Chronic acetaminophen toxicity: lack of consensus

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Introduction

- Acetaminophen is one of the most frequently used analgesics and antipyretic agents.
- However, the easy access to this medication and the population`s unawareness of its toxic effects have contributed to a rise in intoxication cases.
- While acute toxicity occurs mostly from intentional overdose, chronic acetaminophen toxicity is due to unintended inappropriate dosing.
- Management of acetaminophen chronic overdose is not consensual.
Case - Medical and Family History

- 8-year-old caucasian girl
- Chicken-pox

Medical history:
- Asthma (no profilactic therapy; albuterol on SOS)
- Vaccination according to National Portuguese Program; no chicken-pox vaccine
- No regular medical consultation on sickness... advised and medicated by pharmaceutic...

- Family history irrelevant
8-year-old caucasian girl

Chicken-pox

6 days acetaminophen in supratherapeutic dosis
(median dosis in the former 72 hours > 100 mg/kg/day)
- 120 mg/kg/day in the previous 24h
- 80 mg/kg/day in the previous 4 days

On the 6th day of disease
- Persisting fever (TT 38,5ºC, 4/4h)
- Worsening skin lesions

Hospital
Case - Admission

- Febrile (TT 38,1ºC). Hydrated
- **Multiple infected vesiculous** lesions with **impetigo**
- Hb 14,7 g/L
- Leucocytes 3800 /ml N 62.3%, L 22,6%, M 14,8%
- Platelets 130000
- PCR 27,2g/L
- Hemoculture

Intravenous **flucloxacilin** 150 mg/kg/day

**Hidroxyzine** + **Metamisole** magnesium (SOS)
Case - Presentation

- Conscious and oriented
- No pallor. Anicteric.
- No hepatomegaly

- PT 12.9 seconds, aPTT 34 seconds, Fibrinogen 2.3 g/L
- **AST 84UI, ALT 102UI, GGT 50UI.** Albumin 40.8 g/L
- Urea, creatinine and ionogram normal
- **Seric acetaminophen - 14 ug/ml**
- Abdominal ultrasound normal

Paracetamol chronic overdose??
Paracetamol chronic overdose??
She received multiple dosis > 75 mg/kg/day....

High fever (max TT 38,5ºC, 4/4h)

Worsening of skin lesions

DAY 1 – DAY 4
Chicken-pox
Acetaminophen
80 mg/kg/day
(500mg 4/4h)

DAY 5
Acetaminophen
120 mg/kg/day
(500mg 6/6h)

ER

DAY 6
- Elevated transaminases
- Acetaminophen in the blood: 14 ng/mL
Diagnosis

- Chicken-pox with secondary bacterial infection
- Chronic paracetamol intoxication
  - 120 mg/kg/day in the previous 24h
  - 80 mg/kg/day in the 4 days before
    (median diary dose in the 72 hours > 100 mg/kg/day)
- Elevated transaminases
- No signs of hepatotoxicity
- Acetaminophen dosage in blood (6th day): 14 ng/mL*

* Rumack Nomogram
  Toxic values after ingestion 4h > 200; 8h > 100; 12h > 50
  BUT on 6th day???
Paracetamol chronic overdose??
She received multiple doses > 75 mg/kg/day....
Treatment with N-acetylcysteine?

Anti-poisoning Information Center – YES!!?
“median dose in the previous 48h < 150 mg/kg/day, BUT ... with a median dose > 100 mg/kg/day in the previous 72h + and ↑transaminases.. “

- Intravenous N-acetylcysteine NAC
Hospital’s internal protocol
Hospital Dona Estefânia - YES!!

1 - Asymptomatic patients without hepatotoxic risk factors:
   Ingestion > 150 mg/kg during any period of 24h or 7,5 g/day
   → INITIATE NAC

2 - According to timing of hepatic/renal lesion
   Ingestion > 75 mg/kg during any period of 24h or 6g/day:
   → CONSIDERATE NAC

In our case: AST and ALT elevated + detectable seric acetaminophen > 24h after the last dosis
Intravenous N-acetylcysteine administration (7 days)  
(20% NAC 2000mg/10ml)

20-40 kg:
• 1\textsuperscript{st} dose: 150 mg/kg diluted in 100ml of 5% dextrose in 1h  
• 2\textsuperscript{nd} dose: 50 mg/kg in 250ml 5% dextrose in 4h  
• 3\textsuperscript{rd} dose: 100 mg/kg in 500ml 5% dextrose in 16h

• Daily levels of acetaminophen while positive (Koda-Kimble, 2005)  
• Every 12 hours liver function tests (AST/ALT, GGT, AF, ammonia, bilirubin, glycemia, coagulation, gasometry) and renal function tests
When to stop?

- Repeat analysis before stopping the perfusion
- Suspend NAC if:
  - negative acetaminophen levels
  - normal liver function tests (ALT/AST < 2x normal superior limit or AST/ALT < twice the initial value
  - normal renal function tests
- **If anomalous values:** maintain NAC perfusion in the dosis of the 3rd perfusion (100 mg/kg) + repeat analysis every 8h to 16h
- Maintain NAC until INR 1.3 or tendency to stability in 2 consecutive analysis (since INR < 3)
Evolution

- Day 4 Transaminases peak (AST 128, ALT 164, GGT 67)
- Day 2 Acetaminophen in the blood negative (<3 ug/ml)
- Day 7 NAC perfusion stopped

Day 8 Discharge
(analysis at the discharge)
AST 31 U/L; ALT 72 U/L; GGT 52 U/L
Albumin 40.4 g/L
Discussion

• Management of children with chronic acetaminophen toxicity should occur in consultation with a regional poison control center or medical toxicologist

• Multiple supratherapeutic ingestions of acetaminophen:
  - no injury + no unmetabolized acetaminophen → discharge
  - no injury + measurable serum acetaminophen levels → supportive care in the hospital + analytic monitoring
  - hepatic injury + unmetabolized acetaminophen → NAC in the hospital
The optimal mode of delivery and the duration of NAC therapy in this setting have not been established in controlled trials.

The end-point in this setting is either:

- resolution of symptoms
- liver transplantation
- moderate to severe hepatotoxicity at initial evaluation

→ transfer to a liver transplant center
References


3. Heubi JE, Barbacci MB, Zimmerman HJ.


Thank you for your attention