Opioid Tolerance and Dependence in Infants and Children

Julia C. Finkel, MD
Associate Professor of Anesthesiology and Pediatrics
George Washington University Medical Center
Director, Anesthesia Pain Management Service
Children's National Medical Center

Objectives: This lecture will:
1) Review the cellular and molecular mechanisms underlying opioid analgesia, tolerance and dependence to identify potential therapeutic targets that may be used to attenuate the occurrence of iatrogenic induced tolerance and to manage withdrawal.
2) Examine factors affecting the onset of tolerance
3) Review available assessment techniques
4) Review current and investigational strategies to avoid tolerance and manage withdrawal

Introduction:
Opioid tolerance, dependence, and consequently, withdrawal has emerged as a significant issue in ECMO, NICU, and PICU patients as a result of prolonged opioid administration for the well recognized benefits of the impact on stress response, enhanced ventilator synchrony and a general need for sedation.

Definitions:
Tolerance is the decreased pharmacological effect occurring after repeated exposures or by increasing dose requirements to achieve the same effect. It results from cellular adaptations to the drug. Tolerance does not reflect a change in drug metabolism.
Dependence is a physiologic state where continued administration of the drug is necessary to prevent withdrawal.
Addiction represents a complex behavior characterized by the compulsive use of a drug. The use of opioids for analgesia or sedation does not result in psychological dependence or addiction.

Epidemiology:
There are several clinical reports that indicate that the incidence of iatrogenic induced opioid withdrawal approaches 60% (1-3)

Cellular and Molecular Mechanisms:
Opioids act by binding to opioid receptors (subtypes μ,δ,κ) located on neuronal and other cell types. Signal transduction from opioid receptors occurs via binding to G-proteins (inhibitory Gi and Go or stimulatory Gs). The important difference between Gs and Gi/o coupled proteins is their susceptibility to widely different concentrations of opioid agonists and antagonists with the inhibitory G-proteins being stimulated at nanomolar-micromolar concentrations of agonist or antagonist (clinically relevant analgesic concentrations) and the Gs proteins being stimulated at picomolar concentrations of agonist or antagonist. (4,5)

An analgesic cascade results when an opioid agonist (at μmolar concentrations) binds with its receptor, which then undergoes a conformational change and couples with the inhibitory Gi/o proteins which serve to regulate ion channels and activate membrane-bound (phospholipase A2) and cytosolic enzymes (adenyl cyclase, neuronal nitric oxide synthase). The Gi-coupled receptor leads to downregulation of adenyl cyclase and cAMP levels. Activation of the Go-protein regulates an internally rectifying K+ channel and neuronal nitric oxide synthase (nNOS). The 12-lipoxygenase products stimulate the K+ channels. The decrease in cAMP and NO production affect a decrease in the action potential duration and a decrease in neurotransmitter release. Activation of these intracellular events results analgesia.(6,7)

A tolerance/hyperalgesia cascade occurs at a thousand fold lower (pM-nM) concentrations, Opioid agonists have been shown to elicit an excitatory affect mediated by activation of the Gs-proteins which up-regulate adenyl cyclase and increase cAMP which activates protein kinase A(PKA) second messenger system.(8) It has been shown that opioid receptors can be interconverted between inhibitory Gi/Go-coupled and excitatory Gs coupled modes following physiologic changes in the concentration of in the concentration of the GM1 ganglioside.(9,10) GM1 is a glycoprotein which is ubiquitous on the surface of neuronal cell membranes and is synthesized by a cAMP/PKA dependent glycosyltransferase. These processes provide a positive feedback phosphorylation cycle which increase Ca^{++} conduction, decrease k+ conduction increase the action potential duration, neurotransmitter release resulting in the excitatory effects counteracting the inhibitory effects and resulting in tolerance and hyperalgesia. (5)

With chronic opioid administration there are neuro-adaptive changes which are mediated by protein kinase systems. (e.g. PKC, PKA) Opioid receptor desensitization appears to be related to down-regulation, internalization and uncoupling from inhibitory G-proteins. There are differences in the desensitization of opioid receptors between various opioid agonists MSO4 vs. methadone). There is evidence that the mechanisms underlying acute vs. chronic opioid treatment –induced uncoupling from G-proteins may be different with PKA-mediated phosphorylation causing uncoupling of opioid receptors following chronic opioid therapy and PKC-mediated phosphorylation occurs following acute opioid exposure.(11) Up-regulation of the cAMP pathway as a result of supersensitization of adenyl cyclase is a well-established factor in opioid tolerance and dependence. (11)

The NMDA receptor also contributes to opioid tolerance and dependence through upregulation of PKC. Chronic opioid treatment leads to PKC activation and translocation, which phosphorylates the NMDA receptor, gated Ca^{++} channel. This results in the removal of the Mg++ blockade and potentiation of the NMDA receptor. The opening of the Ca+2 channel allows for Ca^{++} influx, which produces a positive feedback loop of amplified responses and further activation of PKC. This in turn, induces iNOS which increases the production of NO and superoxide which can promote neuronal dysfunction by inducing nuclear repair enzymes.(12) Production of NO leads to greater glutamate release in surrounding cells which further stimulates NMDA receptors on surrounding cells. (11)

Factors Affecting Opioid Tolerance

1. Duration of Opioid Receptor Occupancy. The extent of the drug effect is determined by the duration of action and the dosing interval. About 4 hours appears to be necessary for the full development of the biochemical processes involve in the development of acute tolerance to develop.(13) Clinically, withdrawals symptoms tend not appear with administrations lasting less than 72 hours.(14)
2. Tolerance may occur more rapidly with continuous infusions than with intermittent boluses.(15)
3. Synthetic opioids may induce tolerance more rapidly.(13)
4. Pharmacokinetic/developmental factors: MSO4 is metabolized to pro-algesic M3G and analgesic M6G. In premature infants, MSO4 is metabolized primarily to M3G which may accelerate the onset of tolerance.

Clinical Evaluation of Opioid Withdrawal

Clinical Presentation: Abstinence syndromes include neurologic excitability; gastrointestinal dysfunction, autonomic signs, endocrine abnormalities and poor sleep organization (e.g. increased frequency of REM sleep). (16)

Withdrawal Evaluation Tools:
Several scoring systems have been devised to help guide the management of weaning from opioids. Those used in pediatrics were generally described and evaluated in the management of infants of opioid addicted mothers and were not validated in infants and children with iatrogenic opioid tolerance, though the scale described is used most frequently. The Neonatal Abstinence Score is based on nursing observations of acute opioid withdrawal in neonates.(17)

Risk of Withdrawal

1. Related to "tolerogenic" potential of the opioid (fentanyl> morphine > methadone > etorphine). (11)
2. Cumulative dose and duration of administration of the opioid are predictive. Fentanyl >1.5mg /kg or 300mcg/kg/day for 5 days place a patient at 50% risk of withdrawal. A total dose of 2.5 mg/kg or 300 mcg/kg day for greater than 9 days presented a 100% risk of withdrawal.(18)

Prevention of Withdrawal

Conventional strategies:

1. Slow weaning of the opioid.
   For short-term infusions (<3-5 days) this can be done rapidly by 10-15% reductions every 8 hrs as tolerated.
   Long term, high dose infusions require protracted weans of up to 2-4 weeks. When patients are requiring fentanyl, 50 mcg/kg/hr, the tolerated decrement is only about 1 mcg/kg/hr, which is impractical if the patient no longer requires the ICU. Various clinical strategies that have been described include: oral morphine(19), methadone(20), clonidine(21), and subcutaneous fentanyl.(22)

Of these techniques, IV and oral methadone are the most commonly implemented.

When calculating the oral methadone /fentanyl equivalent, 3 times the total daily fentanyl dose (mg) is equivalent to the methadone dose/day(mg). To initiate the wean, 2.4 times the daily fentanyl dose may be used and divided over a q8h schedule. This dose is then reduced by 10-20% every 2-4 days as tolerated.

Investigational Strategies for Preventing Tolerance and Managing Withdrawal

The investigational techniques being examined target the molecular mechanisms know to cause tolerance.

1. Concomitant infusions of opioid and NMDA antagonists.(23) Low dose ketamine(0.1 mg/kg/hr), dextromethorphan and amantadine are being clinically examined.(24,25) These agents can also be implemented to mitigate withdrawal symptoms.
2. Concomitant infusion of opioid agonist and ultra-low dose antagonist (naloxone).(4,5)
3. Use of NOS inhibitors (e.g. 7-NI, a selective NOS1 inhibitor).(26)
4. Opioid rotation. This practice can slow the onset of tolerance since not all opioids cause an increase in cAMP activity (MSO4), but instead, induce tolerance via desensitization (methadone). Oxycodone also has activity at the κ receptor.(27)
5. Dexmedetomidine: An α_2 agonist used to ameliorate opioid withdrawal symptoms.(28,29)

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