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Modified release Paracetamol overdose: A prospective observational study

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Objective: Modified-release (MR) paracetamol is available in Australia in 665 mg tablets of which 69% MR and 31% immediate release. There is concerns that MR paracetamol overdose differs from immediate release particularly, whether patients have higher rates of liver injury or are more likely to require prolonged treatment. To describe the clinical characteristics and outcomes of MR paracetamol acute overdoses.

Method: The Australian Paracetamol Project is a prospective observational study, recruiting patients from Sep 2013–Jun 2017, from 5 clinical toxicology units and calls to the Poisons Information Centre in NSW and Queensland. Included were patients >14 y whom ingested ≥ 10 g or 200 mg/kg (whichever is less) of MR paracetamol over ≤ 8h or developed acute liver injury following a MR paracetamol ingestion. Data collected included demographics, ingestion history, pathology results, treatments and outcomes including hepatotoxicity (ALT > 1000 U/L).

Results: 117 patients were recruited; demographic data, treatments and outcomes are shown in the table. The median dose ingested was 31.9 g, 80 (68%) had an initial paracetamol concentration above the nomogram line (150 mg/L at 4 h). A further 12 (10%) crossed the nomogram after repeat paracetamol measurements, of which five crossed after two non-toxic levels 4 h apart. Six had a double paracetamol peak, in three occurring >24 h post-ingestion. 113 (97%) received acetylcysteine of which 68 requiring prolonged treatment beyond the standard 20–21 h; 38 because of detectable paracetamol concentration at the completion of acetylcysteine (median paracetamol concentration 25 mg/L, IQR: 16-62 mg/L) and 29 because of an ALT >50 U/L (Australian recommendation for continuation). 22 (19%) developed hepatotoxicity, including six treated within 8 h of ingestion. One patient developed hepatotoxicity despite ingesting <10 g and having two non-toxic paracetamol concentrations.

Conclusion: The European Medicines Agency recently recommended suspending marketing of MR paracetamol due to the risks following acute overdose. This study supports their recommendations. Better treatment strategies are required while this product remains on the market.

Table: Patient demographic ingestion and treatment data.

	All Patients (n= 117)
% Females	86 (74%)
Median Age (years) (IQR)	36 (20 – 53.5)
Median weight (kg) (IQR)	75 (60-86)
Median Dose ingested (grams) (IQR)	31.9 (19.9 – 48.9)
Median dose ingested (mg/kg) (IQR)	0.440 (0.3 – 0.7)
Co-ingested gut slowing medications	24 (21%)
Co-ingested Ethanol	29 (25%)
Median time to presentation (hours)(IQR)	3 h (2 – 9)
Received Activated Charcoal	26 (22%)
Median time to activated charcoal (hours)(IQR)	3.5 (1.3 – 5.2)
ALT at presentation not elevated (< 50 U/L or at their baseline)	90 (77%)
Commenced on acetylcysteine	113# (97%)
Median time to acetylcysteine (hours)(IQR)	5 h (3.2 – 10)
• Completing at least 21 h of acetylcysteine	103 (91%)*
• Adjustment to standard acetylcysteine dosing in the first 21 h of treatment	27 (24%)*
• Prolonged acetylcysteine required beyond standard 20.5 h infusion	68 (60%)*

1 patient ingested 7.98 g of MR paracetamol, had 2 non-toxic paracetamol concentrations, and was not initially given acetylcysteine. Subsequently developed hepatotoxicity and acetylcysteine commenced at 96 h post ingestion.

*Percentage of those commenced on acetylcysteine (n = 113)