Acetaminophen Poisoning
Beyond NAC – Role of
Hemodialysis

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Disclosure . . .

I have no disclosures to declare
Learning needs . . .

• By the end of this session, you should be able to
  – Illustrate limitation of N-acetylcysteine (NAC) regimens in massive acetaminophen (APAP) poisoning
  – Analyze different reported cases about the use of extracorporeal therapy in patients with massive APAP ingestion
  – Identify the indications for extracorporeal therapy in case of APAP toxicity

Lets start with a case . . .

• 18 years old F with intentional ingestions of
  – APAP 100 g
  – Ibuprofen
  – Ethanol
• Unremarkable initial physical exam with normal mental status
Patient’s condition progressively worsened

Investigations

- EKG: sinus tachycardia
- Blood gas:
  - pH 7.19 – PCO₂ 28 mm. Hg – HCO₃ 11 mml/L – Lactic acid 8.6 mmol/L

Investigations

- Serum and urine drug screening – normal
- [APAP] – 981 mg/L (6496 μmol/L)
Let's start with a case . . .

• Management
  – Endotracheal intubation
  – Activated charcoal
  – Hemodialysis (HD) – 7 hours
    • Elevated [APAP]
    • Metabolic acidosis
    • Altered mental status

Let's start with a case . . .

• Management
  – NAC
    1. 150 mg/kg over 60 minutes
    2. 12.5 mg/kg/hr prior to HD
    3. 12.5 mg/kg/hr during HD
    4. 6.25 mg/kg/hr after HD
  – Patient was discharged home 48hrs
  Post ingestion
Acetaminophen Poisoning

Acetaminophen poisoning

• APAP poisoning
  – Common in acute suicidal ingestion
    • 20% of single substance fatal exposure – AAPCC 2012
  – Toxicity is variable
  – Few deaths compared to the large number of exposures
  – Antidote: NAC
Massive acetaminophen overdose

- Large ingestion > 500 mg/kg
- NAC is not enough
- Mitochondrial paralysis
  - Altered mental status
  - Early metabolic acidosis
    • Uncoupling oxidative phosphorylation
    • 5-oxoprolinemia

Massive acetaminophen overdose

• 5-oxoprolinemia
Hemodialysis

Acetaminophen poisoning - Hemodialysis

• APAP is highly dialyzable
  – MW 151 daltons
  – Vd 1 L/kg
  – High water solubility
  – Protein binding 8 – 33% in overdose cases
Acetaminophen poisoning - Hemodialysis

- Hemodialysis rarely used
  - Effective antidote – NAC if used early
    - HD is most effective when used early
  - Invasive procedure
  - Not readily available
  - Rapid endogenous clearance > 3 ml/kg/min

Acetaminophen poisoning - Hemodialysis

- Enhance clearance of APAP
- Reduce the burden of APAP
  - NAC 300 mg/kg is not enough
What’s there in the literature about massive APAP overdose?

CVVHD in massive APAP ingestion . . .

BRIEF COMMUNICATION

Massive acetaminophen ingestion with early metabolic acidosis and coma: treatment with IV NAC and continuous venovenous hemodiafiltration

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Background. massive acetaminophen intoxication is a rare but serious life-threatening poisoning. This report details the clinical course and treatment of a 55-year-old male who presented with a four-hour history of ingestion of 200 g of acetaminophen. Due to concerns for hepatic injury, the patient received N-acetylcysteine (NAC) therapy. CVVHD was performed to manage the acid-base disturbance. Flow rate, effluent volume, and serum and effluent drug concentrations were obtained at hourly intervals. During 16 h of CVVHD the acetaminophen level dropped from 1.212 to 2.37 mg/L. Discussion. The average clearance of acetaminophen by CVVHD was 2.53 L/h, with removal of 24 g of acetaminophen over 16 h. As NAC is effective in preventing hepatic injury after acute acetaminophen overdose, the role of dialysis or CVVHD is limited.

Keywords Acetaminophen; Acid-base disorders; N-Acetylcysteine; Hemodialysis; Coma
CVVHD in massive APAP ingestion . . .

• 23 female 1 hr 20 min after ingesting 200 gms of APAP

• Difficult to arouse, answers questions slowly, oriented to place and person

• 20 min later she became confused and her mental status further deteriorated and was intubated

• She developed severe metabolic acidosis and hypotension

CVVHD in massive APAP ingestion . . .

• **Laboratory Values**
  – [APAP](1) 816 mg/L (5440 micromol/L)
  – [APAP](2) 1614 mg/L (10760 micromol/L)
  – ABG 7.17/20.7/12 ➔ pH 6.9 – Lactate 25.2

• **Treatment**
  – Dopamine – phenylephrine – norepinephrine
  – NAC 140 mg/kg PO changed to IV (GI absorption)
CVVHD in massive APAP ingestion . . .

- CVVHD started because of persistent acidosis
- 16 hrs.
  - Metabolic acidosis resolved
  - [APAP] 1212 to 247mg/L (8080 to 1647μmol/L)
  - APAP clearance 42.1 ml/min
  - $t_{1/2}$ was not affected
    - ? Continued absorption

Fig. 1. Series of patient's acetaminophen concentrations (mg/L) over time (h).

CVVHD in massive APAP ingestion . . .

- Post CVVHD
  - Transaminases peaked on day “3”
    - ALT 262 U/L – AST 420 U/L
  - INR peaked on day “2” at 3.3

- Notes
  - No CVVHD details given; blood flow rate and dialysate flow rate
  - No a actual measurement of [APAP] in the dialysant
  - Slower reduction in the burden $\Rightarrow$ ? Clinically significant
NAC kinetics during HD . . .

- NAC pharmacokinetic properties favors removal by hemodialysis
  - MW 163 Daltons
  - Vd 0.24 – 0.5 L/Kg

- Dose adjustment during dialysis
NAC kinetics during HD . . .

- Toxicokinetics of 2 gms NAC in HD patients over 3 hours
  - Dialysis NAC clearance of 5.27 to 5.66 L/kg/hr
  - HD cleared 57% of NAC

NAC removal during HD . . .

Antidote removal during haemodialysis for massive acetaminophen overdose

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NAC removal during HD . . .

Case (1)

- 62 yrs female 11 hrs. after ingesting 60g of APAP
- Depressed level of consciousness and metabolic acidosis
- Laboratory values
  - ABG (1): 7.33/34/17 – Lactic acid 7 mmol/L
  - ABG (2): 7.30/32/15
  - [APAP] (1): 609 μgm/dl (4030 μmol/L)
  - [APAP] (2): 440 μgm/dl (2913 μmol/L)

NAC removal during HD . . .

- Hemodialysis (HD) started 17 hrs. post ingestion (PI) for 3 hrs.
- NAC dose:
  - Loading dose → 150 mg/kg over 1 hr at 13.5 hrs. PI
  - Double second NAC dose during HD → 25 mg/kg/hr
  - Additional half loading dose → 80 mg/kg over 1hr
  - Post HD, NAC infusion resumed → 6.25 mg/kg/hr up to 50 hrs. PI
NAC removal during HD . . .

• Laboratory values post HD
  – ABG: 7.46/23 – Lactate 0.3 mmol/L
  – Peak AST 105 U/L – Peak ALT 70 U/L – Peak INR 1.6

• Full recovery

NAC removal during HD . . .

Fig. 1. Case 1 laboratory values and acetylcysteine dosing. Serum acetaminophen (solid squares), acetylcysteine (triangles) and lactate (diamonds) concentrations are shown on the left y-axis; acetylcysteine dosing rate (dark lines) on the right y-axis. Haemodialysis interval is represented by the vertical grey bars. The Rimack-Matthew nomogram treatment threshold is shown as a solid diagonal line, and dashed lines show the first-order linear regression line fitted to the pre- and post-dialysis acetaminophen concentrations (colour version of this figure can be found in the online version at www.informaimedicalcare.com/cns).
NAC removal during HD . . .

Case (2)

• 59 years male found unresponsive. Last seen 20 hrs. ago

• Laboratory values
  – ABG (1): 7.32/12 – Lactate 12.5 mmol/L
  – [APAP] (1): 903 μgm/ml (5980 μmol/L)
  – [APAP] (2): 663 μgm/ml (4390 μmol/L)

NAC removal during HD . . .

• HD attempted for 3 hours and 20 minutes

• NAC dose:
  – Loading dose → 150 mg/kg IV over 15 minutes
  – Intermittent dose → 70 mg/kg IV every 4 hours
  – NAC infusion → 12.5 mg/kg/hr during the HD

• Laboratory values post HD
  – [APAP] → 273 μgm/ml (1810 μmol/L)
  – ABG: 7.41/25 – Lactate: 0.8 mmol/L
  – AST 1868 U/L – ALT 1961 U/L – INR 1.5
NAC removal during HD . . .

Case (3)

- 22 yrs. Female ingested 60 gms APAP with 2.2 gms pseudoephedrine and 144 mg chlorpheneramine
- Patients was unresponsive
- Laboratory values:
  - ABG (1): 7.39/19/11 – Lactate 8.7 mmol/L
  - [APAP]: 424 μgm/ml (2806 μmol/L)
NAC removal during HD . . .

- HD attempted for 4 hours
- NAC dose:
  - Loading dose $\rightarrow$ 150 mg/kg IV over 15 minutes
  - NAC infusion $\rightarrow$ 12.5 mg/kg/hr
  - NAC increased to 25 mg/kg/hr for 2 hours during HD
  - NAC infusion $\rightarrow$ 6.25 mg/kg/hr
- Laboratory values post HD
  - ABG: 7.49/25

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NAC removal during HD . . .

![Graph showing Acetaminophen concentrations over time](image)
Patients presented with metabolic acidosis and altered mental status ~ 10 hrs. post ingestion

HD reversed metabolic acidosis and fasten APAP and NAC clearance

No one developed coagulopathy

NAC dose was doubled based on pharmacokinetics of NAC studied during HD
Extracorporeal Therapy in Poisoning

Aim:

- Produce evidence based guidelines on the use of extracorporeal therapy (ECTR) to enhance drug elimination in poisoned patients
• Recommendations are based on
  – Quality of evidence
  – Strength of recommendations
EXTRIP Recommendations

• NAC is the main stay of treatment
• APAP is dialyzable drug and ECTR is suggested in patients with
  — Massive APAP ingestion
  — Evidence of mitochondrial paralysis

EXTRIP Recommendations

• ECTR is indicated for:
  — NAC is NOT administered and
    • \([\text{APAP}] > 1000 \text{ mg/L} \ (6620 \ \mu\text{mol/L}) \) – (1D)
    • \([\text{APAP}] > 800 \text{ mg/L} \ (5300 \ \mu\text{mol/L}) \) – (2D)
  — NAC is NOT administered and evidence of mitochondrial paralysis and
    • \([\text{APAP}] > 700 \text{ mg/L} \ (4630 \ \mu\text{mol/L}) \) – (1D)
    • \([\text{APAP}] > 500 \text{ mg/L} \ (3300 \ \mu\text{mol/L}) \) – (2D)
EXTRIP Recommendations

• **ECTR is indicated for:**
  - NAC is administered and evidence of mitochondrial paralysis and
    - [APAP] > 900 mg/L (5960 μmol/L) – (1D)
    - [APAP] > 800 mg/L (5300 μmol/L) – (2D)

EXTRIP Recommendations

• **ECTR is not indicated for:**
  - Reported ingested dose
  - Solely based on [APAP] when NAC is administered

• **Cessation of ECTR:**
  - Apparent clinical improvement
EXTRIP Recommendations

- **Choice of ECTR**
  - Intermittent HD is preferred (1D)
  - Intermittent hemoperfusion (1D)
  - Continuous renal replacement therapy (3D)
  - Exchange transfusion in neonates (2D)

- **NAC dose during HD should be adjusted**

Putting it all together . . .
Putting it all together . . .

- NAC is effective antidote for most APAP poisoning
- NAC alone is not enough in cases of massive APAP ingestion
- ECTR enhances APAP clearance and reduces body burden of parent drug
- Evidence suggest a strong role for ECTR in massive APAP ingestion

THANK YOU . . .
References


