Multimodal Analgesia

(Slides by Randall Malchow)
PAIN – Why should I care?

Injury → Inflammation → PAIN → Physical Emotional Impairment

- Increased Cost
- Increased Resources
- Increased Mortality
- Chronic Pain:
  - Amputation >50%
  - PTPS: >50%
  - Trauma: >50%

Persistent Pain → Poor Outcome

Inflammatory Response → Depression Anxiety

(Slide by Grathwohl)
Multimodal < Stress Response

- Correlates w/ severity of trauma (Seekamp)
- Pain directly accentuates stress response
- Stress response linked to morbidity

- SNS activation:
  - incr NE, epi leading to > HR, BP, ischemia.

- Endocrine response:
  - < thyroid, >aldosterone (> renin, angiotensin, aldosterone) w/ > water and sodium.

- Pituitary changes:
  - > pit w/ > ACTH, GH, vasopressin, inflamm, > fluids

- Metabolism changes:
  - > glucagon, < insulin leading to lipolysis, hyperglycemia, prot catabolism, wound inf.

- Heme changes:
  - Hypercoag (dvt prophylaxis)

- Immune changes:
  - Cytokine prod, IL1, IL6, TNF alpha, leukocyte release.
Multimodal Analgesia

- Rationale and Timing
- Problem with Opioids
- Reg Anesthesia
- Adjuncts:
  - Ketamine
  - Clonidine/Benzodiazepine
  - Gabapentin/ Pregabalin
  - NSAID’s
  - Lidocaine/Mexilitene
  - TCA’s
- Kehlet: analgesia, nutrition, ambulation, glucose control
Rationale

Therapy more effective if directed at multiple sites of action (less dose, less side effects, greater analgesia, greater function)

- Opioids
- $\alpha_2$ agonists
- Centrally acting analgesics
- Tricyclics
- Antiepileptic drugs
- Anti-inflammatory agents (Cox-2 inhibitors, nonselective NSAIDs)

- Local anesthetics
- Opioids
- $\alpha_2$ agonists
- Cox-2 selective inhibitors

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- Anti-inflammatory agents

- Local anesthetics
- Anti-inflammatory agents (Cox-2 inhibitors, nonselective NSAIDs)
- Opioids
- Antiepileptic drugs
Rationale

- Many analgesics are synergistic
- Fewer Side effects w/ lower doses
Preventative Analgesia

- Preemptive Analgesia (preop only)
  - Min benefit

- Preventative Analgesia (periop)
  - Significant Benefit

- Hypersensitivity
  - Peripheral vs Central
  - NI aspect of healing fr trauma, surgery

- Decreasing Acute Pain << Chronic Pain

- Kissen, Anes, 2000
Timing and Duration of Block Critical
Problem with Opioids: “Opioid-Induced Hyperalgesia”

- Universal Problem currently in U.S.; opiate based Pain Clinics
- The Dilemma: Tolerance vs OIH

Mechanisms:
- NMDA (EAA’s)
- Spinal Dinorphin
- Rostral Ventralmedial Medulla pathway (RVM) (+/- pathways)

Characteristics:
- Dose-dependent
- Requires days to weeks to resolve.
- Naloxone unmasks OIH after resolution.
- “Rekindling” w/ low doses later.
Opioids: The Ugly
(as in Benefits Talk)

- Sedation- monitoring, treatment
  - (Payen, ’07) > sedation assoc w/ CV failure/spt in ICU
  - (Lucas, ’07) > sedation linked to death some pts.

- B/T Cell Dysfunction
  - Vallejo, ’04: < Ab prod, NK cell activity, cytokine express, phag act

- Respiratory Depression
  - Avoid Fentanyl patch (duragesic) in acute pain
  - Minimize use of basal rates (0.27 vs 1.65% incidence resp dep)

- GI:
  - Constipation- monitoring, treatment
  - Ileus
  - Nausea/vomiting

- Pruritis

- Bladder Dysfunction
Regional Anesthesia-Part of

- **Epidural Analgesia:**
  - Improves Outcome for
    - Thoracic/ Upper Abd surgery; Mult Rib Fxs (Hedderich)
      - Decr Resp Complications
      - Decr Mortality
    - Amputations (Bach, others)
      - Decreased Acute and Chronic Phantom Limb Pain (PLP)
  - Algorithm for Mult Rib Fractures:
    - # of rib fx + age + pain score + IS/cough = APS
    - Eg >4 RFs + >45 + < IS + VAS>6 = APS

- **CPNB’s**
  - Wounded warriors:
    - Extensive use in military
  - PVB Catheters:
    - Decr Resp complications w/ Mult Rib Fx
  - Richman’s Review:
    - meta-anal of 19 studies in 603 pts:
      - < VAS, n/v, sed, pruritis
  - Vanderbilt:
    - << LOS, > pt sat w/ Home use
Ketamine

- Phencyclidine derivative (think angel dust)

- Mechanism:
  - NMDA receptor antagonist
  - Binds to opiate receptors
  - "Disconnects" (dissociative) thalamus, hypothalamus and limbic systems

- Timing:
  - Before Incision/Opioid
  - During Surgery
  - Postoperative

- < GA requirement if used as adjunct

Ketamine Dosing
Himmelseher, Anes, 2005
## Ketamine: Perioperative

<table>
<thead>
<tr>
<th>Painful Surgery</th>
<th>Before Incision mg/kg</th>
<th>Intraop: ug/kg/hr</th>
<th>Postop: ug/kg/hr</th>
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<tbody>
<tr>
<td>0.5</td>
<td>500</td>
<td>120</td>
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<table>
<thead>
<tr>
<th>Less Painful</th>
<th>Before Incision mg/kg</th>
<th>Intraop: ug/kg/hr</th>
<th>Postop: ug/kg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>250</td>
<td>60</td>
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- If used w/ Morphine PCA, 1:1 mixture effective.
- Analgesic Dose: 1-10mcg/kg/min
- Hallucinations rare at low dose
- Benefits:
  - Synergistic w/ opioids (opioid sparing)
  - < Pain scores (rest and dynamic)
  - Abolishes wind-up (OIH) < N/V, < chronic pain
  - > feeling of well-being; pt satisfaction
Ketamine in Trauma:

- Nikolajsen, Pain, 1996 (Amputees):
  - chronic stump/PLP
  - Ketamine infusion.
  - 100% of pts near complete relief during infusion.
  - Case Rpt, 1997: Oral ketamine x 3mos resolved stump pain

- Other:
  - < mortality in burns (animal)
  - Abolishes OIH
  - Attenuates stress response
  - Hill: > BP, CO in sepsis
  - Bell, 2005: Good review
  - Subramanium, 2004: rev
Clonidine

- a2 agonist- peripheral, spinal (inhib neurons) and supraspinal sites
- Dexmedetomidine -7x > selective (IV qtt only)
- < stress response, ischemia
  Wallace, 2004
- < opioid requirement w/ periop
  oral clon
  Segel, 1991; Park, 1996
- Blunts OIH
  Koppert, Anes 2003:
- Anxiolysis
  Hidalgo 2005
  - Benzodiazepines also very helpful in some pts
- Improves RA
  Dobrydnjov 2005
- < PLP
  Davis, 1993
- Side effects: < HR, BP, sedation

Effective routes:
- Oral (0.1-0.3mg bid)
- Transdermal (0.1-0.3mg/day x 1 wk)
- PNB (1mcg/kg)
- IV 0.3 ug/kg/hr p load 3ug/kg
- IT 15-30 ug
- Epidural 0.5-1 ug/ml adequate
**Gabapentin**

- **Indication:**
  - Neuropathic pain (ANP common after trauma, burns)
  - New Perioperative Analgesic?
  - < hyperalgesia; opioid tol pts
  - anxiolysis

- **Mechanism:**
  - Structurally similar to GABA
  - Yet act @ Ca channel, < EAA
  - Dorsal Horn, Dorsal Root Ganglia

- **Gabapentin (Neurontin)**
  - 300mg tid to 3600/d
  - Dizziness, drowsiness most common

- **Pregabalin (Lyrica)**
  - < side effects, easier to dose, > cost
  - 75-150mg bid
  - Max 600mg/d
Gabapentin, Pregabalin
Clinical Results

- Gilron, 2007, and Tiippana, 2007, Periop Use; excellent reviews
  - < pain
  - 50% Opioid sparing 21/30 DB, RCT
  - Good dynamic pain control
  - > pt satisfaction, function
  - < anxiety, chronic pain

- Burns, Cuignet, 2007:
  - GPN 2400mg / day, Day 3-24
  - < pain
  - < opioid

- Prevention of Chronic Pain:
  - Fassoulaki, 2005
  - Multimodal: GPN, EMLA, Ropiv in wound
  - Periop GPN 400mg qid, POD 0-8
  - < acute pain compared to control
  - < chronic pain at 3, 6 mos (30 vs 57%)

- Phantom Limb Pain
  - Bone, 2002: Chr PLP, 45% < PLP p 5wk
  - Nikolajsen, 2006: no benefit to periop GPN (not multimodal)
**NSAID’s**

- COX-1 (side effects) and COX-2 (nociception); COX-3 acetaminophen?
- Indications: mild-mod pain
- Analgesic, anti-inflam, antipyretic
- No sedation, constipation, nausea
- Up to 50% opioid sparing
- Good dynamic pain
- Ketorolac
  - 15-30mg IV qid x 5days
- Meloxicam (Mobic):
  - 7.5mg – 15mg/day PO
  - Good side effect profile; dosing regimen

**Side Effects (nonselective):**
- GI
- Renal
- Platelet Dysfunction, reversible
- < Bone growth (although helpful w/ HO); NB: hi risk fx’s
- ? CV effects (diclofenac, 2005)
- Closure of PDA; tocolytic
NSAIDs

COX 2 Inhibitors

- Side Effects:
  - <GI, same Renal risk
  - No plt inhibition
  - > cardiac risk

- < Central Hyperalgesia

- Celecoxib (Celebrex) 100-200 bid

- Rofecoxib (Vioxx), Valdecoxib (Bextra) pulled fr market

- Parecoxib: parenteral, in Europe; phase III in US.
Lidocaine /Mexilitene

- **Amputation, PLP:**
  - Wu, Anes, 02:
    - Lido helpful for stump pain
  - Davis, Ortho, ’93:
    - 31 pts w/ long term f/u
    - Mexilitene 150mg/d, titrated to 900mg/d as tol
    - If no benefit on mexilitene, clonidine TD added
    - 58% very good relief only mexilitene
    - 95% very good relief w/ mexilitene + clonidine.
  - BAMC/VUMC experience:
    - Combination: most promising Rx.

- **Burns:**
  - Topical 5% helpful <28% TBSA
  - Jonsson. < pain in mod burn pts w/ IV Lidocaine; no opioids

- **Avoid in Elderly/ coronary dz**
  - Obtain 12 lead EKG prior to Rx

- **Burns:**
  - Jonsson. < pain in mod burn pts w/ IV Lidocaine; no opioids
Tricyclic Antidepressants

- Block reuptake of NE and 5HT at dorsal horn
- Effects: Anti-cholinergic, antihistamine, and anti-alpha-1 receptors.
  - Sedation
  - Constipation
  - Tachycardia
  - Orthostasis
- 3\textsuperscript{o} amines:
  - Amitriptyline
  - Most studied
- 2\textsuperscript{o} amines:
  - Desipramine, nortriptyline
  - Fewer side effects
- Indications: neuropathic, antihyperalgesia, insomnia (subacute and chronic duration)
- Trial of tertiary amine TCA offers the best likelihood of response, but could take weeks for effect
- Elavil 25-50mg qhs
- Screening ECG avoid in patients after acute MI or intraventricular conduction delays.