PAIN MANAGEMENT UPDATES

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Disclosures

- Precedex – have done several pediatric studies for which "I" (my departmental research fund) have been reimbursed. Not presently doing any funded work.
- Ofirmev – on speakers board, but haven't spoken. Writing up a research proposal for T&As.

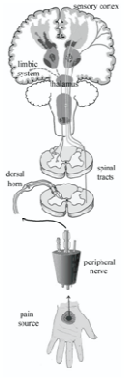
Myths and Hated Sayings

- Infants do not perceive pain
- Children do not remember pain
- Less is better
- Medicating for pain is dangerous
- They're a drug addict they're just drug seeking
- They're going home don't give them anything long acting

Goals

- ~~Dispel myths~~
- Provide some basic guidelines
- Explore adjuvant drugs
- Mention role of regional anesthesia (specifics beyond scope of today's lecture)

Pain Pathways



Definitions

- Pain – refers to both the sensory and emotional experience of noxious events.
- Nocioception – refers to the process of encoding and sensing tissue injury and inflammation.
- Neuropathic pain – refers to pain that persists due to abnormal nerve excitability as inflammation subsides and injured tissue heals.
- Suffering – equates to the emotional distress caused by pain or perceived harm.

Post-op Pain Problems

- CV
  - Increased HR, BP, SVR, Contractility -> increased myocardial O2 demand
- Pulmunary
  - Increased rate of atelectasis through splinting
    - Greater shunting with increases in PVR
    - Greater risk of infection
- GI
  - Reduced motility, increased ileus, N/V
- Longer PACU stays
- Longer Hospital stay
- Chronic Pain

Goals of Pain Control

- Many hospitals have adopted "Pain Free environments"
- Reduce side effects from pain
- Prevent Chronic Pain Syndromes
- Earlier Discharge
  - From PACU & Hospital

Basic Guidelines

- Take a pain history
- Discuss options
- Set realistic goals with the family and patient
- Maintain an ongoing assessment
- Modify initial plan
- Determine what monitoring is required

Narcotics

- Morphine
- Fentanyl
- Dilaudid (hydromorphone)
- Demerol (meperidine)
- Methadone
- Codeine
- Vicodin/ Lortab (hydrocodone)
- Oxycotin (oxycodone)
- Opana (oxymorphone)

Modalities of Administration

- Oral
- Rectal
- Intravenous
- Subcutaneous
- Intramuscular
- Transdermal
- *Intranasal*
- REGIONAL

Narcotic Side Effects

- Histamine release → Pruritis
- Gastrointestinal → N/V
  - → Constipation
- Bradycardia
- Respiratory depression
- Miosis
- Biliary spasm
- Urinary retention
- Excessive Sedation
- Impaired mentation

Sleep Apnea and Narcotic Postoperative Pain Medication

- Morbidity and Mortality Risk Alert from Anesthesia Patient Safety Foundation (2001).
- 8 claims of "unexplained" postoperative cardiopulmonary arrests occurring in hospitalized patients were reviewed.
- All of these patients received parenteral narcotic pain medication and were ultimately diagnosed with sleep apnea.

Sleep Apnea and Sleep Apnea Syndrome

- SA = absence of airflow at the nose and mouth for longer than 10 seconds
- SAS = occurrence of more than 30 apnea episodes over a 7-hour period of nocturnal sleep
- Majority is obstructive vs. central
- In 1990's, 1-4% of the middle aged population was estimated to have SAS (Tierney1989/Boushra1996)

Predisposing Factors S.T.O.P.B.A.N.G.

S noring loud enough to be heard thru closed doors
T ired, fatiqued or sleepy during the day
O bserved to be stopped breathing
P ressure (blood) elevated or being treated
B MI > 35 kg/m^2
A ge > 50 years
N eck Circumference > 40 cm
G ender male

Case #1

A 45-year-old male, 320 lbs and 5'11" (BMI=45), had a rotator cuff repair under general anesthesia. The intraoperative course was uneventful. He was admitted to the ward for overnight pain control. Four hours after surgery, he received an intramuscular injection of meperidine 100 mg with Phenergan® 25 mg. This was repeated 3 hours later when severe pain prevented him from sleeping. Two hours later, nurses making a routine check found him in full arrest. He could not be resuscitated. The internist's preoperative history and physical mentioned his having been diagnosed with sleep apnea.

Case #2

A 32-year-old male presented for an open reduction and internal fixation of an arm fracture, which was satisfactorily performed under general anesthesia. He was discharged to the ward on a fentanyl PCA (patient-controlled analgesia) with a 25 mcg bolus, 12-minute delay, and 25 mcg hourly rate. At night, the nurses heard him snoring loudly. One hour after his last normal vital signs, he was found in respiratory arrest. He was resuscitated, but displayed signs of anoxic brain damage. By questioning the patient's wife, a consultant was able to elicit the husband's history of heavy snoring and nocturnal apneic spells that were felt to be clinically consistent with a diagnosis of sleep apnea.

Obesity and Narcotics

- The number of overweight U.S. children is increasing.
- 15 percent of children ages 6 to 18 were overweight in 2000, up from 6 percent in 1980.
- 10 percent of children 2 through 5 were considered seriously overweight.
- Sources: AHA, NIH, CDC, NHNES. National Center for Health Statistics.

Morphine

- Onset 5-10 minutes IV (30 minutes IM or SQ)
- Dose 0.05 – 0.15 mg/kg IV
- PO:IV conversions 3:1
- Half-life 2-3 hours
  - Metabolized in liver and excreted by kidney so increase dosing intervals
- Well known drug decreases dosing errors

Fentanyl

- 75-100 times more potent than MSO_4
- Dose 1-2 mcg/kg IV, but best given as an infusion 1-5 mcg/kg/hr.
- Tendency towards fewer side effects
- Quicker onset (1-2 minutes)
- Shorter half-life (20-30 minutes) so requires frequent re-dosing
- No PO form (is a oralet form)
- Pruritus (usually nose)
- Truncal rigidity in larger doses (> 5-10 mcg/kg)

Dilaudid

- Generic name hydromorphone
- 5-7 time more potent than morphine
- Less nausea and pruritus than morphine
- Half-life 2-4 hours
- Greater dosing interval vs. morphine
- PO :IV conversion = 4:1
- IV dose = 20-30 mcg/kg q 4-6 hrs.

Demerol

- Relatively high incidence of adverse CNS effects → dysphoria, restlessness, agitation, seizures
- Major metabolite normeperidine has direct CNS toxicity → seizures
- Half-life of normeperidine is 15-20 hrs and it depends on renal excretion therefore is not to be given to patients with renal insufficiency
- Catastrophic interaction with MAO-I
- Small doses used to decrease postoperative shivering

Methadone

- Half-life 12-24 hours. Maintains a prolonged steady state
- In situations where PCA not available may be a good alternative
- Dose 0.1 mg/kg q 4-12 hrs. usually intraoperatively for postoperative pain with use of shorter acting agents to supplement
- Dose daily as a withdrawal drug, but q4hrs as a acute post-operative drug
- PO:IV conversion 1:1

Codeine (methylmorphine)

- Dose 0.5-1 mg/kg PO every 3-4 hrs.
- Usually prescribed with acetaminophen at a ratio of 10:1.
- Elixir forms come 300/30 in 12.5 cc's.
- A prodrug → requires conversion to morphine. Therefore, "nonresponders" may have a deficiency of P-450 2D6 isozyme. Genetic polymorphism present in up to 30% of children.
- Other children may have a polymorphism that results in rapid demethylation and exaggerated response.

Hydrocodone

- Vicodin, Lorcet, Lortabs, Norco
- Dose 0.1-0.2 mg/kg every 4 hours
- Slightly less reported N/V than with codeine
- Also usually comes in a preparation with acetaminophen, but more variability exists in the ratio of the two medications
- Codeine and hydrocodone used to be available as sole elixirs, NO acetaminophen, now no longer commercially available

Oxycodone

- Percocet and Tylox are oxycodone compounded w/ acetaminophen
- Comes in both a SR (slow-release) and IR (immediate-release) form
- Dose 0.1-0.2 mg/kg IR every 4-6 hrs.
- More often for children expected to have a protracted pain course
- Can be ordered without acetaminophen, as oxycodone SR or IR
- IR but no SR in the *elixir* form

- Equivalences
- www.globalrph.com/narcoticonv.htm

Adjuvant Drugs to Narcotics

- NSAIDs
- Ketamine
- Benzodiazepines
- Anticonvulsants
- Neuroleptics
- Antidepressants
- Alpha-2 agonists
- Tramadol

NSAIDs

- All are prostaglandin inhibitors/anti-inflammatories.
- ASA (acetylsalicylic acid) infrequently used post-operatively because of irreversibility inhibiting platelets. Additionally, in children its association with Reye's Syndrome.
- Good for mild pain or when used with an opioid.
- Decreases opioid requirements. NSAIDs should be written at ATC/scheduled doses if being given to help decrease opioid requirements.

NSAIDs

- Ibuprofen 10-15 mg/kg q 6-8 hrs.
- Ketorolac 1 mg/kg IV at one time or initial dose followed by 0.5 mg/kg q 6 hrs. Should write a 3 day limit.
- Naproxen 6 mg/kg bid (decreases # of pills)

COX-2 Inhibitors

- Cyclooxygenase isoenzyme expression is seen in tissue inflammation and injury.
- Inhibition of these enzymes decreases tissue inflammation and hence associated pain.
- Advantages vs. traditional NSAIDS is decreased gastritis and platelet function preservation.
- Risk of nephrotoxicity seems comparable

Perioperative Ketorolac Gastritis/ GI Bleed

- When therapy lasted 5 or fewer days, ketorolac was associated with only a small increased risk of gastrointestinal bleeding; Odds Ratio = 1.17.
- When therapy was prolonged beyond 5 days; the Odds Ratio was 2.20 (Strom 1996).
- Reason most institutions put limits on their orders to 3 days.
- Patients should also be on some form of GI ulcer prophylaxis.

Ketorolac and Bone Healing

- Bandolier Journal (reviews evidence based claims concerning health care)
  - Ketorolac did increase nonunion rates postoperatively in spinal fusion patients.
  - This effect showed synergism with smoking patients.
  - Indomethicin likewise has been shown to increase the risk of nonunion in long bone fractures.
  - COX-2 inhibitors, feldene, low-dose aspirin, and acetaminophen have not been shown to increase rates of nonunion.

COX-2's and MI's

- VIGOR trial looked at VIOXX (rofecoxib) and naproxen and showed a 4-fold increase in incidence of serious CV events after only 100 of expected 8,000 pts were enrolled so trial stopped
- CLASS trial looked at high dose Celebrex (celecoxib) vs diclofenac vs ibuprofen mainly looking at GI effects. Allowed pts on Celebrex w/ CV disease to take ASA as previously prescribed. Found no sig. increased incidence of CV effects, BUT no sparing of GI symptoms either at a sig. higher cost.

NSAIDs

- Tylenol
  - 10-15 mg/kg PO or IV now (Ofirmev^{RX}) q 4-6 hrs
  - Not to exceed 90 mg/kg/d or 4 Gms for adults
  - Care must be taken to monitor the amount of acetaminophen being administered if Tylenol and Tylenol-containing narcotics are being taken concurrently
  - Alternate acetaminophen, w/its hepatotoxicity, with other NSAIDs w/ primarily nephrotoxicity

Ofirmev^{RX}

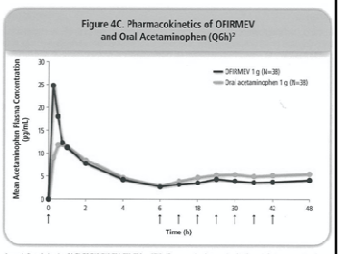
- Acetaminophen injection
- Introduced in Europe in 2002, now used in over 60 countries, just received FDA approval in the USA
- Due to cost issues it's use is limited to patients who can not take PO acetaminophen or those who IV ketorolac is contraindicated
- $10 per 1,000 mg dose (vs $0.68 for 30 mg vial of ketorolac)

Ofirmev^{RX}

- Onset = 15 minutes
- Peak effect = one hour
- Duration = 6 hours
- Levels seen in CSF in 5 minutes
  - ❖ Mechanism of action of acetaminophen is thought to be centrally mediated.

Ofirmev^{RX}

- Verses PO acetaminophen
  - 70% higher C_{max}
  - T_{max} reached 30 minutes earlier
  - Higher plasma C_{max}
    - did not significantly increase adverse reactions
    - nor levels of glutathione conjugates
    - Encourages faster higher peaks in CSF

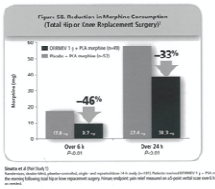


Ofirmev^{RX}

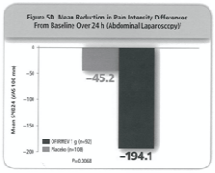
- Decreased opioid consumption vs placebo in:
  - THR/TKR
  - T&A
  - Abdominal surgeries
- Decreased time to first rescue medication, percentage of patients requiring opioids
- Improved patient satisfaction scores

Ofirmev

MSO_4 CONSUMPTION



CHANGES IN PAIN INTENSITY



Benzodiazepines

- May be most useful for post-operative pain likely to produce muscle spasm, ie, scoliosis surgery with instrumentation, large enbloc resections involving upper leg
- Anxiolysis – do NOT provide analgesia, but can be helpful in alleviating situational anxiety

Benzodiazepines

- Valium (diazepam) 0.05 mg/kg PO or IV every 6-8 hrs.
- Increase respiratory depression and hypotension when used with narcotics.

Muscle Relaxants

- Baclofen
  - **Spasticity Adults and Children 12 y and older** PO 5 mg 3 times daily for 3 days. Increase by 5 mg/dose every 3 days as needed up to max 80 mg/day (20 mg 4 times daily)
  - Intrathecal – 50 mcg (1 ml) Onset 0.5 – 1 hr with 4-8 hr duration
- Robaxin
  - Given one hour before the end of surgery for large en-bloc resections or big spine cases to decrease spasticity
  - 0.5-1 Gm for adults
  - 15 mg/kg for children

Anticonvulsants

Block Na+ channels thereby decreasing the afferent input of the pain response

Anticonvulsants

- Carmamazepine (Tegretol) was used, but need to follow levels to avoid hepatotoxicity led to its disfavor.
- Clonazepam (Klonopin) 0.01-0.03 mg/kg increased by 0.01 mg/kg every 3 days to a max. of 0.1-0.2 mg/kg.
- Gabapentin (Neurontin) 10-15 mg/kg divided tid increased by 10-15 mg/kg to a maximum of 50 mg/kg. A larger dose may be given at night to facilitate sleep. Large preoperative doses of 15 mg/kg as a single dose may be given, esp. for large orthopedic and thoracic surgeries.
- Pregabalin (Lyrica) start at 2 mg/k/d divided bid-tid and incr. to max. 4-5 mg/k/d.

Gabapentin

- 1-2 hours pre-op -> 20-60% opioid sparing effect over first 24hrs
- Reduce opioid related side effects
  - Nausea
  - Vomiting
  - Urinary retention
- Side effects
  - Dizziness
  - Sedation

Gabapentin

- Mechanism of Action
  - Inhibits voltage-gated calcium channels
  - These channels are upregulated in the dorsal root ganglia and spinal cord after surgical trauma
  - Inhibits influx of calcium and subsequently inhibits release of excitatory neurotransmitters
- Bioavailability is dose proportional
  - 60% of 900mg → 540mg
  - 47% of 1200mg → 564mg
  - 34% of 2400mg → 816mg
  - 33% of 3600mg → 1188mg

Ketamine

- Phencyclidine derivative that produces "dissociative "anesthesia.
- Noncompetitive antagonism at NMDA receptors
- Bronchodilator
- Sialogogue
- Minimal respiratory depression
- Airway reflexes more likely to be preserved

Ketamine (cont.)

- Introduced as a "monoanesthetic" drug;
  - Analgesia
  - Amnesia
  - Loss of consciousness
  - Immobility

Pharmacokinetics

- Rapid onset, relatively short duration of action, high lipid solubility
- Peak plasma concentrations within 1 minute after IV and within 5 minutes after IM
- Peak concentration in brain can be 4-5 times higher than that in the plasma
- Hepatic clearance with elimination half-time of 2-3 hours

Side Effects

- Hallucinations – 5-30%
  - May be auditory, visual, and proprioceptive
  - More common in >15yrs of age, female, >2mg/kg, hx of personality problems, PTSD, anyone with combat experience
- Loss of skin and musculoskeletal sensations results in decreased ability to perceive gravity and sense of bodily detachment.

Ketamine Side Effects

- Salivation
- Increased HR and systemic BP
- Increased PA pressures
- Increased ICP
- Increased CMRO2 and cerebral blood flow

Clinical Significance

- Reduction of opioid usage
- Possible reversal of opioid tolerance
- Reduction of chronic pain
- Can prevent opioid induced hyperalgesia
- May help decrease central sensitization

Ketamine

- Dosing for infusions
  - 0.15mg/kg one time intra-op dose
  - 0.1, 0.15 and 0.25mg/kg/hr infusion

Alpha-2 Agonists

- Two Agents
  - Clonidine (Duralon)
  - Dexmedetomidine (Precedex)

Alpha-2 Agonists

- Postsynaptic activation in the CNS causes sedation and the inhibition of sympathetic activity with a decrease in BP and HR
- Binding to alpha-2 receptors in the spinal cord has been demonstrated to decrease the need for morphine

Precedex

- Used primarily as an infusion 0.2-0.7 mg/kg/hr
- An initial load of 1 mg/kg may be given over 20 minutes, but likelihood of bradycardia and hypotension greater with bolus dosing

Clonidine

- 2mcg/kg for patients
  - Requiring large amounts of opioids
  - Still in pain
  - Hypertensive and tachycardic
- May repeat 1 mcg/kg q 5 min up to 4-5 mcg/kg

Tramadol (Ultram)

- Synthetic analgesic
- Its exact mechanism of action is unknown
- Similar to morphine, binds to opioid receptors in the brain that transmit the sensation of pain from throughout the body
- Also works in a similar manner as some antidepressant medications by inhibiting the reuptake serotonin and norepinephrine in the brain
- Like other narcotics may be abused

Drugs	Affinity to opioid receptors			Inhibition of uptake	
	μ	*δ*	*κ*	Norepinephrine	Serotonin
+/− Tramadol	++	NA	NA	+++	+++
Morphine	+++++	++++	+++	NA	NA
Codeine	++	+	+	NA	NA
Imipramine	++	NA	++	+++++	++++

Tramadol (Ultram)

- 1-2 mg/kg q 4-6 hours
- Available here as 5mg/ml suspension and 50mg tablets
- Study in adenoidectomy patients showed 3-fold reduction in # of patients requiring postoperative narcotics when 2mg/kg was administered preoperatively (Viitanen 2001)

Tricyclic Antidepressants

- Ex: amitriptyline, imipramine, doxepin
- Block reuptake of norepinephrine, 5-HT, and dopamine in the CNS
- Agents in the group have varying selectivity of action on each of these neurotransmitters
- Inhibition of the firing rates of neurons containing norepinephrine is thought to decrease the excitation or up-regulation of the pain response

Tricyclic Antidepressants

- Used to treat dull aching or "burning" neuropathic pain
- Neuropathic pain seen with nerve entrapment, tumor pressure, crush or ischemic injury, neuropathies, post-herpetic neuralgia, etc.
- A mild decrease in pain intensity and amelioration of sleep disturbances and affective sequelae are the goals

Amitriptyline (Elavil)

- Good for people with sleeping difficulties
- Few reports of cardiac dysrhythmias so should do thorough cardiac history and consider baseline EKG
- Start 0.1 mg/kg q HS and increase by 0.1 mg/k/d q 3-4 days to max of 0.7 mg/kg

Neuroleptics

- Phenothiazines are the most common antipsychotic/neuroleptic used in pain management
- Ex: chloropromazine (Thorazine)
- Antagonize actions of dopamine as a neurotransmitter in the basal ganglia and limbic system
- Have antiemetic properties, especially when nausea is associated with vestibular stimulation
  - Prochlorperazine (Compazine) specifically used for nausea
- Antihistamine effects
- Potentiate analgesia and sedation

Peripheral Catheters/Blocks

- Interscalene → shoulder
- Axillary → arm/hand
- Femoral → skin/muscle biopsies
  - → femoral pinning for traction
- Sciatic → in addition to femoral nerve block to block entire leg
  - → lower leg
- Popliteal → lower leg, ankle, foot

Peripheral Blocks

- Advantages of peripheral over neuraxial blocks
  - Longer acting
  - More site specific
  - Can more safely be done with coagulopathies

TAP Blocks

- Dilute local anesthetic of greater volume usually 1cc/kg per side up to 20cc
- Instilled between transversus abdominis and internal oblique

ASA Guidelines for Post-op Pain Control

- Whenever possible anesthesiologists should employ multimodal pain management therapy.
- Unless contraindicated all patients should receive an around-the-clock regimen of non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 inhibitors.
- Regional blockade with local anesthetics should be considered.
- Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events.
- The choice of medication dose route and duration of therapy should be individualized.