OPIOID TOLERANCE AND WITHDRAWAL IN CRITICALLY ILL CHILDREN

Critically ill children routinely receive opioids for pain management. Prolonged opioid exposure frequently leads to hyperalgesia, tolerance and withdrawal, especially in this patient population because of developmental changes in physiology. This issue of CLIPS briefly summarizes a review article that evaluates tolerance and withdrawal from prolonged opioid use in critically ill children and recommends strategies for management and prevention. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Introduction

Prolonged opioid therapy leads to tolerance, defined as decreasing clinical effects of a drug, and withdrawal, a clinical syndrome that manifests after stopping or reversing a drug.

Appropriate pain management reduces responses to stress and improves clinical outcomes in pediatric patients, whereas inadequately treated pain may cause altered development.

Extensive opioid use following critical illness may cause tolerance resulting in adverse consequences that lead to prolonged ICU and hospital discharge.

The most commonly used analgesic/sedative drugs include morphine, fentanyl, midazolam, and lorazepam, none of which have been well studied in children.

Drug-related complications are likely unreported because opioids are often given in unstudied combinations, as continuous infusions, over extended times, or instead of periodic administration, as intended.

Opioid Induced Cellular Changes

Endogenous and exogenous opioid agonists elicit pharmacologic, physiologic or adverse effects by activating a variety of opioid receptors and their subtypes based on specific binding properties.

Opioid analgesia is mediated by the activation of inhibitory G proteins that ultimately reduce cyclic adenosine monophosphate (cAMP) levels by down-regulating adenylate cyclase (G_i), and hyperpolarization of the neuronal membrane by regulating a K^+ channels (G_o).

Hyperalgesia results from opioid receptors coupling to stimulatory G proteins (G_s), leading to neuronal activation via protein kinase A.

Tolerance results primarily from desensitization of receptors and cAMP upregulation, both of which occur by multiple mechanisms.

1. Neuronal protein kinases play a major role in opioid tolerance: activation of these systems results in opioid receptor phosphorylation, altered function of ion channels, increased expression of immediate early genes (e.g., FosB), and inducible nitric oxide synthase.
2. Different opioid agents produce variable effects on these mechanisms, and therefore have variable potentials for producing opioid tolerance (e.g., fentanyl>morphine>methadone).

Pharmacogenetics of Analgesia and Tolerance

Genetic variations affect different aspects of nociception, analgesia, and opioid metabolism/transport, and may explain differences in analgesic requirements in critically ill children.

The opioid receptors, transport proteins, intracellular signaling proteins and metabolic enzymes involved in opioid analgesia and tolerance contain thousands of single-nucleotide polymorphisms (SNPs).

Development of Tolerance to Opioids

Most factors that affect the development of opioid tolerance have not been investigated in children, with the exception of duration of therapy.

Opioid receptor occupancy less than 72 hours rarely causes tolerance.

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**Development of Tolerance to Opioids**

- Infants in early development have greater vulnerability to opioid tolerance.
  - Preterm newborns develop tolerance earlier and metabolize morphine to morphine-3-gulcuronide (M3G), with anti-opioid effects; while term neonates have more prominent signs of withdrawal and form M6G, with analgesic effects.
- Tolerance is more likely to develop in males than in females.
- Greater tolerance develops with synthetic or short-acting opioids; less tolerance occurs with drugs that cause opioid receptor internalization, decreased receptor phosphorylation by G protein-coupled kinases, and downregulation of receptors.

**Clinical Management Strategies for Tolerance and Withdrawal**

- Validated methods for the assessment of withdrawal in children are scarce. The 12-item Withdrawal Assessment Tool (WAT-1) has shown the greatest promise for assessing opioid withdrawal in children because of its empirical development, ease of bedside use, and psychometric properties.
- Opioid withdrawal must be aggressively treated, combining pharmacologic, environmental, and nursing care to reduce symptoms, suffering, and complications. The mainstay of management is gradual opioid weaning.
- Pharmacological strategies for treatment of opioid withdrawal are included in the table below.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism for Treatment of Opioid Withdrawal</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Methadone</td>
<td>Opioid analgesic, with a prolonged half-life and multiple mechanisms to inhibit tolerance</td>
<td>Effective in pediatric patients; used increasingly for withdrawal in children</td>
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<tr>
<td>Buprenorphine</td>
<td>Long acting μ-opioid partial agonist, with potent analgesic properties and naloxone-reversible respiratory depression</td>
<td>Used as a high dose methadone substitute; not studied in children</td>
</tr>
<tr>
<td>Clonidine</td>
<td>α2-adrenergic agonist, with potent analgesic effects</td>
<td>Has been used to treat opioid withdrawal in neonates, adolescents and adults; but not in critically ill children</td>
</tr>
<tr>
<td>Dexamethomidine</td>
<td>α2-adrenergic agonist, with eightfold greater affinity than clonidine</td>
<td>Initial reports suggest usefulness for preventing withdrawal in adults, with increasing experience in PICU patients; additional studies needed in pediatric populations</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Anticonvulsant; also acts on α2-Δ calcium channels to decrease neuropathic pain</td>
<td>Shows promise in adults; but has not been tested in children</td>
</tr>
<tr>
<td>Propofol</td>
<td>General anesthetic; preclinical and clinical studies suggests usefulness for preventing benzodiazepine and opioid withdrawal</td>
<td>Facilitated rapid weaning and successful extubation in 11 children who required mechanical ventilation</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Opioid analgesic; case reports suggests usefulness in treating morphine-induced opioid tolerance</td>
<td>Little cross-tolerance between morphine and propoxyphene; further evidence required before clinical use</td>
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- Strategies for the prevention of opioid tolerance include:
  - Nurse-controlled sedation management protocols
    - Epidural and other neuraxial analgesia
    - Sequential rotation of analgesics/sedatives
    - Daily interruption of sedative infusions
    - Other promising but experimental therapies such as concomitant infusion of opioid agonists and NMDA antagonists, continuous infusions of opioid agonists and low-dose naloxone, noncompetitive NMDA antagonists, nitric oxide synthase inhibitors and SSRIs

**Recommendations**

- Prevention and delay of opioid tolerance can improve analgesic efficacy, avoid secondary complications, hasten recovery, and reduce prolonged ICU support in critically ill children.
- Specific recommendations to achieve these goals:
  - Match opioid doses to pain intensity, titrate to adequate analgesia and adjust to minimum effective dose.
  - Use short-acting agents for procedural/breakthrough pain and long-acting agents for prolonged/chronic pain.
  - Avoid opioids for sedation/motion control only and utilize intermittent doses of long-acting opioids.
  - Assess patients for opioid withdrawal and manage by gradual opioid weaning, environmental, nursing support and treatment with methadone, clonidine or both, or alternative therapies.
  - Prevent tolerance with practical approaches such as nurse-controlled sedation or analgesic rotation.

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