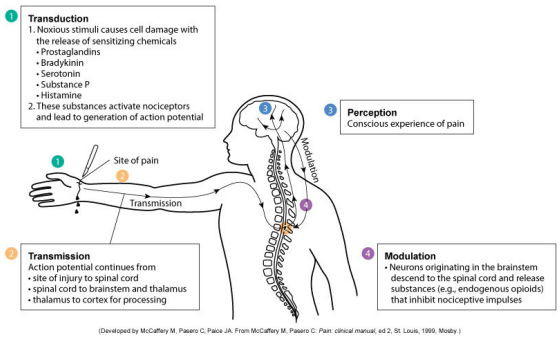
Pain, Anesthetics, Opiates, and NSAIDS

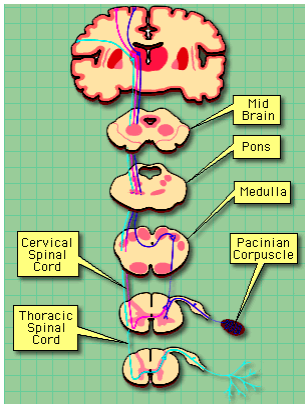
Pain

- Definition: unpleasant sensory and emotional experience
  - Subjective: sensation and emotion
  - Not necessarily correlated with a stimulus
- Purposeful: tells you that damage is being done to the body
  - Seek care
  - Stop the destructive behavior

Neurophysiology of Pain

- Pain transduction – pain stimulus
- Pain transmission – nerve conduction
- Pain perception
- Pain modulation – running interference





Pain Theories

- No Single Integrated Theory Exists
  - Specificity
  - Pattern or Summation
  - Gate Control
    - Large fibers compete for “gate access”
    - Edge out the smaller fibers
  - Endorphin-enkephalin
    - Activate opiate receptors in synapse
    - Opiate receptors
      - mu, kappa, delta

Types of Pain

- Concepts
  - Pain Threshold
  - Pain Tolerance
- Acute – autonomic hyperactivity
  - Catecholamine release: Tachycardia, tachypnea, increased BP, irritability
  - Local muscle rigidity
- Chronic
  - Continuous or intermittent
  - Little or no autonomic hyperactivity

Pain Management

- Stop the stimulus
- Introduce competing stimulus (gate theory)
- Induce natural endorphins
- Increase brain modulation
- Pharmacologic Approaches
  - Inhibit nociceptor sensitivity
  - Inhibit spinal synapse sensitivity
  - Inhibit brain pain receptors
  - Inhibit neuron transmission

Local Anesthetics

- Mechanism: block sodium channels on axons; prevents action potentials
- Selectivity
  - Pain Perception
  - Cold, Warmth
  - Touch
  - Deep Pressure
  - Also block motor neurons
- Combination with vasoconstrictors

Local Anesthetics

- Ester vs Amide
  - Amides breakdown in liver
  - Esters breakdown in blood
- Adverse effects
  - CNS excitation followed by depression, death
  - Cardiovascular system: heart blocks, death
  - Allergic reactions: more common with ester

Local Anesthetics

- Procaine (Novocain)
  - Readily absorbed, not effective topically
  - Not used very often
- Lidocaine
  - Topically, works faster
- Cocaine
  - Also causes intense vasoconstriction

Opioid Analgesics

- Vocabulary
  - Opioid
  - Opiate
  - Narcotic
- Endogenous Opioids
  - Enkaphalins
  - Endorphins
  - Dynorphins

Opioid Receptors

- Mu – most affected by opioid drugs
  - Analgesia, respiratory depression, euphoria, sedation, GI motility
  - Physical dependence
- Kappa – weakly affected by opiod drugs
  - Analgesia, Sedation, GI motility
- Delta – not affected by opioid drugs

Drug actions on Receptors

- Drug actions
  - Opioid agonists
    - Strong
    - Moderate
  - Opioid agonist-antagonists
  - Pure opioid antagonists

Morphine: Prototype Opioid

- Affects central and peripheral receptors
- Major effects
  - Analgesia, drowsiness, mental clouding, reduction in anxiety, euphoria
- Other effects
  - Respiratory depression, constipation, urinary retention, orthostatic hypotension, emesis, miosis, cough suppression, biliary colic, venous pooling

Clinical Considerations

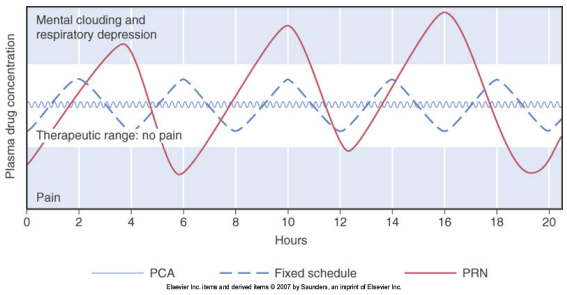
- Respiratory Depression
  - Onset, 4-5 hours depression
  - Do not give if resp < 12 breath/min
- Constipation
- Urinary retention –
  - encourage voiding Q4 hours, I/Os, assessment
- Cough suppression
  - Encourage coughing, assessment

Clinical Considerations

- Biliary colic – suggest alternative drug
- Emesis
- Intracranial Pressure (ICP)
- Euphoria/Dysphoria
- Sedation – fall precautions, dosing
- Miosis – bright light
- Itching

Pharmacokinetics

- Enteral route - onset slower
- Duration ~4-5 hours; 12-24 hours with SR
- Distribution
  - Does not cross blood brain barrier ***well***
  - Most drug is distributed in blood & periphery
- Metabolized by liver
  - Enteral route, 1st pass effect
  - Liver disease



Strong Opioids

- Fentanyl – patch (transdermal)
- Meperidine (Demerol) – benefits/problems
- Oxymorphone, Hydromorphone
- Sufentanil, Lofentanil, Alfentanil
- Methadone – often used to treat opiate addiction
- Heroin

Moderate Strength Opioids

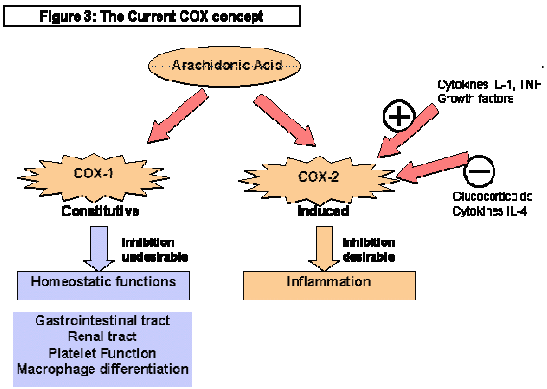
- Codeine
- Oxycodone
- Hydrocodone
- Propoxyphene (Darvon, Darvocet)
  - Little real analgesic benefit above acetaminophen alone (Li Wan Po, Zhang, 1997, BMJ)
  - Inappropriate in patients > 65 yrs (Simon, et al., 2005. J Am Ger Soc)

Other

- Non-opioid
  - Tramadol, Ultram
- Opioid Antagonists
  - Naloxone, Narcan
- General Anesthesia
  - Analgesia
  - Amnesia
  - Paralysis

Prostaglandins

- Inflammatory mediator
- Sensitizes nociceptors and brain pain receptors
- Made from Arachidonic acid
- Manufatured by cyclooxygenase (COX)
  - Two pathways: COX-1 and COX-2
    - COX-1 pathway (virtually all tissues)
      - Stomach lining – limit acid damage
      - Macrophage differentiation
      - Platelet aggregation
      - Renal Function
    - COX-2 pathway (site of tissue injury)
      - Inflammation



COX Inhibitors

- Major classes
  - Inflammatory inhibiting agents (NSAIDS)
  - Non-inflammatory inhibiting agent

NSAIDS: Non-steroidal Anti-Inflammatory Drugs

- NSAIDS
  - Generic term to mean any drug that inhibits inflammation but does not affect cortisol receptors
  - Work by inhibiting COX
  - Selectivity - inhibit both COX-1 and COX-2
  - More selective for COX-2, fewer undesirable side effects

Typical NSAIDS

- "Nonselective" COX inhibitors
  - Aspirin
  - Ibuprofen
  - Naproxen
  - Diclofenac (Voltaren)
  - Indomethacin (Indocin)
  - Sulindac
  - Ketorolac (Toradol)
- COX-2 inhibitors
  - Celecoxib (Celebrex)

Aspiring: Prototype

- Indications
  - Suppression of inflammation
  - Analgesia
  - Reduction of Fever
  - Dysmenorrhea
  - Suppression of platelet aggregation
  - Colorectal cancer prevention
  - Protection against Alzheimer's Disease

Adverse effects

- GI: pain vs ulcer
  - Adjuvant preventative therapy
- Bleeding
- Renal impairment
- Salicylism
- Reye's syndrome
- Pregnancy: Cat D
- Hypersensitivity

Drug Interactions

- Warfarin (Coumadin)
- Glucocorticoids (Steroids)
- Alcohol
- Ibuprofen

Formulations

- Tablets
- Buffered Tablets
- Buffered Solution
- Enteric-coated
- Time released
- Rectal suppositories
- Typical dose
  - 325-650 mg
  - Low dose: 81 mg

Key Differences with other COX-1

- ASA binds irreversibly to COX-1
  - Inhibition of Platelets
- Non-aspirin products do not protect against MI

Other Cox-1 Inhibitors

- Ibuprofen (Advil, Motrin)
- Ketoprofen (Orudis)
- Naproxen (Aleve)
- Diclofenac (Voltaren)
- Ketorolac (Toradol) can be given IM
- Indomethacin (Indocin)
- Nabumetone (Relafen)

COX-2 inhibitors

- More selective for COX-2
- Reduce pain and inflammation
- Do not produce platelet effects
- GI side effects?
- CV safety?
- Drugs:
  - Celecoxib: Celebrex (need to know)
  - Rofecoxib: Vioxx (Off the market)
  - Valdecoxib: Bextra (Off the market)

Acetaminophen

- Inhibits COX, but only in the CNS
- Reduces fever and pain
- Does not inhibit inflammation
- Maximum Dosage: 4gm/day
- Toxic metabolite may damage liver in large doses given over time
- Key point: Acetaminophen is used as adjunct in many drugs. Potential for accidental overdosing.

Aspirin, NSAIDS, Acetaminophen

Use	**ASA**	**NSAID**	**APAP**
Pain	Yes	Yes	Yes
Inflammation	Moderate	Yes	No
Fever	Yes	Yes	Yes
Platelet aggregation (CAD,Stroke)	Yes	No	No