SICKLE CELL PAIN

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OBJECTIVES

- Review the Pathogenesis of Pain
- Describe Types of Sickle Cell Pain
- Present the Pharmacology of Pain Treatment
- Summarize Specific Approaches to pain Management
  - Outpatient Management
  - Management in the Emergency Room/Day Unit
  - Management in the Hospital
Sickle Cell Anemia

Morbidity Profile

- Anemia and its sequelae
- Pain Syndromes
- Organ Failure
  - CVA, ACS, RF, etc.
- Co-Morbidity
Sickle Cell Anemia

Pathogenesis

- Deoxygenation
- Polymerization
- Vaso-occlusion
  - Nociception (Tissue Damage)
Pain Pathogenesis

- Tissue Damage
- Transduction
  - Inflammatory mediators
  - Generation of pain impulse
- Transmission
- Modulation
- Perception
Molecular Mechanism of Pain

Transduction → DH → T → BRAIN

Transmission
Modulation
Perception
Sickle Cell Pain
Types & Pathogenesis

- Acute Pain
- Chronic Pain
- Neuropathic Pain
- Mixed
Sickle Cell Pain
Progressive Disease

Episodic
Relapsing
Rемitting

Chronic
Progressive
Sickle Cell Chronic Pain

- Pain with objective signs
  - Avascular (aseptic) necrosis/Osteonecrosis
  - Leg ulcers
  - Chronic osteomyelitis
- Pain without objective signs
  - “central sensitization”
Central Sensitization

Pain stimulates itself
This lowers the pain threshold
As a result ambient events cause pain
Psychobiology of Chronic Pain

Pain
Emotional Distress
Behavioral Dysfunction
Neuropathic Pain Symptoms

- Burning
- Tingling
- Shooting
- Lancinating

- Electrical
- Numb
- Paroxysmal
- Spontaneous
Prerequisites of Effective Pain Management

- Know & believe the patient
- Know the disease
- Know the pharmacology of analgesics
- Consider Alternative/Complementary RX
- Consider Non-pharmacological RX
- Education
- Legislation
Approaches to Pain Management

- Non-pharmacological
- Pharmacological
- Interventional
- Surgical
Non-Pharmacologic Management of Pain

- TENS
- Vibration
- Massage
- Heat or ice packs
- Menthol cream rub
- Therapeutic exercise
- Music
- Relaxation
- Diversion
- Meditation
- Self-Hypnosis
- Accupressure
- Accupuncture
- Biofeedback
Pharmacologic Management of Pain

1 - Non-opioids
2 - Opioids
3 - Adjuvants
4 - Complementary & Alternative Meds
Opioid Analgesics

- $\mu$ Agonists
- Mixed agonists/antagonists
- Partial agonists
- Antagonists
Opioid Analgesics

μ Agonists

- Codeine
- Hydrocodone
- Oxycodone IR, CR
- Morphine IR, CR
- Hydromorphone
- Meperidine
- Fentanyl
- Oxymorphone
- Methadone (LA)
- Levorphanol (LA)
Opioid Analgesics

• Partial Agonists
  − Buprenorphine (Buprenex, Subutex)
  − Buprenorphine / Naloxone (Suboxone)

• Mixed Agonists / Antagonists
  − Pentazocine (Talwin, Talwin NX)
  − Nalbuphine (Nubain)
  − Butorphanol (Stadol, Stadol NS)
Opioid Analgesics

µ Antagonists

- Naloxone (*Narcan*)
- Nalmefene (*Revex*)
- Naltrexone (*Revia*)
Opioids for Mild-Moderate Pain

- Codeine (Tylenol 3, Tylenol 4)
- Oxycodone IR (Percocet, Percodan, Roxicet)
- Hydrocodone (Vicodin, Lorcet, Lortab)
# Opioids for Severe Pain

## Equianalgesic Dosing

<table>
<thead>
<tr>
<th>Opioid</th>
<th>parenteral</th>
<th>po</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Oxycodone (Oxycontin)</td>
<td>NA</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>1.5 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Levorphanol (Levodromoran)</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fentanyl (Duragesic)</td>
<td>0.1 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1.0 mg</td>
<td>5.0 mg</td>
</tr>
</tbody>
</table>
Methods of Administration of Opioids

Traditional / previously described methods
- PO, IM, IV, SC
- PCA, Nasal
- Transdermal, Transmucosal
- Epidural

Christensen et al – J P Hem/Onc 1996
Shaiova & Wallenstein – JNMA 2004
Yaster et al – Pediatrics 1994
Methods of Administration of Opioids

New recently described methods

- Iontophoresis with pt controlled delivery system
- Nebulization
- Implantable intrathecal delivery system; dose 1/100 of IV
- Topical

Koo et al – Am J Health Sys Pharm 2005
Ballas et al – Am JH 2004; Blood 2002
Smith et al – AJH 2005
Ballas et al – Blood (Suppl) 2004
Opioid Analgesics
Types of Formulations

Immediate Release
- For titration
- Acute pain
- Breakthrough pain

Controlled Release
- Maintenance treatment
- Chronic pain
Metabolism of Codeine

Codeine $\xrightarrow{\text{CYP2D6}}$ Morphine
Morphine

- Naturally occurring μ agonist opioid
- Hydrophilic
- Three formulations: IR, CR, SR
- Histaminergic
- Gold standard for CA pain
- Associated with ACS?
Morphine

- Metabolites: M3G, M6G
- M6G: 4 times more potent
  - Accumulates in renal failure
  - Has long half-life
  - Is a potent analgesic
Prevalent Symptoms due to Morphine Metabolite Toxicity

<table>
<thead>
<tr>
<th><strong>Opioid receptor</strong> (morphine-6-glucuronide)</th>
<th><strong>Non-opioid receptor</strong> (morphine-3 glucuronide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>Impaired cognitive function</td>
</tr>
<tr>
<td>Nausea and emesis</td>
<td>Myoclonus, seizures</td>
</tr>
<tr>
<td>Coma</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>---</td>
</tr>
</tbody>
</table>
Pharmacokinetics of Morphine

- Wide variability in patients with and without SCD
- Increased clearance during painful crises
- Increased clearance in children before puberty
- Increased clearance may be related to anemia, renal or hepatic blood flow

Dampier et al 1995
Faura et al 1996
Methadone

- Potent μ-opioid agonist
- Long half-life
- Short duration of analgesia (4-6h)
- Racemic mixture L&D isomers
  - L-isomer: μ agonist + NMDA antagonist
  - D-isomer: NMDA antagonist
- Inhibits re-uptake of serotonin & NE
- Least expensive opioid
Methadone

- Provides pain relief for 4-6 hrs
- Maintains significant serum level and suppresses heroin/opioid craving for 24hrs
- Methadone related death rose by 390% between 1995 and 2004
- The rise in all poisoning deaths rose only 54% in the same period
## Most Commonly Prescribed Drugs with Potential for QT Prolongation

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>Sumatriptan</th>
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</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Indapamide</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Risperidone</td>
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</tbody>
</table>
Fentanyl

• Approved formulations
  - Oral transmucosal fentanyl citrate
  - Fentanyl effervescent buccal tablet
  - Transdermal fentanyl
  - Parenteral fentanyl
Oxymorphphone

- Numorphan IM, SC, Supp
- IR, CR oral formulations (Opana, ER)
Adjuvants

- Antihistamines
- Anti-depressants
- Anti-convulsants
- Benzodiazepines
- Phenothiazines
- GABA-B Agonist (Baclofen)
- α-2 Agonist (Clonidine)
Antidepressants and Priapism

Trazadone / Desyrel +4
SSRI’s +2
TCA +1
Wellbutrin (Bupropion) 0
Serzone / Nefazodone 0
Remeron (Mirtazapine) 0
Opioid Therapy of Sickle Cell Pain

Side Effects

- Nausea
- Allergy
- Myoclonus
- Sedation
- Respiratory Failure

- Vomiting
- Constipation
- Seizure
- Mental Changes
Common Terms (Cont.)

**Addiction:** Pattern of compulsive drug use characterized by continued craving for an opioid and the need to use the opioid for effects other than pain relief.

**Physical Dependence:** Physiologic phenomenon characterized by the development of withdrawal syndrome following abrupt discontinuation of therapy.

**Tolerance:** Increasing amount of an opioid is required to produce the same effect as was produced with previous lesser dose.
Pseudoaddiction

- Drug-seeking behavior due to poor response to opioids or to low dose of opioids
- Patients may be falsely labeled as addicts and be under-treated for pain when opioids are indicated
- Such behavior is corrected by adequate pain relief including adequate prescribing of opioids
Sickle Cell Pain
Management Places

- Clinic
- Emergency Room
- Day Unit
- Hospital
Sickle Cell Pain
Management in Clinic

- Baseline Data include:
  - History and Physical Exam
  - Past History / Family History
  - Known Complications
  - Medications
  - Comprehensive Lab Data
Sickle Cell Pain
Management in Clinic

- Collection of Baseline Data
- Treatment plan in the ER, Day Unit, Hospital
- Prescribe analgesics if needed
- Education
Sickle Cell Pain

Management in Emergency Room

- Assessment
- Individualize Treatment
  - Refer to treatment plan
- Give analgesics IV every two hours for a total of 3 doses
- Give Adjuvants
- If the pain is resolved, discharge
- If pain persists, admit to hospital
- Treat underlying cause if found
Figure 2. Examples of Pain Scales

0-10 Numeric Pain Intensity Scale

No pain | Moderate pain | Worst possible pain

Visual Analog Scale (VAS)*

No pain | Pain as bad as it could possibly be

* A 10-cm vertical or horizontal baseline is recommended for VAS scales.
Pain Assessment Goals

- **Quantify & Observe**
  - Pain intensity
  - Relief
  - Modify factors
  - Location

- **Trigger**
- **Mood**
- **Sedation**
- **Outcome**
Sickle Cell Pain
Management in the Day Unit

- Assessment
- **Individualize Treatment**
  - Refer to treatment plan
- Give analgesic bolus IV, evaluate every 30 min and give maintenance
- Give Adjuvants
- Discharge within 6 hours
Types of Painful Episodes of Hospitalized Patients with SS

- Isolated acute painful episode
- Acute painful crisis superimposed on a chronic pain syndrome
- Complicated acute painful episodes (example: acute pain & ACS, etc...)
- Neuropathic pain may coexist with any of the above
Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Believe the patient.
- Determine the patient’s therapeutic goal
- Conduct thorough clinical assessment.
- Select the appropriate opioid analgesic, its dose, and frequency of administration based on previous experience.
Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Administer opioid analgesics parenterally (preferably IV) on a regular basis usually every 2 hours in adults (maintenance dose).
- Give non-opioid analgesics and adjuvants in combination with opioid analgesics. NSAIDs are contraindicated in the presence of impaired renal and/or hepatic function and history of gastropathy or asthma.
- Monitor sedation and vital signs with special attention to the respiratory rate.
Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Assess pain severity every 30 minutes.
- Give rescue doses (25-50% of maintenance dose) for breakthrough pain every 30 minutes if adequate pain relief is not achieved.
- If three or more rescue doses are needed in 24 hours or less increase the maintenance dose by 25-50% and follow the same procedure of assessment and dose adjustment.
Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Decrease or skip maintenance dose in the presence of severe sedation or if RR <10/min.
- After 2-3 days of therapy decrease the maintenance dose by 25% every 24 hours and replace with an oral opioid in divided doses on a regular basis.
Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- After **24-48 hours** the oral opioid may be given as needed. If pain relapses escalate the dose into its previous level of administration.

- Patients may be discharged if they are pain free with no co-morbid condition or if pain is adequately controlled with oral analgesics.

- Design a discharge plan with follow up as an outpatient.
Management of Painful Crisis in the Hospital

- **Key Steps**
  - **Fixed Schedule**
  - **PCA Issues**
    - Titration to relief
    - Basal dose
    - Lock out dose / Interval
    - Weaning
    - Switching to Orals
Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Believe the patient.
- Determine the patient’s therapeutic goal.
- Administer IV boluses of either morphine (2.5-10mg) or hydromorphone (0.5-2mg) every 10-15 min. Meperidine (10-25mg) is used only in patients who are truly intolerant of morphine or hydromorphone.
Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Reassess the patient’s perception of pain **10 min** after each bolus. Continue to administer intravenous boluses every **10-15 min** until either the pain scale is decreased **50%**, the pain is relieved, or the patient is sedated. The total loading dose of opioid should be recorded to document the demand dose.

- Start pain controlled analgesia (PCA) by using **50%** of the demand dose of opioid that was used in loading the patient to be delivered with a **6 min** lockout interval. Reassess the patient’s perception of pain every **4-8hrs**.
Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Encourage the patient to control their own pain by reinforcing the quantity of opioid that they can deliver as needed and the equivalent potency when converting from meperidine to morphine or hydromorphone.
Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Determine the hourly use of opioid during the day and give **66%** of the hourly dose as a continuous infusion at night to ensure rest.

- On **day 2 or 3** of hospitalization replace by an equivalent oral dose of opioid analgesic on a fixed schedule around the clock and decrease the PCA dose by **25% every 24 hours**.
Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- After **24-48 hours**, the PCA can be discontinued. Oral breakthrough doses can be administered between fixed doses of oral analgesics.

- Patients may be ready for discharge if they are pain free or if their pain is adequately controlled with oral analgesics.

- Taper the opioid after discharge over the following **1-2 weeks** to prevent symptoms of the abstinence syndrome.

- Resume control of chronic pain utilizing the 3 Step Analgesia Ladder if indicated.
Management of Acute Pain
Superimposed on Clinical Pain

- Keep meds for chronic pain as taken
  - May D/C short acting opioids
- Follow steps for episodic acute pain
- Extra caution
Management of Painful Crisis in the Hospital

Key Steps

- Prevention of withdrawal
- Discharge planning
- Follow-up
Prevention of Withdrawal Syndrome

Methadone
Clonidine