Non-Opioid Analgesics & Adjunctive Medications

PEDIATRIC PAIN MANAGEMENT

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Symptom-Focused
- Pruritus
  - Opioid-Induced
  - Non-Opioid
- Nausea
Approach to Pediatric Pain Management

Multimodal Approach to Management of Pain

- Opioids previously considered foundation of pain management
  ‣ Now a single component of holistic therapeutic planning
COX Inhibitors

Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- **Mechanism of Action**
  - Cyclooxygenase (COX, prostaglandin-endoperoxide synthase)
    - Metabolism of arachidonic acid → prostanoids [prostaglandins (inflammation) and thromboxanes (clotting)]
      - Sensitization of peripheral nerve endings
      - Vasodilation: inflammatory response-associated erythema & edema
    - COX-1:
      - Present in both healthy and diseased states. Integral role in mediation of physiologic functions (gastric mucosa protection, renal blood flow regulation, platelet aggregation)
      - Inhibition leads to unwanted effects associated with NSAIDs: gastric ulceration, coagulation disturbance, renal blood flow compromise, bronchoconstriction
    - COX-2:
      - Inducible isozyme produced in response to trauma or inflammation
      - Inhibition → therapeutic effects of COX inhibitors
Acetaminophen

- Most common antipyretic and analgesic medication currently used in pediatrics
  - Higher utilization since ASA found to be known contributor to Reye’s syndrome
  - Low side effect profile; analgesic and antipyretic efficacy
- Para-aminophenol derivative
- Analgesic and antipyretic effects
  - 1° effects via central COX inhibition
    - Prevents COX activation by reducing heme at its peroxidase site without directly binding or inhibiting cyclooxygenase
    - Avoid peripheral side effects of COX inhibition
      - GI ulceration, renal impairment, platelet impairment
    - Lack of peripheral anti-inflammatory action
  - Additional effects via both central & peripheral mechanisms
    - Action on the opioidergic system
      - Altered dynorphin release
      - Kappa receptor function
    - Noradrenergic and serotonergic activity
    - NO inhibition
    - NMDA release inhibition
### Acetaminophen

- Therapeutic dosing (results in goal serum levels of 10-20μg/mL)
  - IV dosing lacking evidence for significant benefit over PO aside from specific circumstances (gastrointestinal compromise)

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<th>Route</th>
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<th>Dose</th>
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<th>Max Daily Dose</th>
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Acetaminophen and Acute Hepatic Failure

- Acetaminophen toxicity
  - Most common cause of acute liver failure in US
  - Up to 500 annual cases of unintentional overdose → acute liver failure
    - ~150 deaths per year [Fontana]
  - Acute hepatic failure: severe, acute liver injury with encephalopathy & impaired synthetic function (INR ≥1.5) in patient without cirrhosis or preexisting liver disease & with illness duration <26 weeks

- Hepatic metabolism: primarily non-toxic, inactive metabolites excreted by the kidneys
  - Glucuronidation (45-55%), Sulfate conjugation (20-30%), N-hydroxylation and dehydration, typically followed by glutathione conjugation
    - N-acetyl-p-benzoquinone imine (NAPQI): intermediate toxic metabolite
      - Therapeutic doses: NAPQI detoxified 1° by glutathione conjugation (min. oxidation by cytochrome P450)
      - Overdose: overwhelmed glutathione pathway → enhanced oxidation → high levels of oxidation byproducts → fulminant hepatic failure & necrosis
Acetaminophen and Acute Hepatic Failure

- Dosing in Pediatrics [Dimitropoulos]:
  - Do not exceed 50 to 70 mg/kg in 24 hours
  - Dose-dependent toxicity (toxicity varies according to baseline glutathione levels, etc.)
    - Single dose:
      - Minimal toxic dose of 150 mg/kg
      - Toxicity likely at >250 mg/kg
    - Chronic overdose: minimum toxic threshold 150-175 mg/kg daily over 2-4 days
- Combination opioid formularies often avoided in pediatrics as a result
  - Tylenol #3, Vicodin® [hydrocodone], Percocet® [oxycodone]
Nonselective Nonsteroidal Anti-Inflammatory Drugs

Class
- Acetic acid derivatives
  › Diclofenac
  › Indomethacin
  › Ketorolac
- Propionic acid derivatives
  › Ibuprofen (Motrin®, Advil®)
  › Naproxen (Aleve®, Naprosyn®)
- Salicylates
  › Aspirin
    - Only NSAID to irreversibly inhibit COX-1
    - Reye’s Syndrome

Side Effects
- Inhibition of platelet aggregation
- Increased risk of gastrointestinal ulcers & bleeding
- Note: All NSAIDs increase risk of renal disease & myocardial infarction

Common contraindications
- Allergy
- Aspirin-induced asthma
- Peptic ulcer disease, gastric bleed
- Inflammatory bowel disease
- Renal disease
- Third trimester of pregnancy
- History of gastric bypass surgery
- History of (excludes ASA):
  › Transient ischemic attack or CVA
  › Myocardial infarction
  › Coronary artery disease
  › Congestive heart failure
Aspirin and Reye’s Syndrome

- Use of aspirin or salicylates during viral illness associated with increased risk for Reye’s syndrome
  - Microvesicular hepatic steatosis & acute encephalopathy
  - Results from inhibited oxidative phosphorylation & B-oxidation (fatty acid metabolism)
  - Most commonly influenza or varicella zoster virus
  - Signs and symptoms (3-5 days after viral illness begins)
    - Persistent vomiting
      - Electrolyte abnormalities, dehydration
    - Increased somnolence
    - Lethargy
    - Disorientation, confusion, delirium
    - Seizures
    - Loss of consciousness
    - Death (40% mortality rate)
COX-2 Inhibitors

Cox-2 Selective Nonsteroidal Anti-Inflammatory Medications

- Fewer gastrointestinal effects than nonselective COX inhibitors
- Promotion of thrombosis → increased risk of myocardial infarction and cerebrovascular accidents
  ‣ Selective
    • Celecoxib, rofecoxib, valdecoxib
  ‣ Relatively Selective
    • Nabumetone
    • Meloxicam
      - Higher free fraction in synovial fluid due to decreased albumin
      - Marketed for arthritic pain
    • Diclofenac
      - Oral and topical formularies available
Skeletal Muscle Relaxants

- Antispasmodics
  - Decrease skeletal muscle spasm
- Antispastics
  - Act centrally to reduce spasticity
Skeletal Muscle Relaxants

- Methocarbamol (15mg/kg PO or IV q8h)
  - Relatively decreased sedation when compared to other relaxants
  - Contraindicated if history of renal failure and seizure disorder
- Cyclobenzaprine
  - Similar pharmacodynamics to tricyclic antidepressants
  - Contributor to serotonin syndrome
  - Muscle relaxation via central serotonin antagonism (5-HT2A and 5-HT2C)
- Benzodiazepines
  - GABA<sub>A</sub> agonism
- Tizanidine
  - Central α-2 adrenergic agonism
  - Presynaptic inhibition of spinal motor neurons
- Baclofen
  - GABA<sub>B</sub> agonism
- Dantrolene
  - Ryanodine receptor antagonist
  - Decreased intracellular calcium concentration
  - Depressed excitation-contraction coupling in skeletal muscle
Skeletal Muscle Relaxants

- Baclofen Withdrawal Syndrome
  - Signs and Symptoms
    - Increased spasticity
    - Hyperthermia
    - Delirium
    - Respiratory depression
    - Rhabdomyolysis
    - Multi-organ failure
    - Death
  - Treatment
    - Urgent re-initiation of therapy
Benzodiazepines

- **Beneficial effects**
  - Muscle relaxation
  - Anxiolysis
  - Anxiety-related nausea & vomiting

- **Mechanism of Action**
  - Binds GABA$_A$ receptor complex → enhanced interaction between receptor & chloride ion channel
  - Muscle relaxant effects by central potentiation of GABA release

- **When given concurrently with sedating medications, risk of profound respiratory depression**
  - Do not administer within one hour of sedating medications

- **Commonly-used**
  - **Diazepam (PO, IV)**
    - 0.05-0.1mg/kg (PO, IV)
      - Intravenous formulation with severe pain on injection
  - **Lorazepam (PO, IV)**
    - 0.01-0.02 mg/kg IV
  - **Clonazepam (PO)**
    - 0.02-0.06 mg/kg PO

- **Reversal: Flumazenil**
  - 0.01mg/kg over 15 seconds

- **Contraindications**
  - Anticholinergic signs, tachycardia, wide QRS on EKG, seizure history, chronic benzodiazepine use
Local Anesthetics - Lidocaine

- Lidocaine (IV)
  - Proposed effects
    - Analgesia
    - Prevention of 2° hyperalgesia & central sensitization
  - Mechanisms
    - Sodium channel blockade
    - NMDA antagonism
    - G protein uncoupling
    - Reduction of circulating inflammatory cytokines
  - Intravenous dosing
    - 1-2mg/kg bolus
    - 1.5-2.5mg/kg/hr infusion
    - Target serum levels from 1.5-4 mcg/mL
      - Toxicity may occur at 5mcg/mL
NMDA Antagonists - Ketamine

- **Indications**
  - Treatment of therapy-resistant neuropathic pain
  - Prevention of chronic pain with perioperative dosing

- **Proposed Sites of Action [Sleigh]**
  - NMDA channels
  - HCN1 channels
  - Acetylcholine channels
  - Opioid agonism & potentiation
  - Nitric oxide cGMP system
  - Non-NMDA glutamate receptors
  - Reduction in cholinergic neuromodulation
  - Increased dopamine and norepinephrine release

- **Potential Side Effects**
  - Psychedelic symptoms
    - Hallucinations
    - Memory deficit
    - Panic attack
  - Nausea and vomiting
  - Somnolence
  - Cardiovascular stimulation
  - Hepatotoxicity

- **Dosing**
  - 0.15-0.35 mg/kg/hr IV infusion
NMDA Antagonists - Methadone

- Diphenylheptane opioid
- Mechanisms
  - NMDA (via d-isomer/S-met)
  - Opioid (via l-isomer/R-met)
  - MAOI
- High gastrointestinal uptake
  - 80% bioavailability
- Fecal and renal excretion
  - Along with fentanyl and sufentanil, typically considered safe in renal patients
  - Prolonged administration with renal insufficiency may require dose adjustment
- Dosing
  - Interval
    - Q6-12h for analgesia
    - Q24h for opioid withdrawal
  - Simple conversion of oral morphine to oral methadone
    - 30-90 MED, ratio of 4:1
    - 90-300 MED, ratio of 8:1
    - >300 MED, ratio of 12:1
- Potential Side Effects
  - QTC Prolongation
    - Monitor EKG
Gabapentinoids - Gabapentin

- Mechanism of Action
  - \(\alpha-2\delta\) subunits of voltage-gated calcium channels
  - Voltage-dependent Na channels
  - Peripheral and central action
- 60% oral bioavailability
- Absorption via LAT1 transporter saturable (dose-dependent pharmacokinetics)
  - Delayed peak levels and diminished bioavailability at high doses
- Peak plasma concentrations 2-3 hours
- Half life 4-22 hours
- No appreciable metabolism; renal excretion
  - Adjust for renal patients, including post-dialysis supplemental dose

<table>
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<tr>
<th>Renal Function Creatinine Clearance (mL/min)</th>
<th>Total Daily Dose Range (mg/day)</th>
<th>Dose Regimen (mg)</th>
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<table>
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<tr>
<th>Post-Hemodialysis Supplemental Dose (mg)</th>
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<tr>
<td>Hemodialysis</td>
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</table>
Gabapentinoids - Pregabalin

- **Mechanism of Action**
  - α-2 δ subunits of voltage-gated calcium channels
    - Analgesic (2-4x more potent than gabapentin)
    - Anticonvulsant (3-10x more potent than gabapentin)
    - Anxiolytic

- **Pharmacokinetics**
  - Absorption: LAT1 and multiple other transporters
    - Linear pharmacokinetics (no saturation of absorption)
    - Oral bioavailability >90% across dosing ranges
  - Little to no metabolism; excreted unchanged via renal excretion
  - Peak plasma concentrations ½-3 hours, depending on fasted or fed state
  - Half life 6 hours; dosing interval BID to TID
  - Therapeutic dosing 75-300mg daily for patients of adult weight
  - Renal dosing: decreased based on function; include supplemental post-dialysis dose
Antiepileptics - Topiramate

Mechanisms of Action

- GABA_A receptor augmentation
- Sodium channel blockade
- Carbonic anhydrase inhibition
- Glutamate receptor antagonism
  › AMPA/kainate subtype
- Possible serotonin receptor activity
  › 5-HT_2C receptors

Potential Side Effects

- Acute angle closure glaucoma
- Cognitive slowing, word-finding difficulty
  › Na channel blockade
  › GABA_A augmentation
- Paresthesias, metabolic acidosis, nephrolithiasis (calcium phosphate crystals)
  › Carbonic anhydrase inhibition
- Appetite suppression, weight loss
- At high doses, can decrease plasma concentration of estrogen and progestins (OCP therapy)
Tricyclic Antidepressants

- Fused 3-ring moiety used as an analgesic and antidepressant
- Mechanism of Action
  - Block norepinephrine and serotonin uptake into axon terminals
    - Analgesic effects primarily via norepinephrine reuptake mechanism
  - May block some subtypes of serotonin, adrenergic, and histamine receptors
- Narrow therapeutic index
- Analgesic dose substantially lower than antidepressant dose
- Discontinuation syndrome: wean over weeks to months

- Anticholinergic effects prominent with tertiary amine TCAs
  - Amitriptyline, doxepin, imipramine
    - Less commonly with nortriptyline and desipramine, secondary amines
  - Urinary retention, dry mouth
  - Confusion, hallucinations
  - Hypotension
  - Glaucoma exacerbation
  - Cardiac dysrhythmias
    - Sinus tachycardia
    - IV conduction delay
      - QRS prolongation
      - PR, QT interval prolongation
Alpha-2 Agonists

Clonidine

- **Uses**: analgesia, anxiety, withdrawal (opioid, benzodiazepine, alcohol)
- **Common routes**
  - Intrathecal, epidural, transdermal, intravenous, oral
- **Mechanisms**
  - Central (α-2 agonism at dorsal horn of spinal cord)
    - Inhibition of substance P and nociceptive neurons
    - Stimulation of nitric oxide synthesis
  - Peripheral
    - Release of enkephalin-like substance
- **CNS depression, respiratory depression, bradycardia, transient hypertension followed by mild hypotension**
  - More profound side effects noted with dexmedetomidine
- **Elimination half-life 20-25 hours**
Corticosteroids

Glucocorticoid (Methylprednisolone, triamcinolone, betamethasone)

- Inhibition of phospholipase A, inhibiting production of multiple inflammatory genes which encode:
  - Cyclooxygenase
  - Lipoxygenase
  - Cytokine genes
  - Leukotrienes
  - Proinflammatory enzymes
  - Bradykinin
  - Neuropeptides
  - TNF, IL-1, 6, 8
  - C Reactive Protein
  - Leukocyte adhesion molecules

- Note: Due to risk for intravascular injection with resultant neurological deficits, cervical and thoracic epidurals to be performed with non-particulate steroid (dexamethasone)
Bisphosphonates

Alendronate (PO, IV), Neridronate, Pamidronate, Clodronate, and Ibandronate

- Primary mechanism: osteoclastic inhibition —> bone resorption
- Secondary mechanism: interference with inflammatory and nociceptive pathways affecting sympathetically mediated pain

› Inhibition of osteoclasts decreases responsive acidification of extracellular milieu which otherwise leads to:
  - Activation of acid-sensing nociceptive receptors
  - Release of pro-inflammatory cytokines

› Inhibition of macrophage activation prevents the overexpression of NGF which causes neurogenic inflammation

- Neridronate improvement of quality of life and VAS in CRPS type I

- Potential Side Effects
  - Arthralgia, myalgia, fever, flu-like reaction, headache, diarrhea, dermatitis, hypocalcemia
  - Oral: Nausea, dysphagia, GERD, esophagitis, gastric ulcers
Pruritus

Opioid-Induced

- Nalbuphine
  - Low-dose with anti-pruritic activity while avoiding loss of analgesic benefit from opioid agonist therapy: 0.05mg/kg IV or PO q4-6 hours
    - Note: Analgesic dosage: 0.1mg/kg q6h
- Naloxone
  - 0.25-1 μg/kg/h intravenous infusion
  - Doses >2 μg/kg/h likely to reverse opioid analgesia
- Ondansetron (5-HT₃)
  - 0.1mg/kg PO/IV q6h

Non-Opioid Related Pruritus

- Diphenhydramine (H₁ antagonism) 0.5-1mg/kg IV
- Aprepitant (neurokinin-1 receptor antagonist)
  - Inhibition of substance P
  - Three day treatment course with up to weeks of relief from pruritus
    - 3mg/kg on initial treatment day; 2mg/kg on days two and three
Nausea & Vomiting

Origin

- Medullary Chemoreceptor Trigger Zone
  - D2, 5HT3, ACH, Mu2
- Cerebral Cortex
  - 5HT3, ACH
- Periphery
  - D2 (stomach), 5HT3
- Vestibular Region
  - Histamine, ACH

Treatments

- Serotonin Antagonists (5-HT3)
  - Ondansetron 0.1mg/kg q6h
- NK-1 Antagonists (Inhibition of Substance P)
  - Aprepitant
- Steroids
  - Dexamethasone ~0.05mg/kg as effective as larger doses \[\text{DeOliveira}\]
- Dopamine Antagonists
- Benzodiazepines (GABA$_A$)
- Cannabinoids (CB1)
- Antacids
Bibliography


