MEASURING, MANAGING AND MITIGATING CANCER AND TREATMENT PAIN IN INFANTS: Pharmacology

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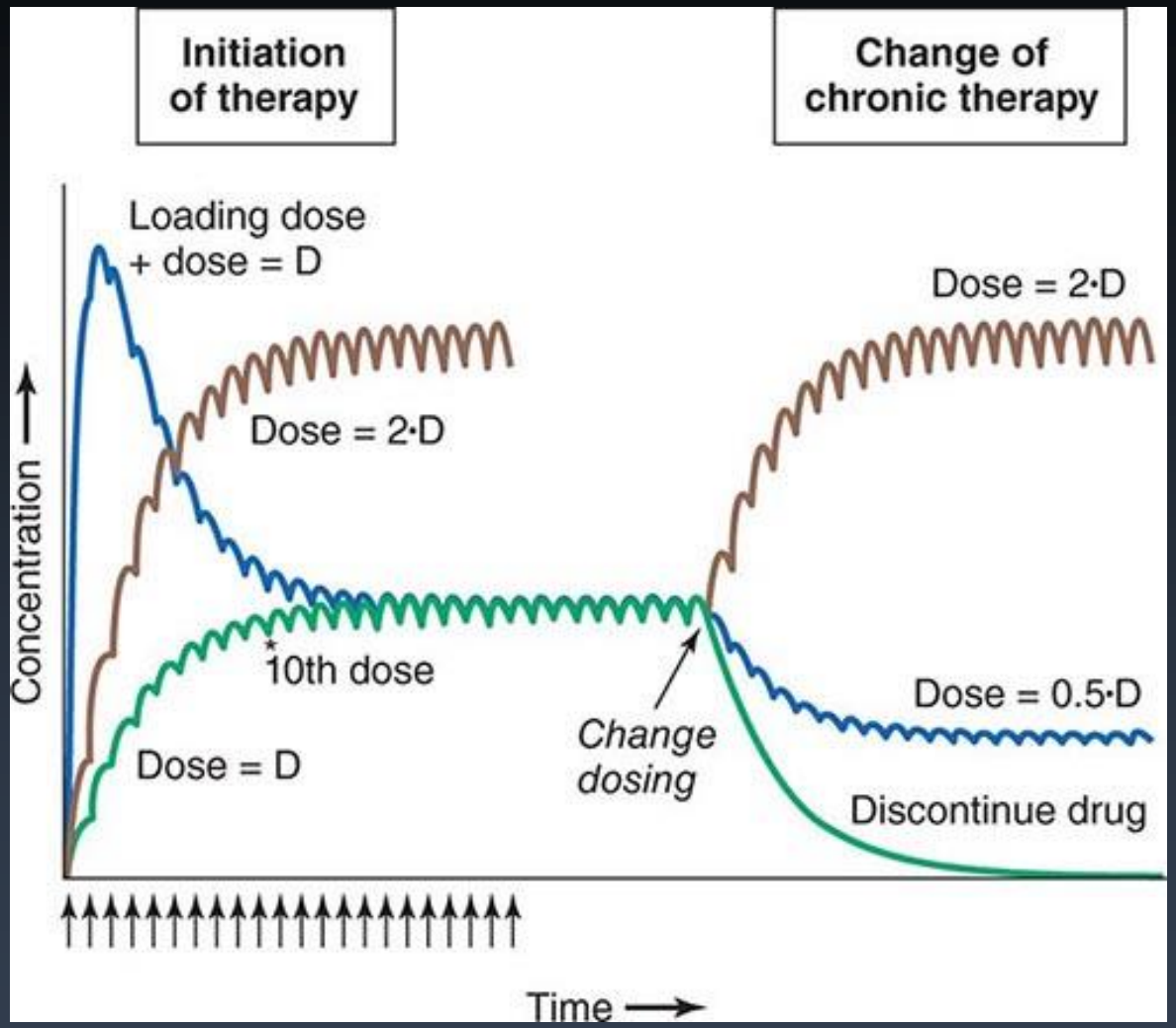
Cancer Pain in Infants

- General Pain Considerations:
  - Procedural/post-surgical vs. persistent
  - Development of chronic pain
  - Non-traditional pain-associated outcomes (both pain and pain med related)
- Infant Specific Considerations
  - Non-verbal signals/anxiety/hunger
  - Pharmacology: developmental changes, PK/PD
  - Geography:
    - In hospital: drugs available, complication handling
    - Where on patient pain is

The Right Way to Treat Pain in Infants

- None
  - hospital/site specific

- But general principles:
  - An invasive airway is not needed (very common)
  - Multimodal
  - Repeated, accurate and consistent pain assessment
  - Reduce/group procedures
  - Phone a friend (even other hospitals)
  - You can always give more, pharmacology doesn't recognize q4h dosing (? How long for infusion to reach steady state)



- Blue: initial bolus, faster steady state
- Green/Brown: infusion, same time to equilibrium
- Same effect when coming off therapy
- Be aware of how long the pharmacology takes to work, and let it work

Pain Receptor Pharmacology

- Pain relief associated with
  - Opiate agonism: morphine
  - Alpha-2 agonism: clonidine/dexmedetomidine
  - NMDA antagonism: ketamine
  - Endocannabinoid agonism
  - COX-(1,2,3) inhibition: acetaminophen
- Pain relief NOT associated with
  - GABA-A agonism: propofol, benzodiazepines
- Avoid strict dosing regimens: highly variable with development, renal/liver function, albumin, plasma enzyme levels etc. – the right dose is the one that works

Non-pharmacologic Therapy

- Smaller, short-timed pain (venipuncture)
  - Reduce not eliminate

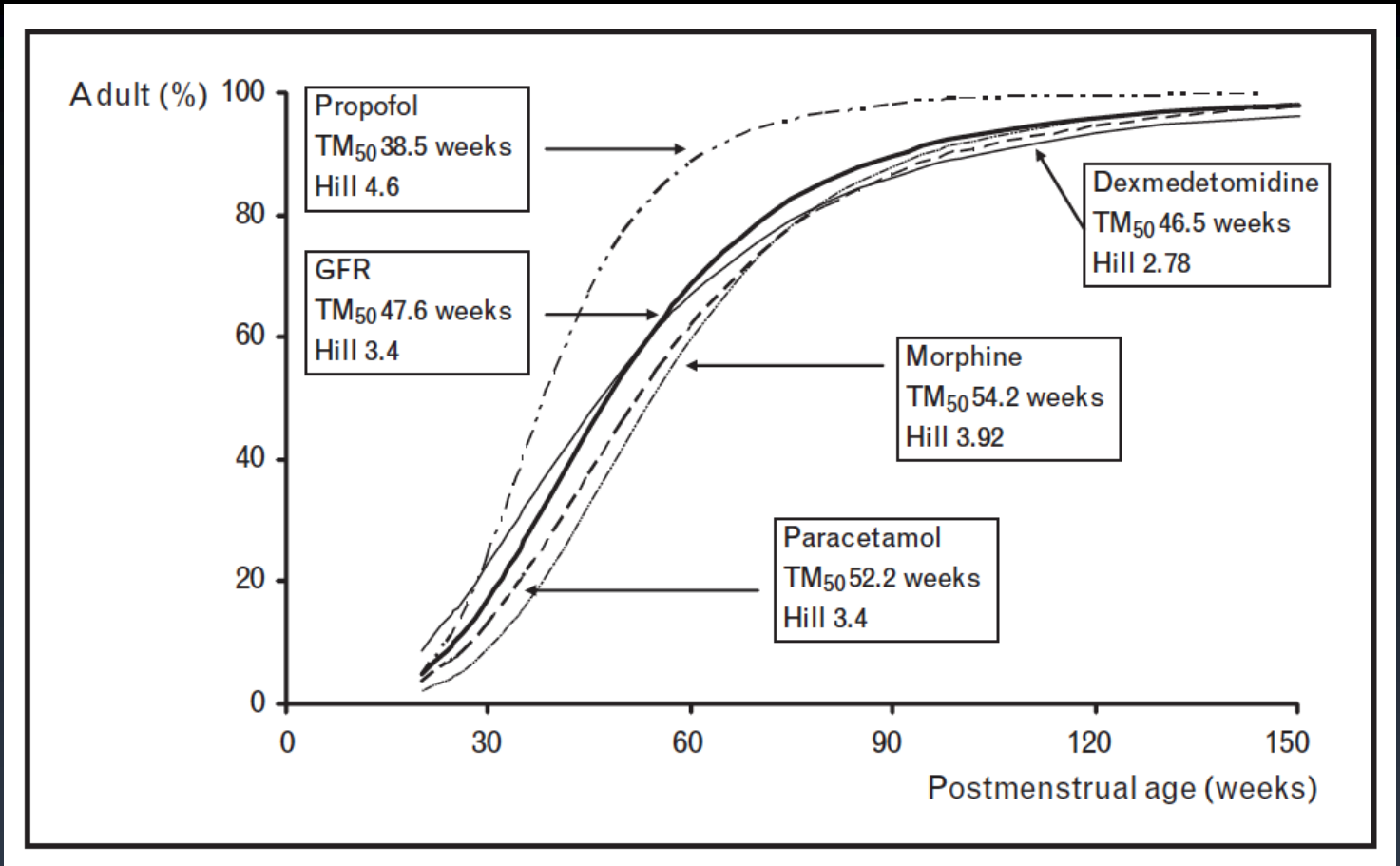
- Sucrose (EEG level verification, unknown mechanism)
  - Oral, not gastric
  - Likely still a stress response
  - Multiple dosing likely better than single
- Breastfeeding
- Reduce other stimuli

Non-Systemic Therapy

- Topical Creams
  - Only very superficial cutaneous procedures (not venipuncture)
  - Like all drugs, let them work
  - Use on intact skin
  - Lower albumin – less bound drug, lower dose to toxicity (epidural run slower)
  - (potential) methemoglobinemia

Opiates

- Opiates 1/3 of "Big Three" of drug errors
- For pain control, no benefit of infusion or intermittent bolus
  - In general, infant population because of clearance
- lower plasma clearance, a higher volume of distribution, decreased protein binding resulting in a greater free fraction, and decreased renal clearance
- Most studies on intubated studies
  - Fentanyl: poor to no studies, poss. increases ventilation
  - Narcotic infusions are not associated with incr/decr risk of intraventricular hemorrhage, periventricular leukomalacia, or death (Aranda 2005, Simons 2003, Anand 2003)



- Morphine: two metabolites that are more potent and renal excreted, more hydrophilic (CNS depression)
- Hydromorphone: biliary excretion
- Both have genetic components

Opiates

- Oral > IV pharmacology – switch to orals ASAP
- Morphine:
  - I: 10 – 40 mcg/kg/hr, start ½ of toddler/children
  - B: 50-100 mcg/kg/dose
  - O: 0.2-0.5 mg/kg/dose q3h
- Hydromorphone:
  - I: 4 - 6 mcg/kg/hr
  - B: 50-100 mcg/kg
  - O: 40 - 80 mcg/kg q 3 - 4h

Opiates

- Codeine: please don't ever use
- Tramadol: in infants not used routinely
  - Renal excretion, follows renal maturation
  - IV: bolus 1-2.5 mg/kg q 4-6 hr
  - IV: infusion 0.07-0.25 mg/kg/hr.
- Equilibration:
  - Pain: morphine/HM ~7 min
  - Resp: HM ~7min, morphine ~60 min

Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study

S Willmann[1], AN Edginton[1,2], K Coboeken[1], G Ahr[3] and J Lippert[1]

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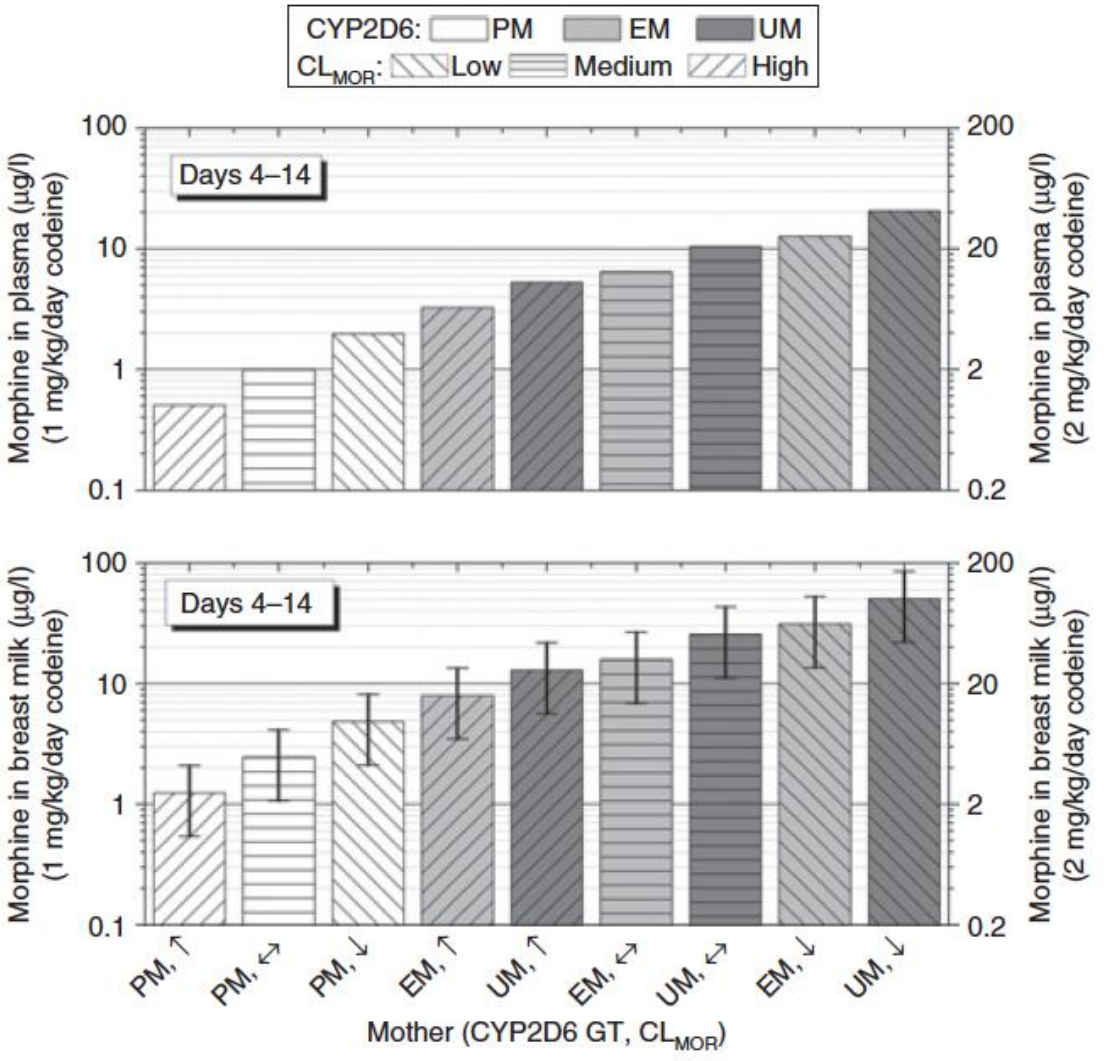
- Dose transmitted in breast milk to therapeutic levels
- Genetic component
- Importance of non-rigid dosing guidelines



Opiate Side Effects/Complications

- Pruritus
- Constipation (peripheral antagon)
- Withdrawal still happens
  - Changes in receptor density in minutes
  - ~5 days more significant
  - Recommended weaning: ketamine -> opiate -> benzo
  - Wean 10-20% per day, symptom dependent
  - Neonatal abstinence score (NAS): score range 0-43, 0-7 none, 8-10 mild, 13-16 moderate, >17 severe

Cancer Care Ontario (CCO) protocol for management of constipation due to medication in (adults)	
Step 1	Non-pharmacological measures
Step 2	Start Patients on opioids on step 2 Sennosides (Senokot) up to 8 daily Docusate (Colace) up to 8 daily
Step 3	Add Magnesium Hydroxide or change sennosides to bisacodyl (Dulcolax) tablets 5-15 mg daily
Step 4	Add Lactulose 15 mL 2-4 times daily
Step 5	Glycerin or bisacodyl suppository or Sodium phosphates (e.g. Fleet®) enema.

NSAIDS

- Not FDA approved for patients < 6 months (renal function)
- Evidence that ibuprofen less toxic than ketorolac
- Likely okay for short term use, without renal impairment
- Not routine use, talk to pain team

Acetaminophen

24 to 30 weeks gestation – 20 to 30 mg/kg/day
31 to 36 weeks gestation – 35 to 50 mg/kg/day
37 to 42 weeks gestation – 50 to 60 mg/kg/day
1 to 3 months postnatal – 60 to 75 mg/kg/day

Regional Anesthesia

- Role for indwelling catheters/wound catheters
- Lumbar/Caudal Bupivicaine 0.2-0.3 mg/kg/hr
- Thoracic Bupivicaine 0.10-0.13 mg/kg/hr
  - For both, reduce rate 1/3 after 24-48 hours
- Difficult to predict absorption in epidural space, best to avoid narcotics in neonate/infant
- Highest failure rate:
  - Threaded caudal catheters
  - Age of patient
- May reduce cancer spread/recurrence
- Likely larger academic centers, but discuss with your anesthesia department.

Conclusions/Take Home

- Under treatment leads to chronic pain, cognitive changes
- Use multimodal, WHO pain ladder
- Culture of accurate pain measurement
  - vs hunger, anxiety
- Frequent, smaller dosing regimens, esp in acute pain/post-surgical
- Many (most) drugs renal excreted, adjust dosing
- Better integration with pain teams for invasive pain treament