Opioid Conversions □ When, Why and How

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WHAT HAS BEEN YOUR TOUGHEST PAIN CASE???

□ Write down what the circumstances surrounding the case
□ Write down what was done
□ Tell us what worked and what did not work
□ Tell us what frustrated you about this case and if anything about it was rewarding

THE PROBLEM (McPherson – Demystifying Opioid Conversion Calculation – 2010)

□ Ask 15 experts □ get 15 answers
□ We can agree
□ Patients switch from one opioid to another
□ Patients switch form on route to another
□ Patients switch from on formulation to another
□ Conversion charts are often based on:
□ Anecdotal information
□ Unidirectional information
□ Single dose studies
□ No regard for patient variability

NOCICEPTION

□ Nociceptors
□ On C-fibers and A-delta fibers

□ Nociceptor activation
□ Noxious stimuli, bradykinins, histamine, inflammation, prostaglandins (sensitize receptors)
□ Depolarization of neuron
□ Substance-P is released and mediates neuronal inflammation
□ Nerve growth factor also is released with inflammation

NEURONAL ACTIVITY

ref #3
**EXCITATORY DORSAL HORN ACTIVITY**
- Release of Substance P
- Release of glutamate
- Release of aspartate
- Excitatory Amino Acid Receptors (e.g., NMDA)
- Central neuronal depolarization
- Pain signal sent to brain via spinothalamic tract

**INHIBITORY DORSAL HORN ACTIVITY**
- Glycine
- GABA
- Serotonin
- Norepinephrine
- Opioid receptors (endorphins)
- Stimulation of large afferent neurons (TENS)

**NORMAL NOCICEPTION**
- Spinalthalamic to brain (modulation via endorphins)
- Central inhibitory pathway

**PAIN=SUMMATION OF EXCITATORY AND INHIBITORY FACTORS**
- Pain management pharmacology=
  - Manipulation of pain pathway
NOCICEPTIVE PAIN AND PHARMACOLOGY

- Opioids—affinity for CNS opioid receptors
  - **NOTE** effect not only presynaptic release of substance P in the dorsal horn but also on opioid receptors in the brainstem and midbrain exacerbating inhibitory modulation

NEURONAL PLASTICITY

- Nerve damage or extended/constant/intense bombardment of nociceptive pain fibers
  - Abnormal activity or distribution of voltage-gated sodium channel
    - they fire spontaneously or continuously rather than only when stimulated
  - NMDA receptors (voltage sensitive) activated
  - changes in neuron (hard wire changes)
  - Sprouting of sympathetic fibers from normal targets (blood vessels) to pain fiber cell bodies
  - Sprouting of presynaptic non-pain nerve fibers into what is normally pain fiber areas of the dorsal horn

NEURONAL PLASTICITY

- Nerve damage or extended/constant/intense bombardment of nociceptive pain fibers
  - change in the neurotransmitters and neuroreceptors
    - Decreased substance P production in pain fibers
    - Increased substance P production in non-pain fibers
    - Change in/loss of the opioid receptors
    - Change in NMDA receptor may inhibit opioid receptor

NEURONAL ACTIVITY

ref #3

ref #5
NEURONAL PLASTICITY

- Abnormal pain generator and a reorganized receiver (connections, neurotransmitters, and receptors)
- Helps explain abnormal sensation

ABNORMAL SENSATIONS

- Spontaneous pain (paroxysmal or constant)
- Burning, shooting, lancinating
- Hyperalgesia
- Exaggerated painful response to a normally noxious stimulus
- Allodynia
- Painful response to a normally non-noxious stimulus (light touch–burning)

N-methyl-D-aspartate RECEPTOR

- NMDA receptor
  - A stimulated NMDA receptor may inhibit opioid receptors
  - Neuropathic pain may involve heightened NMDA receptor activity

Methadone

- Why talk about methadone?
  - From 1998 to 2006 the number of Rx increased by 700%.
  - Between 1999 and 2005 deaths that had methadone as a contributor increased nearly 5 fold (4,462) (may be understated since many states do not specify drugs in overdoses)

Methadone History

- Developed because of opium shortage and named after Adolph Hitler (Adolophine) in WW II
- Polamidon discovered in 1942 by German pharmaceutical industry, turned over to military and not developed (too toxic)
- Found to be effective but with high potential for dependence
- By 1950 used for treatment of opioid abstinence syndrome
Methodone

History
- In 1960's pharmacokinetics worked out and by the 1970's it was established that once a day dosing could enable heroin abstinence.
- 1973 regulations for special registrations for methadone dispensing and prescribing.
- 1976 APHA sued and the prescribing and dispensing of methadone for analgesia no longer needed special registration.
- 2007: 40mg disperse tab can only be Rx by registered clinics.

Methadone

- Affect Mu and Delta receptors.
- Also blocks NMDA receptors (ref 21).
- Shown effective in acute pain.
- Chronic/Persistent pain.
- Neuropathic pain.

ADVANTAGES
- Can be taken orally or by injection.
- Very bioavailable.
- Receptor site affinity (Mu, Delta, NMDA).
- Inexpensive.
- Longer administrative intervals.
- No active metabolite.
- Rapid onset of action.

DISADVANTAGES
- Stigma to addiction therapy.
- Fear of regulators.
- Lack of education.
- Lack of experience.
- Lack of pharmaceutical company promotion.
- Because of high volume of distribution, get accumulation in tissue.
- Can be problem in elderly.
- Must individually dose because of long unpredictable half-life.

METHADONE

- Dose ratios to achieve equianalgesia influenced by previous opioid.
- Tolerance to opioids may be dependent on NMDA receptor.
- At high morphine doses, metabolites may produce constant activation of NMDA receptor, requiring more morphine to maintain pain relief.
- Can even see severe myoclonic jerking.
- Conversion to Methadone (which has NMDA antagonist activity) and no excitatory metabolites can result in dramatic decrease in the MS requirements as excitatory metabolite effects are blunted and over time decreased.
- Has been noted to stop myoclonic jerking.
- Conversion have been made with 3-68% of expected equianalgesic dose.

Ref 55,56
CONVERSION RATIO

Ref #57

ORAL MOPHINE EQUIVALENT DAILY DOSE = NON-METHADONE : METHADONE

<table>
<thead>
<tr>
<th>Mg</th>
<th>Ratio</th>
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<tbody>
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<td>2:1</td>
</tr>
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<td>30-99</td>
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Methadone Conversion

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20 mg Oral Oxycodone = 30 mg Oral Morphine
Patient on 100 mg Oxycodone Q12 Hours
Equal to 300 mg Oral Morphine Equivalents (24 hours)
300/12 = 25
Oral Methadone dose = ?

Torsade de Pointes Associated with High Dose Methadone

- Retrospective case series
- Patients from methadone maintenance programs in US and pain management center in Canada
- 17 methadone related patients who developed torsade de pointe (bradycardia induced?)
- Mean daily methadone dose 397+/−283 mg
- Mean QTc interval 615+/−77 seconds
- No control group, no baseline EKG, NO CAUSE and EFFECT can be shown
- Recommendations 2009??

Methadone

- Noted Problems!!!!
  - Starting Dose if opioid naïve??
  - When do you increase dose after initiation?
  - High dose methadone patient admitted to hospital for surgery how do we convert to non-methadone opioid?
  - Lack of data in neuropathic pain
  - Variable half-life

Methadone

- Suggestions when initiating Methadone
  - Carefully note dose and length of therapy of previous opioid use
  - Carefully use NEWER ratios for conversion
  - Note degree of opioid tolerance
  - Carefully consider age, general condition, and medical status of patient
  - Consider concurrent medication
  - Type, severity, and duration of pain
  - Acceptable balance between pain symptoms and analgesia

Opioid Conversion Chart

- Demystifying Opioid Conversion Calculations (A guide for effective dosing)
  - Mary Lynn McPherson □ American Society of Health System Pharmacists, Bethesda, MD 2010.
  - (Whose □ slide rule □ are you using???)
Other Opioids and Conversions

- Need to know
  - What is being treated
  - How is patient doing on present dose
  - How long has the patient been treated on this dose
  - What are the other drugs used to treat the patient
  - What is the end point

Case Studies

- Compression Fracture
- Low Back Pain
- Metastatic Breast Cancer

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SUMMARY

A Weight with Needles on the pounds
To push, and pierce, besides
That if the Flesh resist the Heft
The puncture: coolly tries
That not a pore be overlooked
Of all this Compound Frame
As manifold for Anguish
As Species: be: for name:
Emily Dickinson, 1861

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