Development of Liver Injury Despite Early Acetylcysteine Treatment in Paracetamol Overdose

Naura Syafira (1,2), Andis Graudins (1), Anselm Wong (1)
1. Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia
2. Faculty of Medicine, Universitas Indonesia, Special Capital Region of Jakarta, Indonesia

Background & Aim

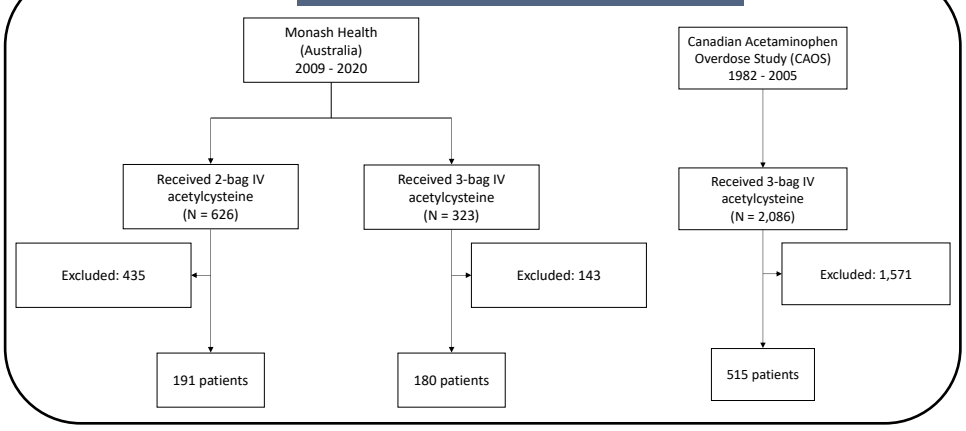
- Paracetamol is the most frequent drug used for deliberate self-poisoning (DSP) in Australia.[1] Paracetamol poisoning is the most common cause of acute liver injury in developed countries such as Australia[2] and Canada[3].
- Acetylcysteine is an effective antidote for paracetamol poisoning and its efficacy is greatly affected by the time of administration.[4]
- Recent modifications for paracetamol overdose treatment in Australia includes adapting the new two-bag IV acetylcysteine regimen and recommendation for repeating liver transaminases in all patient.[5]
- Aim: To investigate and compare the incidence of acute liver injury (ALI) in patients receiving the newer regimen (2-bag IV acetylcysteine) to the older protocol (3-bag IV acetylcysteine) in those receiving early acetylcysteine treatment (≤8 hours post overdose).

Methods

Retrospective cohort study comparing the incidence of ALI in patients receiving the 2-bag (Australia) and 3-bag (Australia & Canada) IV-acetylcysteine regimens.

- Inclusion Criteria:
  - Acute single ingestion
  - Normal ALT (<40IU/L) on presentation
  - Received acetylcysteine within 8 hours post-ingestion
  - Treated with acetylcysteine per Rumack-Matthew Nomogram (MJA guideline)
- Primary outcome was **ALI (peak ALT >150IU/L during admission)**. The secondary outcome included **hepatotoxicity (peak ALT >1,000IU/L during admission)** and **elevated ALT (peak ALT ≥40IU/L during admission).**

Figure 1. Participant Selection



Results

Table 1. Comparison of Liver Injury Incidences between 2-Bag and 3-Bag Acetylcysteine Treatment Regimen

	3-BAG MONASH HEALTH	2-BAG MONASH HEALTH	3-BAG CAOS
ALI*	2.2% (4 / 180)	1.6% (3 / 191)	2.9% (15 / 515)
	Difference: -0.6%; p 0.7; OR 0.7 ; 95%CI 0.2 – 2.6)	Difference: -1.3%, p 0.4; OR 0.5; 95%CI 0.2 – 1.7	
ELEVATED ALT§	3.9% (7 / 180)	3.7% (7 / 191)	14.8% (76 / 515)
	Difference: -0.2; p >0.9; OR 0.9; 95%CI 0.4 – 2.5	Difference: -11.1%; **p <0.0001**; OR 0.2 ; 95%CI 0.01– 0.5	
HEPATOTOXICITY	1.7% (3 / 180)	0.5% (1 / 191)	1% (5 / 515)
	Difference: -1.2%; p 0.4; OR 0.3; 95%CI 0.02 – 2.1	Difference: -0.5%; p >0.9; OR 0.5; 95%CI 0.05 – 3.9	

*ALI included patients with peak ALT >1,000IU/L; §Elevated ALT included patients with peak ALT >150IU/L & >1,000IU/L.

Figure 2. Elevated ALT Grouping Based on ALT

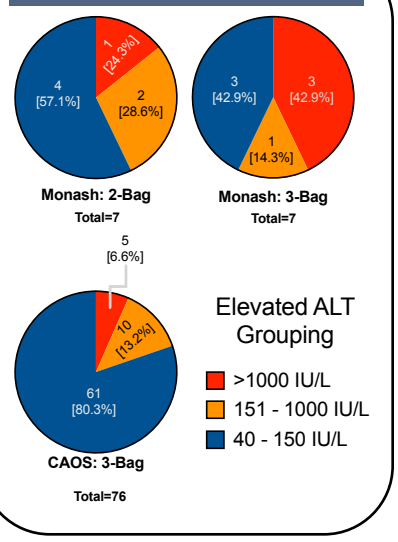
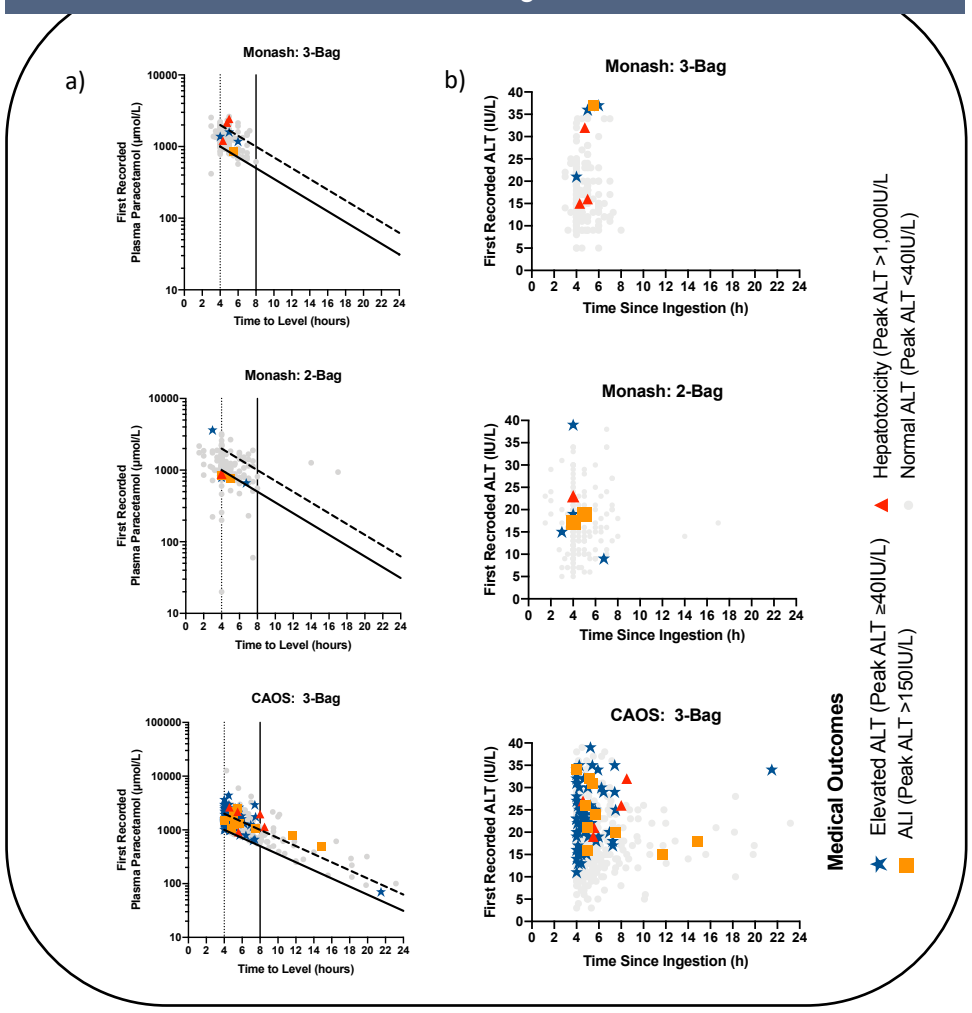


Figure 3. Medical Outcomes. a) First recorded plasma paracetamol concentration vs time to level; b) First recorded ALT concentration vs time since ingestion



Solid and dashed sloped line represent 1,000 µmol/L and 2,000 µmol/L treatment line, respectively.

Discussions

Liver Injury (Acute Liver Injury & Hepatotoxicity)

- Developed in **small proportion** of our patient receiving both 2-bag and 3-bag acetylcysteine regimen, similar to Cairney et al.[6] who looked at patients receiving acetylcysteine within 8 hours post ingestion *or* presenting with normal ALT.
- **Similar efficacy to prevent ALI** of 2-bag regimen to 3-bag regimen as reported by Wong et al.[7] and **to prevent hepatotoxicity** of 2-bag regimen to 3-bag regimen as reported by previous studies.[7-10]

Elevated ALT

- Three-bag CAOS had **significantly higher** proportion of patients with elevated ALT than the 2-bag Monash Health. However, there was no apparent difference in comparison of the 2-bag Monash Health to the 3-bag Monash Health.
  - Might be caused due to **improved medical care** in the Monash Health group given the CAOS data was from decades earlier.

Conclusion & Future Direction

- Liver injury (ALI, hepatotoxicity) **could still develop** in patients who received acetylcysteine ≤8 hours post-ingestion and presented with a normal ALT.
- The incidence of liver injury **was similar** in patients receiving the 2-bag and 3-bag regimen.
- Our findings **support the new Australia and New Zealand's recommendation** to re-evaluate patient ALT concentrations prior to ceasing acetylcysteine in early presenters. The recommendation to repeat blood test **could be adapted worldwide.**

Abbreviations. ALT: alanine aminotransferase; MJA: Medical Journal of Australia

Reference.