Opioid-Induced Neurotoxicity in Hospice

Introduction[1,2]

Opioid-induced neurotoxicity, or OIN, is a term used to describe neuropsychiatric symptoms that can result from opioid use. This syndrome is thought to be caused by an accumulation of opioid metabolites, specifically binding to N-methyl-D-aspartate (NMDA) receptors causing a hyperactive state. Opioid-induced neurotoxicity symptoms mimic other disorders and therefore may be inappropriately managed.

Assessment[1-5]

Opioid-induced neurotoxicity typically develops within a few days to a week of initiating an opioid or surpassing a threshold dose of opioid that causes metabolite buildup. Opioid-induced neurotoxicity should be suspected when patients receiving opioids present with any of the following symptoms:

- Myoclonus – uncontrollable twitching and jerking of muscles, appearing at first during sleep and in severe cases progressing to seizures
- Hyperalgesia – (severe pain response to a stimulus that normally produces only mild pain response)
- Allodynia – (painful response to a stimulus (such as light touch) that is normally not painful)
- Worsening of pain despite escalating doses of opioids and/or pain becoming more diffuse
- Delirium – decreased consciousness and awareness, cognitive deficit, or perceptual disturbance

Risk Factors [1,4,6]

- Use of opioids with active metabolites, including morphine, codeine, meperidine, oxycodone, and hydromorphone (Fentanyl and methadone do not have active metabolites and are less likely to cause OIN)
- Large doses of opioids or rapid dose escalation
- Decreased renal function
- Advanced age
- Dehydration
- Drug-Drug interactions
    - CYP3A4 inhibitors increase morphine concentration, leading to heightened opioid effects (amiodarone, diltiazem, verapamil, grapefruit juice, antifungals)
    - Coadministration of psychoactive drugs (e.g., benzodiazepines, antipsychotics, phenothiazines) may exacerbate symptoms

Management[2,3]

- **Dose Reduction**
    - Recommendations suggest a 25% reduction in opioid dose
    - Ideal for patients with decreased renal function
    - If patient experiences increased discomfort, consider opioid rotation
- **Opioid Rotation**
    - Switch to an alternative opioid dose at 25-75% of the calculated equivalent dose (to account for incomplete cross tolerance)
    - Add breakthrough dose ~ 10-15% of daily dose every 1-2 hours as needed

- **Hydration**
  - Increasing hydration in a dehydrated patient can reverse symptoms of opioid neurotoxicity
  - Oral hydration is preferred for patients able to tolerate oral fluids; otherwise consider IV hydration at 30-50ml/hour
- **Adjuvant Medications**
  - Adjunctive medications are used to treat individual symptoms
    - Benzodiazepines (clonazepam, lorazepam, diazepam) to treat myoclonus
    - Alternatively, baclofen and cyclobenzaprine may also provide comfort
  - Addition of an NMDA antagonist (methadone or ketamine) can reduce opioid requirements for pain management – theoretically breaking the cycle of NMDA receptor stimulation

Implications for Hospice[2,5]

Opioid-induced neurotoxicity is a potential adverse effect of opioids but is often misdiagnosed. Physiological changes, disease progression, and concurrent medications increase the risk of developing opioid-induced neurotoxicity in hospice patients. Clinicians should be aware and carefully assess patients presenting with neuropsychiatric symptoms. Timely diagnosis and familiarity with management options is fundamental to minimizing discomfort and resolving symptoms.

References

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