The Management of Neuropathic Pain and the Use of Adjuvant Analgesia in Children

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...another disclaimer

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer | Phoenix, AZ | May 4-5, 2015

8th Annual Pediatric Pain Master Class | Minneapolis, MN | June 20-26, 2015

- Appreciate high prevalence of neuropathic pain children with serious illnesses
- Define neuropathic pain and describe main causes in pediatric patients
- Develop a step-by-step treatment approach for neuropathic pain
Multimodal Analgesia

Injury

Thalamus

Opioids
- Pre-synaptic nerve terminal
  - Neurotransmitter release
- Post-synaptic nerve terminal:
  - Membrane hyperpolarization
  - \( \Rightarrow \) suppress neuronal excitability

Acetaminophen (Paracetamol)

NSAIDs

No Needless Pain

That's why we're called

No Needless Pain
Integrative Pain & Symptom Management

- A Pediatrician’s Top 10 Apps for Distraction & Pain Management
- http://NoNeedlessPain.org

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Injury
  - Thalamus
  - Integrative (non-pharmacological) therapies
  - Periaqueductal grey (endorphins)
  - NSAIDs
  - Acetaminophen (Paracetamol)
  - Opioids

Neuropathic Pain

- Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (IASP 2008)
- Grading System: (1) Definite, (2) Probable; (3) Possible
- (...but, not all lesions in the somatosensory system lead to neuropathic pain)
**Prevalence**


- Prevalence of neuropathic pain in children unclear

**Potential Causes Include**

- **Spinal cord injury**: “pain arising as a direct consequence of affecting the somatosensory system”
- **Tumor related**: direct tissue and nerve injury; advanced unresectable solid tumors
- **Phantom limb pain**: 60 - 80% of adult patients with amputation experience phantom sensations in their amputated limb, majority are painful. [Sherman RA, Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: Results of a survey. Pain. 1984;18: 83–95.]
- **Metabolic neuropathies**: toxic and metabolic neuropathies (eg, lead, mercury, alcohol, infection)
- **Neurodegenerative disorders**: Hereditary neurodegenerative disorders (Fabry disease, X-linked lysosomal disease caused by deficiency α-galactosidase), mitochondrial disorders, and primary erythromelalgia

**Potential Causes Include**

- **Cancer-directed chemotherapy**, including
  - **Vincristine**: 50% painful peripheral neuropathy, muscle camps, numbness, tingling (hand, feet)
  - **Cisplatin**: Paresthesias in extremities
Neuropathic Pain Assessment

- Currently there are no validated neuropathic pain scales for children <18 years

- Adults

  - NPS® Neuropathic Pain Scale - 12 items
  - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_nps.htm)


- Pain Quality Assessment Scale (PQAS) - 20 items
  - [http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm](http://www.mapi-research.fr/t_03_serv_dist_Cduse_pqas.htm)


- Children simultaneously may experience different qualities, including

  - Nociceptive Pain
  - Somatic Pain
  - Visceral Pain
  - Psycho-social-spiritual Pain (“Total Pain”)
  - and/or Neuropathic Pain

- Be creative when measuring pain: a single pain score often will not be enough:

  - “How would you rate the burning pain in your feet”
  - “On a scale of zero to 10, how is your constant pain in your back?”
  - “How much does your heart hurt?”
  - Ask fluffy toy if patient is in pain

Current Status: Call for Action

- Large number of children with advanced cancer and non-malignant serious conditions experience neuropathic pain

- However, neuropathic pain is not routinely assessed

- Children are often not effectively treated
Case Report: Clark

- 15-year-old, relapsed T-cell lymphoma, weight: 72 kgs
- Onset of chemotherapy-induced bi-pedal neuropathy VAS 9/10
- Abdominal pain (hemorrhagic cystitis)
- Unresponsiveness versus over sedation
- Autonomic changes at feet

NSAIDs for Neuropathic Pain


Opioids for Neuropathic Pain


- Multi-mechanism agent

Case Example: Multimodal (Opioid-sparing) Analgesia

**Non-Opioids**
- Acetaminophen / Paracetamol
- NSAIDs

**WHO-Principles**
- “By the clock”
- “By the child”
- “By the appropriate route”
- “By the WHO ladder”

**Opioids**
- Tramadol (“weak”)
- Morphine (“strong”)

**Integrative Therapies**
- Massage
- Heat/cold
- Deep Breathing
- Biofeedback
- Hypnosis
- etc.

**COX-2-INHIBITOR:** Celexcoix 200 mg BID

**OPIOID:**
- Hydromorphone PCA 1.35 mg/hr (max. 52 boluses/day [1.35mg])

**Rotation:**
- Methadone 30 mg/day [5 mg IV Q4h -> 10 mg IV Q8h] plus Hydromorphone PCA bolus 2mg IV, lockout 10 minutes
- PO 10 mg TID -> 12.5 mg TID

Integrative, rehabilitative & supportive therapies

- Expected part of treatment protocol; Age-appropriate modalities include
- **Physical** (massage, TENS, comfort positioning, allowing family for close contact/touch)
- **Rehabilitation** (physical therapy, occupational therapy)
- **Behavioral** (deep breathing, imagery, hypnosis, smartphone/tablet “apps”)
Case Report: Clark

- Integrative & supportive therapies
- Behavioral Therapies
  - Breathing
  - Imagery
  - Hypnosis
- Individual Psychotherapy
- Physical Modalities

TENS
- Physical Therapy
- Stockings
- Make-a-wish

Case Example: Multimodal (Opioid-sparing) Analgesia

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- etc.

Adjuvants
- Alpha-Agonist
- Anticonvulsants
- TCA/Antidepressants
- NMDA-receptor-channel blockers
- Na-receptor-channel blockers
- Antispasmodics
- Benzodiazepines
- Corticosteroids
- Muscle relaxants
- Radiopharmaceuticals
- Bisphosphonates
- etc.

Case Report: Clark

(1) TRICYCLIC ANTIDEPRESSANT
- Amitriptyline 25 mg -> 50 mg QHS

(2) Ca-channel α2-δ ligand
- Pregabalin 50 mg QHS -> 300 mg BID

(3) CORTICOSTEROID
- Dexamethasone 10 mg BID

(4) LIDOCAINE
- 5% patches Q12h on/off
Tricyclic antidepressants (TCA)

- 61 RCTs (20 antidepressants): TCAs are effective; NNT of 3.6 (for the achievement of at least moderate pain relief) Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005454


- Secondary amine TCAs (e.g. nortriptyline) better tolerated than tertiary amine TCAs (e.g. amitriptyline) with comparable analgesic efficacy Max, N Eng J Med 1992;326:1250-6; Rowbotham, J Pain 2005,6:741-6; Watson, Neurology 1998,51:1166-71

Amitriptyline

- Dosage: initial 0.1 mg / kg -> titrate to 0.4 mg / kg p.o. [max. 20-25 mg] (usually not up to 1-2 mg / kg / day) once at night -
  - wean: decrease gradually!
- Effect: days - weeks; depends on length of symptoms
- Adverse effects: arrhythmia: EKG (QTc, WPW?), anticholinergic / antihistamine (dry mouth, constipation, blurred vision, sedation)

Nociceptive Pathways & Primary Sites of Action of Analgesics
Case Report: Clark

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   - 5% patches Q12h on/off

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**Gabapentinoids: Ca-channel α2-δ ligands**

- Voltage-gated Ca-channel
- α2-δ subunit [dysfunction/? upregulation role in neuropathic pain]
- Presynaptic nerve terminal
- Postsynaptic nerve terminal
- Glutamate
- Substance P

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**Gabapentinoids**


  - 42% improved compared to 19% on placebo

  - NNT for effective pain relief in diabetic neuropathy 2.9; post herpetic neuralgia 3.9


  - No overall evidence for superior efficacy for either of these drugs in neuropathic pain, although lower cost may favor gabapentin

**Gabapentin**

* Pediatric Dosage: gradually increasing from 3-5 mg/kg/dose TID to 10-20 mg/kg/dose TID, max. 1,200 mg/dose TID

* [Extended release: 300 -> 1800 mg Qday: No pediatric data]

* wean: decrease gradually x 1-2 weeks!

* Infant dosing Q6h?

* Effect: days - weeks

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**Nociceptive Pathways & Primary Sites of Action of Analgesics**

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**Case Report: Clark**

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  * 5% patches Q12h on/off
Glucocorticosteroids

- Possibly helpful:
  - Nerve root / nerve trunk compression (e.g. tumor infiltration brachial plexus / lumbosacral plexus)
  - Spinal cord compression
  - Bone metastasis
  - Bowel obstruction
  - Lymphedema

- Effect:
  - Antiedematous (ameliorate painful nerve or spinal cord compression)
  - Antiinflammatory
  - Directly lyse some tumors (e.g. lymphoma)

Case Report: Clark

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  - 5% patches Q12h on/off

Other Sodium Channel Blocker

- Adult experience:
  - Efficacy of IV lidocaine supported by RCTs
    - (1) Oskarsson P et al, Diabetes Care, 1997;20:1594-1597
  - Oral mexiletine, tocainide, flecainide are analgesic in neuropathic pain
  - High side effect liability from oral drugs -
    - generally considered third-line
  - Mexiletine: 2 mg/kg TID?
  - Lidocaine (systemic or local): Decrease of neuropathic pain related to decrease of ectopic ongoing activity in injured afferent nerve fibers
IV Lidocaine - Pediatric Experience

- Nausea after 4 days?
  Neuropathic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mcg/mL

- Side Effects: Allergic reaction (serious, but rare), dose related: numbness around mouth, dizziness, slurring of speech, hallucinations, muscle twitches, seizures
  [Reference: R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. The journal of supportive oncology. 2004 Jan-Feb;2(1):90-4.]

- Case Series (n=5) after anti-GD2 antibody therapy in children with neuroblastoma: 1mg/kg/hr

- Case report: end-of-life cancer care: 2.1-3 mg/kg/hr

- Case report 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain; IV lidocaine (9.3–14 mcg/kg/min)

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Opioid induced tolerance and hyperalgesia

- Opioid binding-pocket
- mu-receptor
- Gi/o proteins

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Opioid induced tolerance and hyperalgesia

- Opioid
- mu-receptor
- Uncoupling stimulation
- Generation of other neuromodulators
- Activation of protein kinase-C
- Inhibition of Ca channels
- Nerve transmitter release
- Alter characteristics of neuron => neuronal excitabilty
- Membrane hyperpolarization (K+ channel)
- Genes
Opioid induced tolerance and hyperalgesia


NMDA-Receptor Channel Blocker

Excitatory NMDA (N-Methyl-D-Aspartat) Receptor channel complex

1. Membrane potential at resting level
   -> channel blocked by Magnesium

2. Membrane potential changed as a result of excitation
   ↓ Opioid-sensitivity
   - Central (dorsal horn) sensitization
   - radiation of pain
   - spontaneous pain
   - Hyperalgesia, allodynia
NMDA-Receptor Channel Blocker

3. Phencyclidin (PCP) - binding sites [uncompetitive NMDA receptor antagonists with moderate affinity]
- Ketamine
- Methadone
- Levorphanol
- (Dextrometorphan?)

Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture [S(+)-enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]
- Sedative-Hypnotic-Dissociative Dosing: 1-2 mg/kg/dose IV
- Analgesic (subanesthetic) Dosing: IV: 1.5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
- PO: 0.2-0.5 mg/kg TID-QID and PRN (sc, sl, intranasal, pr, spinally)
- Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dysphoria, vivid hallucinations) -> at low-dose??
Low-dose Ketamine

* Action which may contribute to analgesic effect: Meller S, Pain 1996. 68:435-6
  * Cholinergic transmission
  * Noradrenergic / serotonergic re-uptake inhibition
  * μ, δ, κ - opioid-like effect
  * Interactions with other Na-/Ca- channels

Low-dose Ketamine - Adult Evidence


Low-dose Ketamine - Pediatric Evidence

* no RCT’s, few case reports:
  * Rakel RE. J Pain 2007;8(6):515-21 n = 11, terminal cancer, age 3-17
  * Starting dose: 0.1-0.2 mg/kg/hr (max 1 mg/kg/hr)
  * Lorazepam 0.025 mg/kg BID
  * n = 8/11: ↓ Pain; ↓ Opioid requirements (28-100%)
  * No psychotropic side effects, no hallucinations
  * 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain. IV lidocaine (9.3–14 mcg/kg/min) and later ketamine (2 mcg/kg/min) in combination with fentanyl (0.8-1.2 mcg/kg/hr) provided good analgesia without significant side effects for the last 20 days of her life. J Palliat Med. 2012 Jan;15(1):27-30. doi: 10.1177/1525865111423684. Epub 2011 Mar 6.
Ketamine


- Steady-state oral/parenteral ratio unclear
- Bio-availibilty 93% IM/IV; 20% PO
- Ketamine -> norketamine
- Potency ketamine: norketamine 3:1 (anesthetic); 1:1 (analgesic)
- Plasma half-life: ketamine 1-3 hrs; norketamine 12 hrs
- Maximum blood concentration of norketamine: oral > IV


Case Report: Clark

Subanesthetic-dose Ketamine-PCA

Day 1: 4 mg/hr [0.9 mcg/kg/min] plus 4 mg bolus
  ↑ 8 mg/hr [1.9 mcg/kg/min] plus 8 mg bolus
Day 2: ↑ 12 mg/hr [2.8 mcg/kg/min] plus 12 mg bolus
Day 3: ↑ 16 mg/hr [3.7 mcg/kg/min] plus 16 mg bolus
Day 5: ↑ 24 mg/hr [5.6 mcg/kg/min] plus 16 mg bolus

3 unsuccessful trials of decreasing/discontinuing dose

Day 8: Change to 40 mg PO PRN
Day 10: 40 mg PO TID [plus 40 mg PRN]
Day 14: Discontinued [changed to PRN only]

- Hypertonic at baseline, initially MAP increase by 10-15 mm/Hg
- Absent benzodiazepine -> no psychotropic adverse effects

Ketamine

CONVERSION

- Steady-state oral/parenteral ratio unclear
- Bio-availability 93% IM/IV; 20% PO
- Ketamine -> norketamine
- Potency ketamine: norketamine 3:1 (anesthetic); 1:1 (analgesic)
- Plasma half-life: ketamine 1-3 hrs; norketamine 12 hrs
- Maximum blood concentration of norketamine: oral > IV

Low-Dose Ketamine: Case Example

Case 2:
17-year-old Hydromorphone PCA Start: Ketamine

Number of Hydromorphone PCA Boluses
55 -> 20/day [↓ 64% over 3 days]

Opioid Use
71 mg/day -> 32 mg [↓ 55% over 4 days]

Pain Score:
Bolus Response Hydromorphone: VAS 9/10 -> 7/10
Bolus Response Ketamine: VAS 9/10 -> 2/10
Usual Pain Scores: VAS 9/10 -> 2-3/10 [over 4 days]

Breakthrough Pain
↓↓↓

Function
↑↑

Case Report: Clark

Case Report: Clark at Home

Methadone: 10 mg PO TID -> 12.5 mg PO TID -> 10 mg PO TID

Hydromorphone: 10 mg PO Q1h PRN (0-3/day)

Pregabalin: 300 mg BID

Amitriptyline: 50 mg QHS

Ketamine: 40 mg PO PRN Q1h (discontinued after 2 weeks)

Lidocaine Patches: Discontinued after 3 weeks
Other Adjuvant Analgesics / Co-analgesics

- **α-Adrenergic Agonists**
  (Dexmedetomidine; clonidine)
  - Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory G\(_i/0\) proteins
  - Decrease postoperative opioid consumption, pain intensity, and nausea. Recovery times are not prolonged.

- **Capsaicin: 2 Metaanalyses**

- **Benzodiazepines**: gamma-aminobutyric acid (GABA) receptors

- **Sensory-Selective (Nociceptive-Selective) Nerve Blockade**

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Thalamus
- Periaqueductal grey (endorphins)
- Integrative (non-pharmacological) therapies
  - TCA
  - SSRIs
  - Methadone
  - Tramadol
- Stimulation of inhibiting GABA system
  - Baclofen
  - Benzodiazepines
  - Valproate
- NMDA-Channel Blockers
  - Ketamine
  - Methadone
- Acetaminophen (Paracetamol)
  - Opioids
  - NSAIDs
- Sodium-channel blockade
  - Carbamazepine
  - Lidocaine

Inhibitors of excitatory glutamate systems:
- Gabapentin/Pregabalin
- Carbamazepine
- Valproate
Other Adjuvant Analgesic/Coanalgesics

- **Muscle relaxants**: Baclofen; Cyclobenzaprine (Flexaril®)
- **Bisphosphonates**: Osteoclast inhibitors -> metastatic bone pain
- **Antispasmodics**: Hyoscine butyl bromide (Buscopan®) [not in USA], hyoscyamine (Levsin®); oxybutynin (Ditropan®), glycopyrrolate (Robinul®)
- **β-ray emitting osteotrope radio pharmaceutical**: e.g. Samarium-153-EDTMP
- **Anti-TNF α agent** [treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpAs)] adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi).

Interventional management of neuropathic pain in adults

- **4 weak recommendations** based on the amount and consistency of evidence, including degree of efficacy and safety, are:
  - (1) epidural injections for herpes zoster
  - (2) steroid injections for radiculopathy
  - (3) spinal cord stimulation (SCS) for failed back surgery syndrome
  - (4) SCS for CRPS type 1 (who do not respond adequately to noninvasive treatments and sympathetic nerve blocks)

  Based on the available data, we recommend not to use sympathetic blocks for PHN nor radiofrequency lesions for radiculopathy

Regional anesthesia approaches to pain management in PPC

  - central neuraxial infusions
  - peripheral nerve and plexus blocks or infusions
  - neurolytic blocks
  - implanted intrathecal ports & pumps for baclofen, opioids, local anesthetics, and other adjuvants
Management of Neuropathic Pain in Pediatric Palliative Care:
Suggested “Non-Evidence-based” Step-by-Step Approach

(1) Identify and treat underlying disease process (radiation?) (corticosteroids?)

(2) Integrative therapies; manage comorbidities (anxiety, sleep disturbances)

(3) Opioid (plus non-opioid) analgesics [consider Tramadol or Methadone]

(4) Tricyclic Antidepressant (or Ca-channel α2-δ ligand) ± ketamine

(5) Tricyclic Antidepressant and Ca-channel α2-δ ligand

(6) Lidocain patch (if localized pain)

(7) NMDA-receptor-channel blocker [benzodiazepine? α-agonist? IV lidocaine?]

(8) Regional anesthesia

Conclusions

* Neuropathic pain often under-assessed and under-treated
* Treat underlying cause, if possible and appropriate
* Careful step-by-step approach (combining integrative, rehabilitative, pharmacological and interventional therapies) warranted
* First Line medications: Opioids (?), Amitriptyline, Gabapentin
* Apply WHO principles for acute pain
* Low-dose Ketamine may represent a potent adjuvant analgesia
* Possible Indications: Neuropathic & Nociceptive Pain
* May reverse Opioid-induced hyperalgesia & Opioid tolerance; ↑ opioid efficacy ↓ opioid adverse effects

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Further Training

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