg

Parenteral Opioid Rotation

- Use equianalgesic conversion chart as a guide
- Includes IV and subcutaneous routes
  - morphine, hydromorphone, fentanyl
- Determine hourly infusion rate
- Adjust rescue doses at 25-50% of hourly rate, higher for incident pain
- Rescue doses may be administered every 10-60 minutes
Spinal Anatomy

- Epidural Space
- Arachnoid Membrane
- Intrathecal Space (Subarachnoid Space)
- Dura
- Pia Mater
- Spinal Cord
- Nerve Root

Intraspinal Opioid Delivery Systems

- Implantable pump
- Tunnelled catheters
- Delivery to epidural or intrathecal space
- Improvement in mental clarity
- Improvement in sedation
- Potential improvement in comfort

Nursing Issues

- Loss of subjective input for symptom assessment
- Inability to provide informed consent
- Advance care planning
- Nurse:patient ratio
- Safety issues
- Use of restraints

Family Support

- Distress
- Anxiety
- Fatigue
- Home care issues – safety
- Reduced level of communication
- Overall impact on quality of life
- Family counseling and support groups

Case Study

- 68 year-old man
- Metastatic prostate cancer
- Active in the community
  - Fund raising
  - Symphony
  - American Cancer Society

Case Study – Problem of Pain

- Metastatic lesions throughout spine
  - Primarily lumbar and thoracic region
  - Hormone refractory
  - Undergoing radiation therapy

- Pain management
  - Implantable intrathecal pump 3 years - hydromorphone
  - Morphine CR 30 mg q 12 hours
  - MSIR 15 mg q 2-3 hours prn
Pain Crisis
- Acute exacerbation of pain during second day of XRT
- Opioid titration
  - 100 mg q 12 hours
  - MSIR 30 mg q 2-3 hours pm
- Other medications
  - Gabapentin 1200 mg/day
  - Celebrex 200 mg/day
  - Lexapro 10 mg/day

Delirium Crisis
- Acute cognitive changes 48 hours after opioid titration
  - Inattention, confusion, restlessness
  - Family up with patient throughout the night
  - Admitted to hospital
- Laboratory Values to Consider
  - Creatinine 1.4
  - Electrolytes: Na+ 145, K+ 4.8
- CT head negative

Assessment of Delirium
- Initial Medications
  - Haloperidol
  - Lorazepam
  - Morphine gtt
- Pain Consult
- Psychiatric Consult
- Assessment
  - Acute delirium related to rapid opioid titration
- Plan
  - Discontinue all medications
  - Begin olanzapine and hydromorphone

Outcome
- Mentation improved over the next week
  - 1st – restlessness subsided
  - 2nd – focus improved
  - 3rd – memory and interaction
- Patient resumed normal activities in the community within 6 weeks
- Patient died 6 months later

Happy Campers