Pharmacologic Management of Pain in Infants and Children: Opioids and NSAIDs

Julia C. Finkel, MD
Associate Professor of Anesthesiology and Pediatrics
George Washington University
Vice Chief for Pain Medicine and Research
Division of Anesthesiology and Pain Medicine
Children's National Medical Center

A. Opioids

Objectives: This review 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
5) Outline the use of various opioids and NSAIDs

Introduction:
Opioid tolerance and 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 □.□.□ 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 pM concentrations of agonist or antagonist. (4,5)

An analgesic cascade results when an opioid agonist (at □molar 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. 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 MSO_4 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 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 po 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 (MSO_4), but instead, induce tolerance via desensitization(methadone). Oxycodone also has activity at the receptor.(27)

References:

1. Tobias JD, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit Intensive Care Med, 1994: 504-7.
2. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion, 1994.
3. Tobias JD, Schleien CL, Haun SE. Methadone as treatment for iatrogenic narcotic dependency in pediatric intensive care unit patients Crit Care Med, 1990:1292-3.
4. Crain SM, Shen KF. Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment Proc Natl Acad Sci U S A, 1995:10540-4.
5. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability Pain, 2000:121-31.
6. Crain SM, Shen KF. Modulatory effects of Gs-coupled excitatory opioid receptor functions on opioid analgesia, tolerance, and dependence Neurochem Res, 1996:1347-51.
7. Suresh S, Anand KJ. Opioid tolerance in neonates: mechanisms, diagnosis, assessment, and management Semin Perinatol, 1998:425-33.
8. Avidor-Reiss T, Bayewitch M, Levy R et al. Adenylylcyclase supersensitization in mu-opioid receptor-transfected Chinese hamster ovary cells following chronic opioid treatment J Biol Chem, 1995:29732-8.
9. Wu G, Lu ZH, Wei TJ et al. The role of GM1 ganglioside in regulating excitatory opioid effects Ann N Y Acad Sci, 1998:126-38.
10. Wu G, Lu ZH, Ledeen RW. Interaction of the delta-opioid receptor with GM1 ganglioside: conversion from inhibitory to excitatory mode Brain Res Mol Brain Res, 1997:341-6.
11. Liu JG, Anand KJ. Protein kinases modulate the cellular adaptations associated with opioid tolerance and dependence Brain Res Brain Res Rev, 2001:1-19.
12. Mayer DJ, Mao J, Holt J, Price DD. Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions Proc Natl Acad Sci U S A, 1999:7731-6.
13. Hovav E, Weinstock M. Temporal factors influencing the development of acute tolerance to opiates. J Pharmacol Exp Ther 1987;242:251-6.

14. Anand KJ, Barton BA, McIntosh N et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med 1999;153:331-8.
15. Dewey WL. Various factors which affect the rate of development of tolerance and physical dependence to abused drugs. NIDA Res Monogr 1984;54:39-49.
16. Anand KJ, Arnold JH. Opioid tolerance and dependence in infants and children. Crit Care Med 1994;22:334-42.
17. Kron RE, Finnegan LP, Kaplan SL et al. The assessment of behavioral change in infants undergoing narcotic withdrawal: comparative data from clinical and objective methods. Addict Dis 1975;2:257-75.
18. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med 1994;22:763-7.
19. Yaster M, Kost-Byerly S, Berde C, Billet C. The management of opioid and benzodiazepine dependence in infants, children, and adolescents. Pediatrics 1996;98:135-40.
20. Tobias JD, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. Intensive Care Med 1994;20:504-7.
21. Deutsch ES, Nadkarni VM. Clonidine prophylaxis for narcotic and sedative withdrawal syndrome following laryngotracheal reconstruction. Arch Otolaryngol Head Neck Surg 1996;122:1234-8.
22. Tobias JD. Subcutaneous administration of fentanyl and midazolam to prevent withdrawal after prolonged sedation in children. Crit Care Med 1999;27:2262-5.
23. Elliott K, Kest B, Man A et al. N-methyl-D-aspartate (NMDA) receptors, mu and kappa opioid tolerance, and perspectives on new analgesic drug development. Neuropsychopharmacology 1995;13:347-56.
24. Elliott KJ, Brodsky M, Hyanansky A et al. Dextromethorphan shows efficacy in experimental pain (nociception) and opioid tolerance. Neurology 1995;45:S66-8.
25. Suresh S, Anand KJ. Opioid tolerance in neonates: a state-of-the-art review. Paediatr Anaesth 2001;11:511-21.
26. Herman BH, Vocci F, Bridge P. The effects of NMDA receptor antagonists and nitric oxide synthase inhibitors on opioid tolerance and withdrawal. Medication development issues for opiate addiction. Neuropsychopharmacology 1995;13:269-93.
27. Ross FB, Smith MT. The intrinsic antinociceptive effects of oxycodone appear to be kappa-opioid receptor mediated. Pain 1997;73:151-7.

Oral opioid Use:

Oral Opioid Analgesia
Codeine, Oxycodone, Hydrocodone, Methadone, MSO_4

Typically used when transitioning from parenteral opioids in inpatients and for postoperative and chronic pain management. They are frequently used in combination with acetaminophen or NSAID.

Oral administration of opioids is confounded by the interindividual variation in bioavailability of drug which makes equianalgesic conversation or assumptions about equipotent between agents ("MSO_4" equivalents) impossible. They are all agonist at the μ opioid receptor. The consideration made in choosing one or another would include formulation (liquid vs. tablet) combination with acetaminophen or NSAID and potency in patients requiring higher dose and tolerability.

Adverse effects within this group and are similar for equipotent dose given and is dose related. With the preparation that come in fixed combination with acetaminophen, aspirin or ibuprofen, these NSAIDs but not exceeds recommended doses in those whose requirements have escalated.

<u>Codeine</u>:
Most commonly used oral opioid in pediatrics. Rapidly absorbed from GI tract. PO bioavailability of 60 to 70%. Peak serum concentration 1-2h. 10% undergoes hepatic demethylation to morphine MSO_4, though 10-20% of the population lacks the enzyme for demethylation. It is available as a elixir and in tablet form. Dose 0.8-1 mg/kg q 4h.

<u>Oxycodone and Hydrocodone</u>:
Semisynthetic opioids. PO bioavailability 50-60%. Peak serum concentration reached 1-2h t ½ β 2.5 to 4h. Dose 0.1 mg/kg q 3-4h. Hydrocodone comes as an elixir in combination with acetaminophen (167mg acetaminophen/2.5 mg per 5 ml). OxyContin q 12 hr sustained release available in 10,20,40,& 80 mg tablets. Must be swallowed whole and not crushed.

<u>MSO_4</u>
Frequently used in oncology population. Bioavailability 15-64%. Doses (not approved for Peds). Moderate to severe pain 0.2 to 0.5 mg/kg/dose q 4-6h (immediate release), 0.3-0.6 mg/kg/dose po q 12h (controlled release).

References:
1. Kalso E. Vainco A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 1990;47:649-646.
2. Beaver WT, Wallenstein SL, Rogers A, et al. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular codeine and of oral with intramuscular oxycodone. J Clin Pharm Ther 1978;207:92-100.

Methadone:

A synthetic opioid agonist with unique properties that make it suitable for acute perioperatve use, chronic pain therapy and possibly the most suitable opioid to use when addressing neuropathic pain because of the d-isomers inhibitory activity at the NMDA receptor.

The analgesic half-life is 4-6h with single dose but the duration may be increased to 12h with chronic dosing. The plasma half-life is 15-60h with outliers to 120h. It has a large V_D and is 60-90% protein bound to AAG.

The range of oral methadone administered to hospitalized children with cancer pain or with injuries due to trauma in one series of 180 was 0.1- 1.1 mg/kg /day[1]. In another series of children < 10 yr of age, the initial daily dose of methadone ranged from 0.2-0.4 mg/kg b.i.d.-t.i.d. with a max of 1 mg/kg/day[2].

Tramadol HCl:

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. Its mechanism of action, however, is tri-fold and not strictly that of an opioid. Tramadol and the only pharmacologically active M_1 metabolite posses a weak affinity for the m-opioid receptor and has a reuptake inhibitory effect on serotonin and noradrenaline (NA). Increased synaptic levels of 5-HT decrease excitability of spinal nociceptive activity and the NA antinociceptive effect is via alpha-2 adrenoreceptor mechanisms.(1,2) Tramadol has been postulated to also have a peripheral analgesic effect because of its ability to decrease propofol injection pain.[3] The synergism of opioid and monoaminergic mechanisms results in a significant reduction in the side effects profile relative to opioids and extends the analgesic benefit to opioid insensitive pain.(2)

In the U.S., tramadol is only formulated as a 50 mg tablet though virtually everywhere else in the world, it is available in po liquid, iv and suppository form. Many of the studies done to date in children have been done outside the U.S. using these other formulations. A po liquid formulation is anticipated in this country in the near future. FDA trials for pediatric labeling have been completed over this past year.

Pharmacokinetics: (following oral absorption in adults)

Bioavailability is 20% following single dose and 90% in multiple dose studies. Peak serum concentration occur within 2h. V_D is 306 l. The elimination half-life is 5h for tramadol and 9h for the M_1 metabolite.(4) The drug is metabolized in the liver (~85%) and is renally excreted (90%).

Adverse effects:

Tramadol is generally well tolerated in clinical trials. The most common side effects reported are (1.6-6.1% incidence), nausea (more with IV than po), dizziness, drowsiness, sweating, vomiting and dry mouth.(5)

The incidence of side effects with tramadol children is significantly less than in adults.(6) Tramadol should not be used in patients receiving MAO inhibitors because of its monoamine uptake inhibition.

Based on studies done outside the U.S. in children ≥ 12 mos, a dose of 1-2 mg/kg po q 4-6h is used (max 8 mg/kg/day).(7,8,9) Results of a recently completed multicenter trial examining tramadol 1-2 mg/kg in children and adolescence ages 7-16 revealed a side effect profile of vomiting 10%, nausea 9%, pruritus 7% and rash 4%.(Anesthesiology 2001;95:A1233)

Dose: Efficacy has been demonstrated with a dose of 1-2 mg/kg every 6h with a maximum of 8 mg/kg/day. In the above mentioned trial comparing 1 vs. 2 mg/kg po in postoperative patients ages 7-16, the 2mg/kg group required 50% less rescue opioid. (Anesthesiology 2001;95:A1232)

Tramadol promising analgesic for both acute and chronic pediatric pain management given its low side effect profile relative to opioids and NSAIDs and as new formulation are made available in the U.S., its versatility of use in this population will expand.

References:

1. Schug SA, Dickenson AH, Strauburger W, et al.: Current concepts on the mechanisms of action of tramadol. In: Abstract Booklet on Symposium "Current concepts on the mechanisms of action of tramadol". 9th World Congress on Pain, Austria Center Vienna, 25 August 1999.
2. Shipton EA: Tramadol-Present and Future. Anaesth Intensive Care 2000;28:363-374.
3. Pang WW, Huang PY, Chang DP, Huang MH. The peripheral analgesic effect of tramadol in reducing propofol injection pain: a comparison with lidocaine. Reg Anesth Pain Med 1999;24:246-249.
4. Daver P, Desmeules J, Collart L: Pharmacology of tramadol. Drugs 1997;53(Suppl 2):18-24.
5. Scott LJ, Perry CM: Tramadol: A review of its use in perioperative pain. Drugs 2000;60(1):139-176.
6. Ratcliffe S, Repas C. A comparison of adverse effects of tramadol in children and adults. 3rd International Symposium of Paediatric Pain 1994;182.

7. Bamigbade TA, Langford RM: The clinical use of tramadol hydrochloride. Pain Reviews 1998;5:155-182.
8. Bosenberg A, Ratcliffe S: The respiratory effects of tramadol in children under halothane anaesthesia. Anaesthesia 1998;53:960-964.
9. Barsoum MW. Comparison of the efficacy and tolerability of tramadol, pethidine, and nalbuphine in children with postoperative pain. Clin Drug Invest 1995;9:183-190.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

Though many NSAIDs do not have appropriate pediatric labeling, they experience widespread use in the pediatric population. The MSO_4-sparing effect is approximately 30%.

NSAIDs non-selectively inhibit cyclooxygenase which is necessary for the conversion of arachidonic acid to prostaglandins. Disruption for this process reduces the prostaglandins mediating inflammation as well as those involved with homeostatic functions such as platelet aggregation, renal blood flow and prostaglandin mediated protection of the gastric mucosa which accounts for all the attendant risks of using NSAIDs.

Pharmacokinetics:

In general, all NSAIDs are rapidly absorbed orally. Peak plasma concentrations occur within 2-3h. They are highly protein bound to albumin and are oxidized by the liver by cytochrome P-450 or conjugated by glucuronide.

Individual Drugs:

The most commonly used agents are:

Ibuprofen has an antipyretic and anti-inflammatory effect in children at a dose of 5-10 mg/kg (max daily dose 40 mg/kg/day) and is given on a q 6h schedule. It comes in tablet and liquid form which makes it useful as part of a preoperative premed in young children.

Naproxen is given as 5-7.5 mg/kg bid (max daily dose 15 mg/kg/day).

Ketorolac is available as an intravenous injection, and 10 mg tablets. The optimum dose of oral ketorolac in children is not known. Its bioavailability of 80%, suggests that 1mg/kg should establish a serum concentration similar to a 0.25 to 0.5 mg/kg IV bolus.

Recommended Reviews:

Morris, JL, Rosen, DA, Rosen KR. Nonsteroidal Anti-Inflammatory Agents in Neonates. Pediatr Drugs 2003:5(6): 365-405

Kokki, H.Nonsteroidal anti-inflammatory drugs for postoperative pain: a focus on children. Pediatr Drugs 2003:5(2):103-123

Litalien, C.Jacqz-Aigrain, E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. Pediatr Drugs 2001:3(11): 817-858