From Methadone & Heroin Overdose to Rhabdomyolysis to Acute Renal Failure to Leg Compartment Syndrome to Pain Management: One Patient’s Journey in the ICU

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Objectives

- To detail the journey of one of my patients in the ICU
- To discuss rhabdomyolysis, acute renal failure (ARF), and leg compartment syndrome in terms of what occurred in this patient
- To discuss difficulties encountered with CVVHD and what was done to overcome this
- To discuss pain management in methadone patients and to clarify misconceptions that exist
- To provide a framework for how to approach methadone patients in terms of pain management
History of Initial Presentation

February 12\textsuperscript{th}:

- M.G. a 45 y.o. male was found lying on the ground for \(~20\text{hrs}\) with vomitus present beside him

- Patient took methadone and heroin which lead to his unconscious state
M.G.’s Signs and Symptoms

- Unconscious
- Pain in left buttock and hip, and left knee and ankle
- Numbness in his left leg
- Anuric
Initial Significant Lab Investigations

- Scr 278µmol/L, CrCl ~ 30mL/min, Urea 12.4mmol/L
- CK 44,760 Tp 0.046
- P 1.86mmol/L, K 7.4mmol/L
- AST 503U/L, ALT 172U/L, ALP 111U/L
- WBC 40.8
What is happening?

- M.G. developed rhabdomyolysis 2º to his unconscious state and heroin use
- M.G. developed ARF 2º to rhabdomyolysis
- M.G. developed leg compartment syndrome (a cause of rhabdomyolysis)
M.G.’s Medical History

- Attention Deficit Disorder
- Anxiety
- Heroin addict
- GERD (?)
- Bipolar Disorder(?)

Medications:
- Olanzapine 15mg po OD
- Welbutrin XR 300mg po OD
- Methadone 7mg po OD
- Rabeprazole 10mg po OD
Initial Medical Treatment

- NS at 125mL/hr
- 3amp of NaHCO₃ in 1L D5W
- Thiamine 100mg po OD x 3 days
- Multivitamin i tab po OD
- Methadone 7mg po OD
- Olanzapine 15mg po OD
- Wellbutrin XR 300mg po OD
Rhabdomyolysis

**Definition:**
- Dissolution of skeletal muscles that produces a non-specific syndrome that causes extravasation of intracellular contents from myocytes to the circulatory system

**Hallmark Lab Investigations:**
- Elevation of serum muscle enzymes (CK > 100,000 U/L), myoglobinuria
- Renal failure
- Electrolyte abnormalities

**Signs and Symptoms:**
- Muscle tenderness
- Evidence of necrosis
- Increased muscle tone
- Generalized malaise
- Nausea
- Discoloured urine

Causes of Rhabdomyolysis

- **Traumatic or Compression**
  - Multiple trauma, crush injuries, vascular or orthopedic surgery, coma, *immobilization*

- **Non-traumatic (Exertional)**
  - Normal muscle: extreme exertion, environment heat illness, sickle cell trait, seizures, hyperkinetic states
  - Abnormal muscle: metabolic myopathies, malignant hyperthermia, neuroleptic malignant syndrome

- **Non-traumatic (Non-Exertional)**
  - Alcoholism, *drugs/toxins*, infections, electrolyte abnormalities, endocrinopathies, inflammatory myopathies

## Millimolar Concentrations of Solutes in ICF and ECF

<table>
<thead>
<tr>
<th>Solute</th>
<th>ICF (mM)</th>
<th>ECF (mM)</th>
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<tr>
<td>K</td>
<td>140.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Na</td>
<td>15.0</td>
<td>145.0</td>
</tr>
<tr>
<td>Mg</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Ca</td>
<td>&lt;0.001</td>
<td>1.8</td>
</tr>
<tr>
<td>Cl</td>
<td>4.0</td>
<td>115.0</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>10.0</td>
<td>25.0</td>
</tr>
<tr>
<td>P</td>
<td>40.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

What Happens at the Cellular Level?

- Electrolyte Abnormalities:
  - K and P leak out of the muscle cell causing hyperkalemia and hyperphosphatemia
  - Ca enters the muscle cell causing hypocalcemia

- Na-K pump dysfunction
Complications of Rhabdomyolysis

- Muscle Cell Destruction
  - Electrolyte Disturbances & Metabolic Acidosis
  - Coagulopathies
  - Hypovolemia
  - ARF

Cridge LM. Critical Care Nursing. 2003; 23(6): 14-32.
Treatment Options for Hypovolemia in Rhabdomyolysis

- Goal: To enhance clearance of toxic intracellular contents from the circulation and from the kidneys

- Restoring intravascular volume & inducing solute diuresis
  - Mannitol

  - NaHCO$_3$

Criddle LM. Critical Care Nursing. 2003; 23(6): 14-32.
Trauma Service: Rhabdomyolysis Algorithm
This is a guideline only and not to be calculated for individual clinical judgment.

**Obtain Serum CK**

Obtain CK every 6 hours until 3 consecutive values decline

- Yes: >20,000
  - NO: 1.2% mannitol bolus: 0.5 gm/kg
  - 2. 1800 mL 5.22% NaCl + 101 mEq NaHCO₃
  - 3. Begin 28% mannitol at 0.1 gm/kg/hr
  - 4. Begin 0.22% NaCl + 100 mEq NaHCO₃ 2.5 ml/kg/hr

**Monitor Urine Output Hourly**

- No: bolus with mannitol 0.5 gm/kg
  - Yes: >200 ml/hr
    - Make urine mannitol NaHCO₃ infusion
      - Reduce mannitol and saline by 50%
        - urine output maintained >250 ml/hr x 2 hr

**Monitor Urine pH Every 4 Hours**

- <6: bolus with 31 mEq NaHCO₃
  - Recheck urine pH after 2 hours
    - pH < 6.0 or urine pH < 6.0 with NaHCO₃
      - VBG or ABG daily while on NaHCO₃

**Monitor ABG pH**

- pH ≥7.5
  - STOP NaHCO₃
    - Use 0.45% NaCl only

**Continue Treatment**

- Yes: STOP Treatment
  - No: CK <20,000
    - Continue mannitol diuresis.

Algorithm for care of patients with rhabdomyolysis at Oregon Health & Science University Trauma Service. AGB indicates arterial blood gas; CK, creatine kinase; DI, 5% dextrose solution; NaCl, sodium chloride; NaHCO₃, sodium bicarbonate; VBG, venous blood gas.

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M.G.’s Progress

- NS and NaHCO₃ were initiated and his condition did not improve

![Serum Creatinine Levels graph](image-url)
Electrolytes (K and P)

**Phosphate Levels**
- Phosphate levels range from 0.5 to 3 mmol/L.
- Dates range from 13/02/2007 to 19/02/2007.

**Potassium Levels**
- Potassium levels range from 0 to 8 mmol/L.
- Dates range from 13/02/2007 to 19/02/2007.

The graphs show a general decrease in potassium levels over time, while phosphate levels show an increase.

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**Dates and Levels**
- **Phosphate (mmol/L)**:
  - 13/02/2007: 1.5
  - 14/02/2007: 1.8
  - 15/02/2007: 2.0
  - 16/02/2007: 2.3
  - 17/02/2007: 2.5
  - 18/02/2007: 2.7
  - 19/02/2007: 2.9

- **Potassium (mmol/L)**:
  - 13/02/2007: 8
  - 14/02/2007: 7.5
  - 15/02/2007: 7.0
  - 16/02/2007: 6.5
  - 17/02/2007: 6.0
  - 18/02/2007: 5.5
  - 19/02/2007: 5.0
Indications for Dialysis

- Refractory fluid overload
- Hyperkalemia
- Metabolic acidosis
- Azotemia
- Signs of uremia
- Severe dysnatremias
- Hyperthermia
- Overdose with a dialysable drug/toxin

ARF Requiring CVVHD

- CVVHD: Continuous Venovenous Hemofiltration Dialysis
- Blood is pulled from extracorporeal circuit from a dual-lumen central venous catheter by a roller blood pump
- Blood is anticoagulated before the hemofilter to prevent clotting of the hemofilter
- Blood returns to the patient via the other port of the venous catheter

Mueller BA. Critical Care. Acute Renal Failure. 49-82.
CVVHD

Mueller BA. Critical Care. Acute Renal Failure. 49-82.
Problem Encountered With CVVHD

- M.G.’s hemofilter repeatedly clotted upon initiation of dialysis
- Anticoagulation within the filter was instituted with no effect
- Hematology was then consulted
How was the problem resolved?

- Systemic IV heparin was given with an aPTT goal of 50-85.
- Dialysis was successful commenced when aPTT was within this range.
- Evidence (?)
M.G. was initially prescribed cefazolin 1g IV q24h for prevention of infection due to fasciotomy (discussed later).

M.G. was then thought to have acquired aspiration pneumonia:
- Prescribed ceftriaxone 1g IV q24h & metronidazole 500mg IV q12h.
Dose Adjustments in ARF and CVVHD

- Cefazolin was changed to 2g IV q12h when the patient was on dialysis
- Ceftriaxone and metronidazole do not require dose adjustments
- But more complications came...

More problems…

- M.G. was intubated and was clinically not improving with respect to his infection (↑ WBC, ↑ O₂ requirements, ↑ sputum production, mucoid & purulent sputum)

- Aspiration pneumonia → HAP

- Antibiotics were changed:
  - Ceftazidime 2g IV q12h (ON dialysis)
  - Ceftazidime 1g IV q24h (OFF dialysis)
  - Metronidazole 500mg IV bid remained

Leg Compartment Syndrome

- Limb-threatening and life threatening condition observed when perfusion pressure falls below tissue pressure in a closed anatomic space.

- Untreated can lead to tissue necrosis, permanent functional impairment and if severe, renal failure & death.

Definitions

- **Fascia** – thick layers of tissue that separates groups of muscle in the arms and legs from each other (does not expand)

- **Compartment** – confined space that contains muscle tissue, nerves, and blood vessels

Pathophysiology & Treatment

- Introduction of excess fluid or extraneous constriction leading to $\uparrow P$ and $\downarrow$ tissue perfusion, until no $O_2$ is available for cellular metabolism
  - Compression of nerve and blood vessels

- Treatment: fasciotomy
Fasciotomy

- A surgical procedure that cuts away the fascia to relieve pain and tension

- Painful as it is, the procedure requires cutting through nerves and blood vessels

Initial Pain Management

- Sedation/Analgesia:
  - Midazolam 6mg/hr
  - Fentanyl 100mcg/hr

- M.G. required increasing amounts of pain medications (up to 200mcg/hr of fentanyl)

- What is going on?
Questions:

- How do you manage ACUTE PAIN in methadone patients?
- What pain medication options exist?
Methadone Facts

- MOA: mu and delta agonist that blocks the NMDA receptor
- Same analgesic potency as morphine
- Duration of action: analgesia 4-8 hrs
- **Methadone maintenance therapy:**
  - purpose is to maintain a sufficiently high level of tolerance that the addict’s usual dose of heroin or other opioids produces little or no high

Common Misconceptions of Opioid Use in Opioid Dependent Patients

1.) Maintenance opioid agonist therapy (OAT-with methadone) provides analgesia

2.) Use of opioids for analgesia may result in addiction relapse

3.) Additive effects of opioid analgesics and OAT may cause respiratory and CNS depression

4.) Reporting pain may be manipulation to obtain opioid medications, or drug seeking, because of opioid addiction

Misconception #1

- Patients receiving maintenance therapy with methadone do not derive sustained analgesia from it
  - Duration of analgesia is 4-8 hours, suppression of opioid withdrawal is 24-48 hrs

- **Tolerance:** the need for ↑ doses of a medication to achieve its initial effects
  - explains why opioid tolerant patients derive little pain relief from maintenance opioids

Misconception #1 cont’d

- **Hyperalgesia**
  - Neuroplastic changes in pain perception that yields an increase in pain sensitivity
  - Outcome → opioids have less potent analgesic effects
  - Doverty *et al*.: pts receiving methadone therapy tolerate cold-pressor pain only half as long as do matched controls
    - Both groups received morphine 2.2mg as a bolus, followed by continuous infusion 1.2mg/hr for 1 hr to reach plasma concentration of 20ng/mL

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Misconception #2

- No evidence to suggest that exposure to opioid analgesics in the presence of acute pain ↑ the rate of relapse

- Kantor *et al*: retrospective study of pts enrolled methadone maintenance enrolled who received opioids after surgery
  - 50 pts (25 hospitalized & 25 non-hospitalized)
  - No difference in relapse rates between the hospitalized and non-hospitalized pts

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Misconception #3

- Theoretical risk of severe respiratory & CNS depression
  - Not supported by clinical or empirical experience
  - Tolerance develops to these effects

- Respiratory
  - Very rare with titrated oral dosing

- CNS effects
  - May occur within the first few days, especially in elderly patients & in rapid dose escalation

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Misconception #4

- Patients receiving OAT typically receive treatment doses that block most euphoric effects of co-administered opioids (theoretical).

- It is important to keep in mind that there may be an appropriate reason for drug seeking behaviour (as was the case with M.G.).

**Framework for Managing Pain**

- Evidence: guidelines drawn up from case reports, retrospective studies and opinions from experts in the field
- **Continue** methadone maintenance dose
- Use **short-acting** opioid analgesics
- Use **conventional analgesics**, including opioids, to aggressively treat the painful condition
- Write continuous scheduled dosing orders rather than PRN dosing

Management Options in Methadone Patients

- **Use of adjuvant agents**
  - NSAIDs, acetaminophen
  - Neuropathic pain medications (gabapentin, TCAs)

- **Opioids**
  - PCA
  - IV in the acute setting (convenience & rapid dose titration)

- **Mixed agonists and antagonist analgesics**
  such as pentazocine, nalbuphine, butorphanol
  **should be avoided** as they may precipitate acute withdrawal in pts


PCA in Acute Pain Management in Methadone Pts

- Used successfully for treatment in patients who are opioid dependent

- Advantages include:
  - Easy to use & standard practice in acute pain setting
  - Promotes maintenance of a stable blood opioid concentration
  - Patients appreciate being in “control”

Disadvantages of PCA

- Potentially difficult to optimize dose size & lock out time (pt variability)
- Pts might use PCA dose for psychological rather than analgesic purposes
- PCA device needs to be tamper-proof
- Frequent need of opioid might be perceived as drug seeking behaviour

What was M.G.’s pain management?

- Conversion of equi-analgesic dose of fentanyl 200µg/hr to hydromorphone

- Hydromorphone 5mg IV q4h ATC
- Hydromorphone 2-3mg IV q2h PRN for breakthrough
- Acetaminophen 975mg PO q6h ATC
- Gabapentin 300mg PO od
Recent Update to Pain Management

- Switched now to:
  - Hydromorph Contin 12mg PO bid
  - Hydromorphone 2-4mg PO q2h PRN for breakthrough
- Still on acetaminophen and gabapentin
- No role for NSAIDs as pt has ARF
Implications to Practice

- Management of acute pain in methadone pts is complex
- Evidence (?)
- Remember the principles!!
- If you are concerned about drug seeking behaviour – do some research on why the pt may be experiencing pain (type of surgery, what was involved in the surgery)
- Monitor side effects to ensure that the patient is not oversedated (especially in the setting of ARF → accumulation of the opioid & metabolites)
Follow Up on Other Issues

- M.G. renal function is slowly recovering (Scr 460)
  - No further dialysis
- Fasciotomy has been closed up and wound healing nicely
- HAP → improved and off antibiotics
Questions