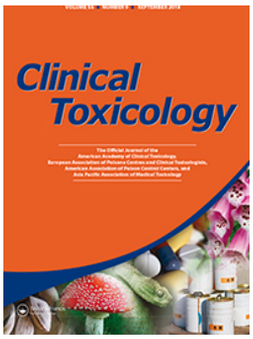

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CLINICAL RESEARCH

Modified release paracetamol overdose: a prospective observational study (ATOM-3)

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ABSTRACT

Background: Modified-release (MR) paracetamol is available in many countries as 665 mg tablets of which 69% is MR and 31% is immediate release. There are concerns that MR paracetamol overdose has higher rates of liver injury despite standard treatment algorithms. The objective of this study was to describe the clinical characteristics and outcomes of acute MR paracetamol overdose.

Methods: Prospective observational study, recruiting patients from January 2013 to June 2017, from five clinical toxicology units and calls to two Poisons Information Centres in Australia. Included were patients >14 years who ingested ≥10 g or 200 mg/kg (whichever is less) of MR paracetamol. Data collected included demographics, ingestion history, pathology results, treatments, and outcomes including hepatotoxicity (ALT >1000 U/L).

Results: In total, 116 patients were recruited, 85(73%) were female. The median dose ingested was 32 g (IQR: 20–49 g) and median time to presentation was 3 h (IQR: 2–9 h). 78(67%) 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 67 received prolonged treatment beyond the standard 21 h. This was because of an elevated paracetamol concentration at the completion of acetylcysteine in 39 (median paracetamol concentration 25 mg/L, IQR: 16–62 mg/L). 21 (18%) developed hepatotoxicity, including six treated within 8 h of ingestion. Activated charcoal and double doses of acetylcysteine did not significantly decrease the risk of hepatotoxicity.

Conclusions: Drug regulatory authorities are considering restrictions on MR paracetamol preparations. Following an acute MR paracetamol overdose, this study found that many patients had a persistently elevated paracetamol concentrations, many required prolonged treatment and some developed liver injury despite early acetylcysteine treatment. Furthermore, activated charcoal and increased acetylcysteine did not appear to significantly alter the risk of liver injury. Hence, research into better treatment strategies is required.

Trial registration: Australian Toxicology Monitoring (ATOM) Study – Australian Paracetamol Project: ACTRN12612001240831 (ANZCTR) Date of registration: 23/11/2012.

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Paracetamol; modified-release acetylcysteine; overdose; activated charcoal; hepatotoxicity

Introduction

Modified-release (MR) paracetamol is available in various formulations with differing MR content. In Australia, New Zealand, and many countries in Europe, MR paracetamol is available in 665 mg tablets containing 69% MR and 31% IR paracetamol. In Australia, it is available in pharmacies without the need for a prescription or consultation with a pharmacist in packets of 96 tablets (63.84 g). There are increasing concerns that MR paracetamol in overdose differs from standard immediate release (IR) products and that current treatment guidelines for MR paracetamol ingestions are inadequate [1]. The European Medicines Agency, Pharmacovigilance Risk Assessment Committee, recommended in September 2017 that marketing of MR paracetamol be suspended due to these concerns. They concluded "on balance that the risk following overdose with these medicines outweighs the advantage of having a longer-acting preparation" [2]. These recommendations were endorsed in December 2017 by the Co-ordination Group for Mutual Recognition and Decentralized Procedures-Humans (CMDh) (CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway) [3].

The 2015 Australian and New Zealand guidelines for MR paracetamol ingestion recommended commencing

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Supplemental data for this article can be accessed here.

acetylcysteine in any patient who ingests a toxic dose of paracetamol (defined as 200 mg/kg or 10 g whichever is less) [4], and the administration of activated charcoal for those presenting within 4 h of ingestion. Two paracetamol concentrations should be taken 4 h apart and the first at least 4 h post-ingestion. Intravenous acetylcysteine is continued if either paracetamol concentration is above the nomogram line (150 mg/L at 4 h) or the concentration is rising. Near the completion of acetylcysteine, alanine aminotransferase (ALT) and paracetamol concentration are repeated, with acetylcysteine continued if ALT is greater than 50 U/L (or above baseline) or paracetamol concentration is greater than 10 mg/L (66 μmol/L) [4]. The standard dose of acetylcysteine administered in Australia is 300 mg/kg over 20–21 h given as either a 2 or 3 bag infusion. It is also recommended to increase standard acetylcysteine doses in those with an initial paracetamol concentration that is double the standard nomogram line [4]. Most commonly this is a doubling of the dose in the 100 mg/kg/16 h bag to 200 mg/kg/16 h.

The object of this study was to describe the clinical characteristics and outcomes of MR paracetamol acute overdoses. Particularly the impact on paracetamol kinetics, acute liver injury, treatment duration, and outcomes of those following current guidelines.

Methods

Design and setting

This study is nested within the Australian TOxicology Monitoring (ATOM) Collaboration. The ATOM studies are prospective observational studies which investigate various drugs and toxins in overdose. Patient consent is obtained to collect clinical data and clinical samples. ATOM is a multi-center collaboration which recruits patients through up to five toxicology units in Australia and through calls to the New South Wales (NSW) and Queensland Poisons Information Centers (PIC) from hospitals in these two states. The MR paracetamol sub-study collected clinical data and aimed to collect at least three paracetamol samples in the first 24 h of admission at >4 h post-ingestion, 4 h later, and 1–2 h before completion of the 21 h of acetylcysteine treatment. The ATOM study has ethical approval from Human Research and Ethics Committees in NSW and QLD to cover all involved institutions.

Selection of participants

Patients were included who ingested a potentially toxic dose of MR paracetamol, defined as a dose of greater than 10 g or 200 mg/kg (whichever is less) over a period of less than 8 h. We recruited patients ≥14 years prospectively from NSW from January 2013 until June 2017 and from QLD from April 2015 to June 2017. Recruitment periods varied between the two states, as recruitment could not commence until ethics approval was finalized. Patients were not excluded if they also co-ingested IR paracetamol or agents that slow gut emptying (i.e., opioids or anti-cholinergic agents), as management is not altered by these co-ingestants.

Methods and measurements

Data was collected on a preformatted clinical datasheet and from medical records. Data collected included demographic information, overdose exposure (time and dose ingested), co-ingestions including ethanol, laboratory investigations, treatments, and outcomes. All patients had a weight recorded, 20 patients did not have an ALT measured more than 24 h post-ingestion. In these patients, the ALT was assumed to remain unchanged. All these patients had two paracetamol concentrations below the nomogram line, and were at low risk for liver injury.

Paracetamol concentrations were performed in 40 different hospital laboratories (where the patient was treated). All hospital laboratories are accredited by The Royal College of Pathologists of Australasia. Their allowable limits of performance for paracetamol assays are 3 mg/L up to 30 mg/L and ±10% for paracetamol concentrations >30 mg/L. The average coefficient of variation of hospital laboratories across Australia is 3.4%. The limit of quantification varies between laboratories from 1 to 10 mg/L.

Outcomes

Pharmacokinetic

- Paracetamol concentrations, including whether the initial paracetamol concentration was greater than the nomogram line (150 mg/L at 4 h), or crossed on subsequent testing.
- Paracetamol concentrations at the completion of the standard 20–21 h acetylcysteine regimen.
- Paracetamol ratio: to compare paracetamol concentrations between patients, at different time points, the paracetamol ratio was calculated for each patient who had a paracetamol concentration taken between 4 and 16 h post-ingestion.

$$\text{Paracetamol ratio} = \frac{\text{First paracetamol concentration taken} \geq 4\text{ h post-ingestion (but} \leq 16\text{ h)}}{\text{Paracetamol concentration on the (150 mg/L at 4 h) standard nomogram line at that time point}}$$

Ratios were not done after 16 h because the Prescott nomogram is validated as predicting risk to 15–16 h [5,6].

- Area under the curve (AUC): to compare paracetamol body burden between those patients who did and did not receive activated charcoal, area under the paracetamol concentration curve (AUC) 8–24 h was calculated. Patients were included for analysis if they had at least three paracetamol concentrations taken ≤24 h post-ingestion. With the first level taken at or before 8 h. Where necessary 8 h concentrations were interpolated,

and 24 h concentrations were interpolated or extrapolated based on $\log_2$-linear decline or incline on two nearest samples (see Supplementary Figure S1).

Clinical outcomes

- Acute liver injury: there are various cut-offs for acute liver injury, traditionally the main outcome measure is hepatotoxicity, defined as a peak ALT >1000 U/L [5]. Others considered included ALT >50 U/L (the typical upper limit of normal and Australian indication for continuing acetylcysteine therapy after completion of the initial regimen) [4] and ALT >150 U/L (the UK indication for continuing acetylcysteine therapy after completion of the initial regimen) [7].
- Complications: coagulopathy (defined as an INR >5.0), severe acute kidney injury (AKIN classification stage 3) [8] and hepatic encephalopathy.
- Liver transplant and death.

Statistical analysis

Descriptive data were reported as means with 95% confidence intervals (CI) for normally distributed data, medians, and interquartile ranges (IQR) for non-normally distributed data, and frequencies and percentages for categorical data. Continuous variables were compared using unpaired *t*-tests or Mann–Whitney tests.

To assess the relationship between activated charcoal administration and initial paracetamol ratio and AUC 8–24 h, we used a linear regression model with the paracetamol ratio and AUC dependent variables transformed into base 2 logarithm ($\log_2$) units. For the initial paracetamol ratio analysis, only patients with greater than 1 h between activated charcoal administration and initial paracetamol ratio were included. All patients who received activated charcoal and who could have an AUC calculated were included in the AUC analysis. Analyses were adjusted for patient age, sex, weight ($\log_2$ kg), and dose ingested ($\log_2$ g) or dose ingested/weight ($\log_2$ g/kg).

Logistic regression models were used to assess whether activated charcoal or increased acetylcysteine dose were associated with a decreased risk of hepatotoxicity. Covariates considered for entry into the model included time to acetylcysteine, age, sex, dose ingested/weight, co-ingestion of ethanol, paracetamol ratio, and AUC from 8 to 24 h. These were first analyzsed by bivariable models and only variables with $p < .10$ were included in the multivariable models. Due to the small number of acute liver injury outcomes, only 2 to 3 variables were included in each model.

Calculations of interpolated and extrapolated concentrations and AUC were performed using Excel and GraphPad Prism (version 7©2017 GraphPad Software Inc., La Jolla, CA). Statistical analyses were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. StataCorp LP, SA, College Station, TX).

Table 1. Patient demographic ingestion and treatment data.

	All patients ($n = 117$)
% Females	85 (73%)
Median Age (years) (IQR)	36 (20–53)
Median weight (kg) (IQR)	75 (60–85)
Median Dose ingested (g) (IQR)	32 (20–49)
Median dose ingested (g/kg) (IQR)	0.440 (0.3–0.7)
Co-ingested agents that slow gut emptying (i.e., opioids or anti-cholinergic agents)	24 (21%)
Co-ingested Ethanol	29 (25%)
Median time to presentation (h)(IQR)	3 h (2–7.5)
Received Activated Charcoal	26 (22%)[a]
Median time to activated charcoal (h)(IQR)	3.5 (1.3–5.2)
ALT at presentation not elevated (<50 U/L or at their baseline)	89 (77%)
Commenced on acetylcysteine	113 (97%)
Median time to acetylcysteine (h)(IQR)	5 h (3.1–10)
Completing at least 21 h of acetylcysteine	103 (91%)[b]
Adjustment to standard acetylcysteine dosing in the first 21 h of treatment	27 (24%)[b]
Prolonged acetylcysteine required beyond standard 20.5 h infusion	67 (59%)[b]

[a]Twenty-four received single dose activated charcoal.
[b]Percentage of those commenced on acetylcysteine ($n = 113$).

Results

Demographics

We recruited 116 cases; 85 (73%) were female and median age was 36 years (IQR: 20–53). The median time to presentation was 3.0 h (IQR: 1.8–7.5 h), with a median dose ingested of 32 g (IQR: 20–49 g, range: 11–207 g). Sixteen (14%) ingested a mixture of IR and MR paracetamol, all these patients ingested >10 g of MR paracetamol and MR paracetamol was the main paracetamol product ingested. Patient demographic data, co-ingestions, and treatments are shown in Table 1.

Outcomes

Paracetamol concentrations

Seventy-eight (67%) had an initial ≥4 h paracetamol concentration greater than the nomogram line. A further three presented >48 h post-ingestion with ALT >1000 U/L and an undetectable paracetamol concentration. Serial paracetamol concentrations were measured with a median of four paracetamol concentrations per patient (IQR: 2–5, range: 1–13 paracetamol concentrations per patient). Figure 1 shows the paracetamol concentration versus time plots according to ingested dose and stratified according to outcome.

Of those that had a 4–16 h paracetamol concentration measured the median paracetamol ratio was 14 ($n = 103$, IQR: 0.6–2.7) with 37 (32%) having an initial paracetamol concentration more than double the nomogram line (paracetamol ratio ≥2). Seven patients who had an initial non-toxic paracetamol concentration crossed the nomogram line (150 mg/L at 4 h) on subsequent testing taken at least 4 h after the first. A further five crossed after two initial non-toxic paracetamol concentrations. Six patients in this study had a double paracetamol peak, of which three had the second peak >24 h post-ingestion. Three of these patients were late nomogram line crossers and two developed hepatotoxicity

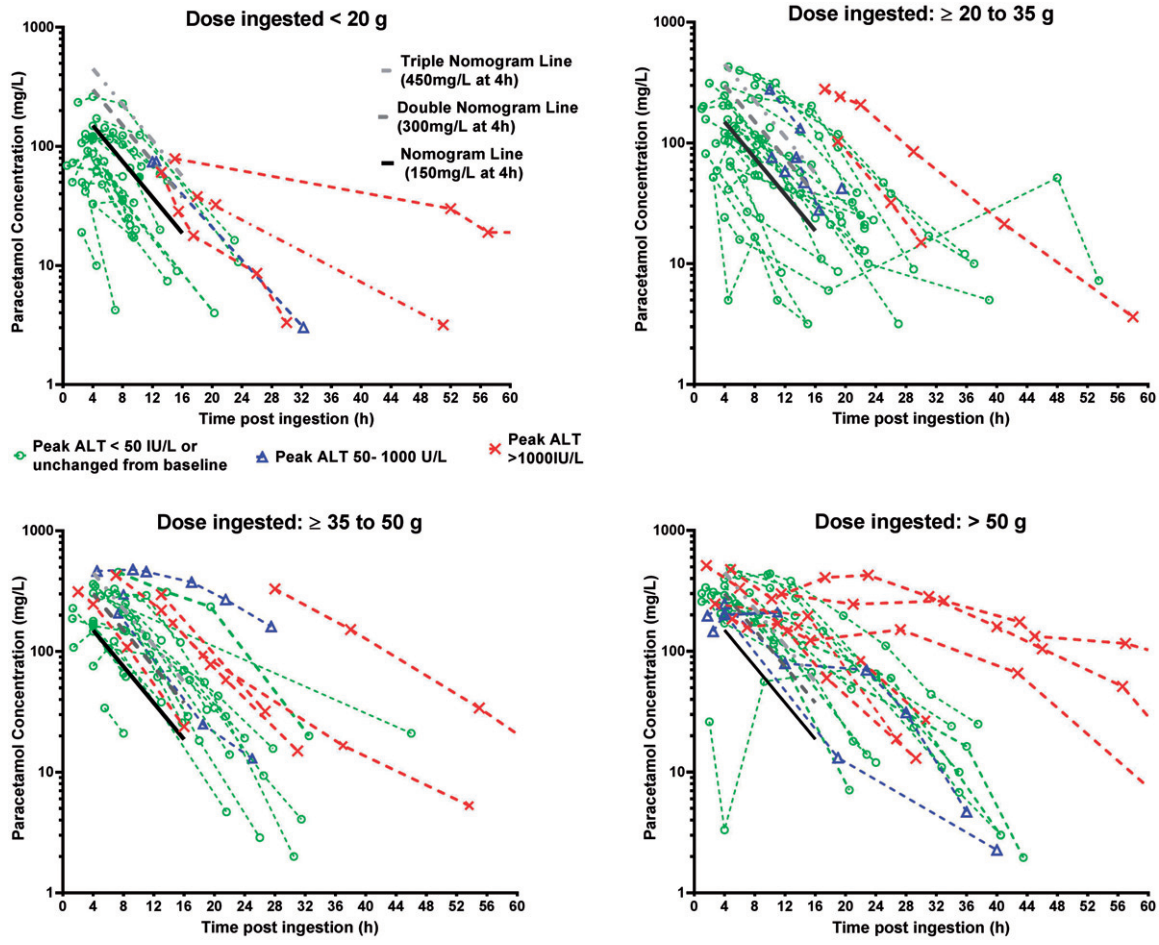

Figure 1. Paracetamol concentration (mg/L) versus time post-ingestion (h) stratified according to ingested dose and outcomes. Circles (green lines) represented those patients whose ALT remained <50 U/L or at baseline. Triangles (blue lines) peak ALT between 50 and 1000 U/L. Crosses (red line) peak ALT >1000 U/L (hepatotoxicity).

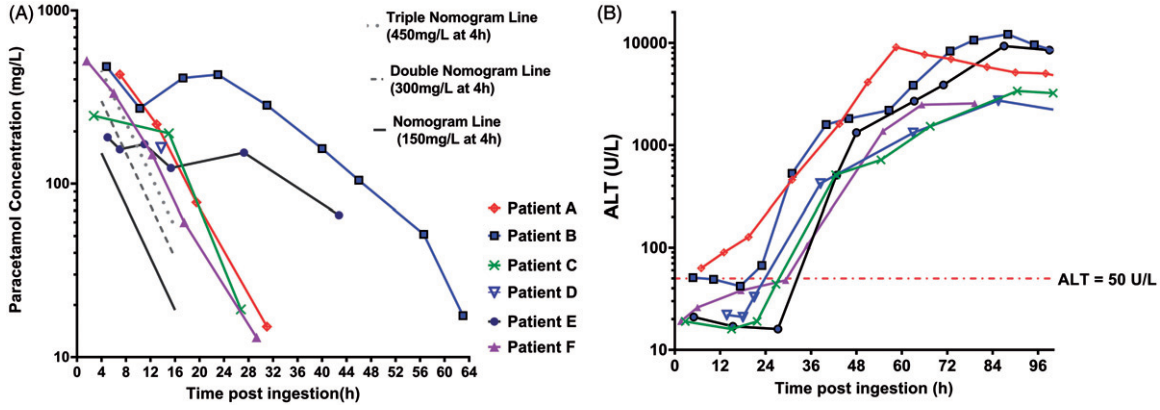

Figure 2. Patients who developed hepatotoxicity despite acetylcysteine within 8 h of ingestion, paracetamol concentrations (A) and ALT (B) versus time post-ingestion plots. For clinical details, refer Table 2.

despite treatment with acetylcysteine within 8 h of ingestion (Patients B and E, Figure 2 and Table 2).

Acute liver injury

Twenty-one (18%) developed hepatotoxicity; Figure 3 shows a flowchart of the timing and treatments of the patients and the subsequent outcome. Those who developed hepatotoxicity had a significantly longer time to treatment than those who did not, 16.5 h ($n = 21$, IQR: 6.8–22.4 h) versus 4.5 h ($n = 92$, IQR: 3–7.8) ($p < .0001$). Six patients who developed hepatotoxicity had treatment commenced within 8 h of ingestion. Figure 2 and Table 2 shows the clinical details of these six patients including their paracetamol and ALT concentrations and treatment data.

Table 2. Clinical details of patients who developed hepatotoxicity despite acetylcysteine treatment within 8 h of ingestion.

Patient –ID Age/ Gender (weight kg)	Paracetamol Dose (g)	Co-ingestions	Initial ALT (U/L)	Activated charcoal time post-ingestion (h)	Acetylcysteine commenced time post-ingestion (h)	Increased acetylcysteine given	ALT Peak (U/L)	INR Peak
A – 63F (60 kg)	47.88 g MR	Ethanol	63	9.5 h (50 g)	7 h	Increase in third infusion of standard[a] 21 h regimen from 100 mg/kg/16 h to 200 mg/kg/16 h	9080	2
B – 32M (75 kg)	135.66 g MR	Nil	51	4.5 h (50 g)	5 h	Increase in third infusion of standard 21h regimen from 100 mg to 200 mg/kg/16 h with increased acetylcysteine continued for subsequent infusions.	12163	3
C – 51F (113 kg)	79.8 g MR	Ethanol	16	3.5 h (50 g)	3 h	Standard acetylcysteine for 21 h was completed then restarted 8h post-completion as elevated paracetamol concentration. Standard 3 bag regimen restarted with increase in acetylcysteine in the third infusion from 100 mg to 200 mg/kg/16 h.	3381	1.9
D – 55M (61 kg)	63.84 g MR	Ethanol	22	Nil	5.5 h	Standard acetylcysteine	2730	1.4
E – 42F (51 kg)	59.85 g MR	Clonazepam + mirtazapine,	21	Nil	6.5 h	Standard acetylcysteine	9321	1.6
F – 52F (54 kg)	59.85 g MR	Temazepam, diazepam + quetiapine + carbamazepine (20g)	26	4.5 h (50 g) + 25 g × 3 doses 6 hrly.	4.5 h	Increase in third infusion of standard 21 h regimen from 100 mg/kg/16 h to 200 mg/kg/16 h.	2480	1.6

[a]Standard acetylcysteine regimen 300 mg/kg over 20–21 h.

Fourteen (12%) developed a peak ALT >50 U/L but ≤1000 U/L of which 7 had a peak ALT ≥150 U/L. Two of which had been treated with acetylcysteine within 8 h of ingestion, both these patients had an initial ALT <50 U/L on presentation.

The results of the multivariable analysis looking at associated risk factors for hepatotoxicity are shown in Figure 4. Larger ingested dose (in 0.1 g/kg increments), higher paracetamol ratio and longer time to acetylcysteine were all associated with a significant increased risk of hepatotoxicity (Figure 4) and acute liver injury (Supplementary Figure S2). Even when adjusted for the administration of activated charcoal and time to acetylcysteine, a larger ingested dose (mg/kg, 100 mg/kg increments) and an increased paracetamol ratio was associated with a significantly increased risk of hepatotoxicity, adjusted OR: 1.46 (95% CI: 1.15–1.86, $p = .002$) and 2.13 (95% CI: 1.32–3.45, $p = .002$), respectively (Figure 4).

Complications

There was one death in this study, an 87 M who died from respiratory failure secondary to aspiration 30 h post-ingestion. Of the 21 patients who developed hepatotoxicity no patient required a liver transplant or developed hepatic encephalopathy. The median ALT of this group was 5300 U/L (IQR: 3500–10,500 U/L). With a median peak INR of 2.0 (IQR: 1.5–4.6, range 1.4–10.3), five patients had a peak INR >5.0. Two patients developed acute renal injury with a peak creatinine of 500 and 600 μmol/L (AKIN stage 3); neither required dialysis.

Treatments

Activated charcoal

Activated charcoal (50 g) was administered in 26 (22%) of which 24 had only a single dose of activated charcoal. One patient had a second dose of 25 g and another had three further 25 g doses. The median time to activated charcoal was 3.5 h (IQR: 1.3–5.2 h), nine had charcoal >4 h post-ingestion. Seventeen ($n = 17/26$) who received activated charcoal had an initial paracetamol concentration ≥1 h post-charcoal administration. While 79 in the no charcoal group had a paracetamol ratio calculated. A doubling of ingested dose was associated with approximate doubling of the paracetamol ratio ($p < .001$) [Table 3(A) and Supplementary Figure S3]. Furthermore, a doubling in the patient's weight was associated with a halving of the paracetamol ratio ($p = .03$) (Table 3(A)). As ingested dose and weight had almost opposing effects, dose ingested/weight (g/kg) was included in the adjustment. With a doubling of dose ingested/weight (g/kg) being associated with an almost doubling of the paracetamol ratio ($p < .001$). The administration of activated charcoal showed a trend to a lower paracetamol ratio but this was not significant (Table 3(A)).

The area under the paracetamol concentration versus time post-ingestion curve was determined from 8 to 24 h post-ingestion, to enable comparison of paracetamol body burden between those who received and did not receive activated charcoal. Twenty-three patients who received activated

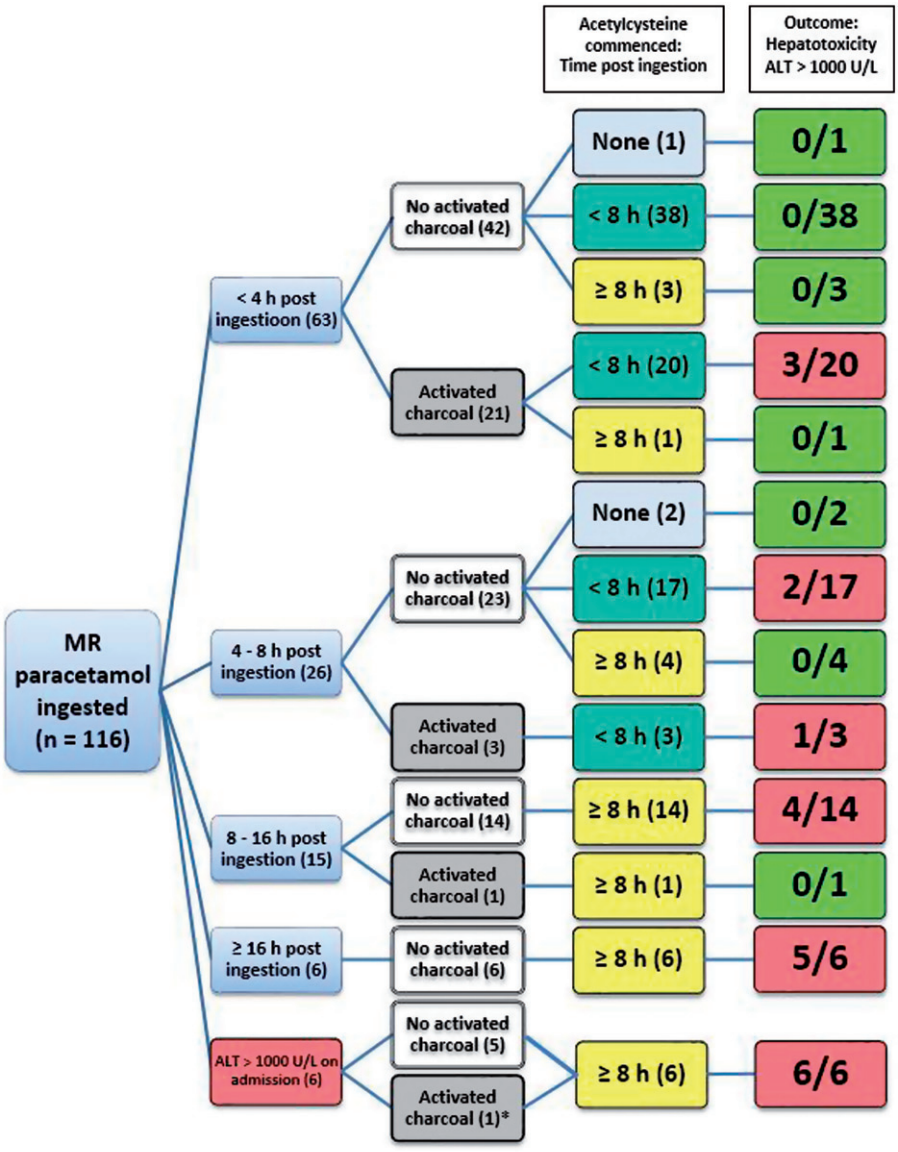

Figure 3. Flowchart of the timing and treatments of the patients and their subsequent outcome.

charcoal ($n = 23/26$) and 62 who did not receive activated charcoal had an initial paracetamol concentration within 8 h of ingestion; of these 17 and 40 respectively had enough data to calculate AUC from 8 to 24 h (Supplementary Figure S1). The linear regression model showed that AUC 8 to 24 h correlated with the dose of paracetamol ingested (Table 3(B)), and with the paracetamol ratio (correlation coefficients 0.6687, $p < .001$) (Supplementary Figure S4). Weight appeared to have less influence on AUC 8–24 h then on paracetamol ratio, this is expected as AUC is dependent not only on dose but is related to clearance. There was some evidence supporting a modest effect of activated charcoal on AUC (Table 3(B)). AUC 4–24 h was also calculated, but there was sufficient data for this analysis in only 34 patients. The results of the linear regression model were similar to those found with AUC 8–24 h (data not shown).

The effect of activated charcoal on hepatotoxicity was examined by multivariable analysis. Activated charcoal did not appear to have any large effect on the risk of subsequently developing hepatotoxicity, even when adjusted for dose (mg/kg in 100 mg/kg increments) or time to treatment (adjusted OR: 3.77 [95% CI: 0.64–22.33, $p = .144$]) (Figure 4).

Acetylcysteine treatment

Acetylcysteine was commenced in 113 (97%) patients, at a median time of 5 h (IQR: 3.1–10 h), 78 were treated within 8 h of ingestion and 103 completed at least a 20–21 h course of acetylcysteine. The majority, 67 (59%) received prolonged acetylcysteine beyond 20–21 h. Acetylcysteine was continued either because of an elevated paracetamol concentration or an elevated ALT >50 U/L near completion of the standard 21 h acetylcysteine infusion (current Australian recommendations for continuation of acetylcysteine) or both. Thirty-nine patients had an elevated paracetamol concentration, median paracetamol concentration of 25 mg/L (IQR: 16–62 mg/L, range: 5–426 mg/L), 12 of which also had an ALT >50 U/L.

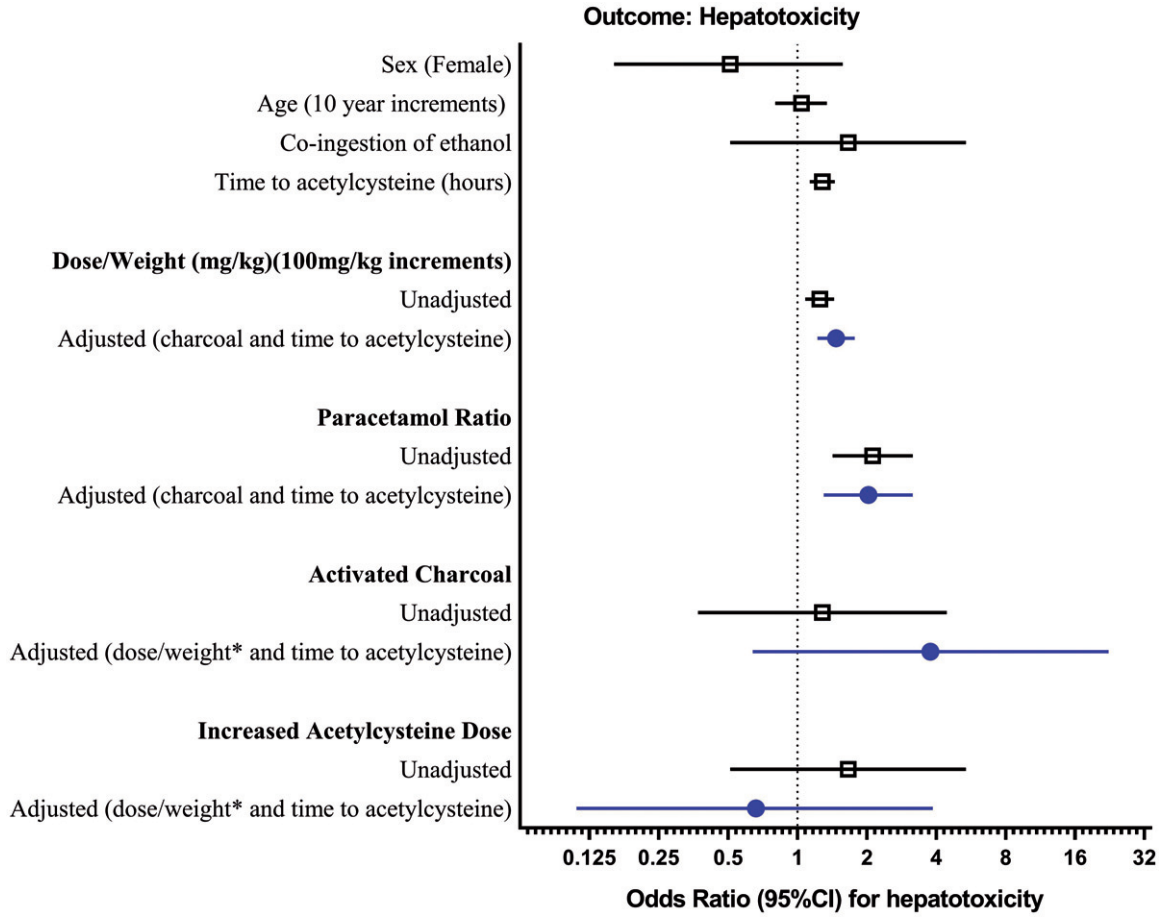

Figure 4. Forest plot of odds ratio (95% CI) from the logistic regression model, for risk of hepatotoxicity (maximum number of subjects included =107).
*Dose ingested/weight (mg/kg) as 100 mg/kg increments

Table 3A. Linear regression model results for Paracetamol Ratio response in $\log_2$ units ($n = 95$ in multivariable model).

Variable	Unadjusted		Adjusted	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Age (10 year increments)	−0.01 (-0.16, 0.15)	0.920	−0.02 (-0.17, 0.13)	0.780
Female	−0.07 (-0.82, 0.67)	0.844	0.16 (-0.54, 0.87)	0.644
Weight ($\log_2$ kg)	−0.97 (-1.86, -0.09)	0.030		
Dose Ingested ($\log_2$ grams)	0.91 (0.54, 1.27)	<0.001		
Dose per weight ($\log_2$ g/kg)	0.90 (0.58, 1.22)	<0.001	0.95 (0.60, 1.31)	<0.001
Activated Charcoal	−0.45 (-1.37, 0.47)	0.329	−0.34 (-1.16, 0.48)	0.418

Table 3B. Linear regression model results for AUC 8-24 hours response in $\log_2$ units ($n = 54$ in multivariable model).

Variable	Unadjusted		Adjusted	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Age (10 year increments)	0.16 (-0.04, 0.36)	0.114	0.09 (-0.08, 0.26)	0.309
Female	−0.70 (-1.56, 0.16)	0.110	−0.35 (-1.11, 0.41)	0.359
Weight ($\log_2$ kg)	−0.59 (-1.73, 0.54)	0.300	−0.56 (-1.54, 0.42)	0.258
Dose Ingested ($\log_2$ grams)	1.02 (0.64, 1.40)	<0.001	0.88 (0.46, 1.29)	<0.001
Activated Charcoal	−0.90 (-1.74, -0.06)	0.036	−0.60 (-1.34, 0.14)	0.111

A further 21 had acetylcysteine continued because of an ALT >50 U/L. Seven patients did not meet the criteria for prolonged acetylcysteine but due to concerns from the treating doctor (i.e., large ingested dose) acetylcysteine was continued.

Twenty-seven (24%) patients who received acetylcysteine had an increased dose within the first 21 h, most commonly a doubling of the dose from 100 mg/kg/16 h to 200 mg/kg/16 h in the "third bag". Of those that received increased acetylcysteine 18 received prolonged acetylcysteine beyond the standard 20–21 h regimen.

The effect of increased acetylcysteine dose on hepatotoxicity was examined by multivariable analysis. Increased acetylcysteine dose did not appear to have any significant effect

on rates of hepatotoxicity, even when adjusted for dose ingested (mg/kg, 100 mg/kg increments) and time to treatment (adjusted OR: 0.66 [95% CI: 0.11–3.86, $p = .644$]) (Figure 4). There were not adequate numbers to utilize AUC as a variable. These models were also repeated for other definitions of acute liver injury reaching similar conclusions (Supplementary Figure S2).

Discussion

The European Medicines Agency, Pharmacovigilance Risk Assessment Committee advised to suspend marketing of MR paracetamol due to concerns that "overdoses with modified-release paracetamol products can be unpredictable in their pharmacokinetics, and complex to manage" [3]. "The Committee could not identify means to minimize the risk to patients, or a feasible and standardized way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations" [2]. Furthermore, the committee concluded that MR offers little benefit over IR paracetamol in therapeutic use [2,3]. The sole advantage is a dosing regimen that is three rather than four times a day [9,10]. This observational prospective study of MR paracetamol ingestion offers further support of these concerns. In particular, we found that many patients had prolonged and unpredictable elevated paracetamol concentrations. Furthermore, some patients developed hepatotoxicity despite early presentation, activated charcoal, and increased acetylcysteine doses.

There are two previous retrospective case series of MR paracetamol in the literature. Salmonson et al. report 53 cases from the Swedish PIC with a median ingested dose of 20 g of which 43 (81%) were treated with acetylcysteine [1]. Ten (19%) patients had persistently elevated serum paracetamol concentrations of which six (11%) had a second paracetamol peak. Furthermore, three developed hepatotoxicity despite acetylcysteine within 8 h of ingestion. Graudins et al reported results of 42 patients with a median ingested dose of 20 g [11]. Of these 29 (69%) received acetylcysteine and 10 (24%) had prolonged acetylcysteine treatment. Two in this series developed hepatotoxicity, one of which was treated within 8 h of ingestion. Our larger case series with a higher median ingested dose (32 g) more than doubles the number of reports of patients requiring prolonged treatment due to erratic absorption and high rates of hepatotoxicity, sometimes despite early and/or higher doses of antidotes.

The multivariable analysis (Figure 4), found that dose ingested (mg/kg), initial paracetamol ratio and time to treatment were associated with an increased risk of hepatotoxicity. Those who ingest large doses of MR paracetamol are of particularly concern as the pharmacokinetics appears to become more unpredictable with persistently elevated paracetamol concentrations and double peaks (Figure 1).

The guidelines for the management of MR paracetamol, including recommendations for decontamination and acetylcysteine dosage are based on little evidence or on IR ingestion. Of particular concern in this study were the six patients who developed hepatotoxicity despite early acetylcysteine treatment. Four of these patients had received charcoal and three an increased dose of acetylcysteine above the standard regimen (Figure 2 and Table 2). The administration of activated charcoal or an increased acetylcysteine dosage did not appear to lower the risk of hepatotoxicity. This is in contrast to large (≥40 g) IR paracetamol ingestions, where recent observational data from 200 patients found that those who received activated charcoal and/or increased acetylcysteine treatment had much lower rates of hepatotoxicity [12].

These observations raise questions about optimum treatment particularly in large MR ingestions. The current standard acetylcysteine regimen delivers an early bolus of acetylcysteine. From human simulated overdose data of 80 mg/kg, MR paracetamol results in a delayed time to peak concentration when compared with IR paracetamol [13]. Hence, one could hypothesize that higher doses of acetylcysteine are required later when these peak concentrations occur. With large MR ingestions, paracetamol concentrations may remain extremely elevated well beyond the initial bolus dose and in some cases even beyond 24 h.

Furthermore, activated charcoal use was not associated with a significantly lower initial paracetamol ratio or lower rates of hepatotoxicity, but did appear to have possible modest effects on the AUC measures (Table 3(B)). It is important to note that a major limitation of this analysis is the low numbers receiving activated charcoal: 26 (22%). In a study of massive (≥40 g) IR paracetamol ingestion where a similar proportion (25%) received activated charcoal; those who received activated charcoal had a significantly lower paracetamol ratio with a decrease in paracetamol ratio of 45% [12]. A similar magnitude effect was not seen in this study, but we could not exclude smaller benefits. These might be found with future larger studies.

The limited efficacy of a single dose of charcoal may be because of the capacity of MR paracetamol to form pharmacobezoars. Only two patients in this study received more than one dose of activated charcoal. *In vitro* models mimicking gastric fluids found extended-release paracetamol products (Pinex® Retard 500 mg), formed firm and lasting pharmacobezoar, and drug release was prolonged within the pharmacobezoar [14]. Hence repeated doses of activated charcoal may be more effective.

From the limited number who received activated charcoal, we found activated charcoal administration was associated with an increased risk of liver injury even when adjusted for dose ingested and time to treatment (Figure 4). This likely reflects doctors administering activated charcoal to those patients who took large overdoses. In large MR paracetamol ingestions it appears that a single dose of activated charcoal may be insufficient. Although activated charcoal did not appear to alter the risk of liver injury in this case series, we still recommend this treatment. As in the awake and alert patient charcoal is a low risk intervention and further studies are required to determine its efficacy in MR paracetamol ingestion [15,16].

There are various limitations to this study, first some cases were not recruited as identification of cases through the two PICs relied on PIC staff to notify the study investigators of eligible patients. During the same time period the NSW PIC

received approximately 200 calls regarding MR paracetamol ingestion of ≥10 g that may have been eligible for inclusion. The median ingested dose in this case series was quite large and this might represent bias by the PIC to refer cases that ingested large doses. However, a standard 96 pack in Australia contains 63.84 g, thus large overdoses are not remarkable. We only recruited patients who ingested a toxic dose of MR paracetamol (10 g or 200 mg/kg whichever is less), it is possible we missed cases that ingested less than this and subsequently developed liver injury. We are aware of one such case in the study period, where a patient developed hepatotoxicity after ingesting 7.98g of MR paracetamol had two initial paracetamol concentrations well below the nomogram line and falling. Acetylcysteine was not commenced, 2 days later she developed abdominal pain and vomiting and was found to have hepatotoxicity. She received IV acetylcysteine and made an uneventful recovery with a peak INR of 1.2.

Other limitations include accuracy of dose and time of ingestion data relies on patient history. The numbers who developed hepatotoxicity despite early treatment were low; hence we were unable to determine if factors such as co-ingestion of agents that slow gut emptying were associated with an increased risk of liver injury. Furthermore, the number of patients receiving activated charcoal and increased acetylcysteine were also low making analysis of these treatments limited. This is not a randomized study so it is difficult to draw firm conclusions about treatments such as charcoal and increased acetylcysteine doses being ineffective. Larger numbers receiving these treatments may have shown some benefit. However, we do demonstrate that these treatments appeared to be not as effective in situations where they would generally be regarded as effective. Furthermore, a limitation of the AUC 8–24 h analysis is that many patients were not included if an AUC could not be calculated. Hence, limiting the conclusions from this analysis in regards to the effect of activated charcoal.

Despite these limitations this case series highlights that treatment of MR paracetamol ingestions may be inadequate. Particularly in large overdoses ≥40 g where single dose activated charcoal and increased acetylcysteine dose did not seem to have the same benefit at reducing rates of hepatotoxicity as in IR paracetamol ingestions. We suggest that these patients should have repeat paracetamol concentrations to guide increased and prolonged acetylcysteine doses and/or repeated doses of activated charcoal. Many questions remain and while this product remains available further research is required to determine if more vigorous decontamination (such as repeat or multiple dose of activated charcoal or whole bowel irrigation) would be of benefit and whether acetylcysteine doses should be continued longer and increased routinely or just in those ingesting larger overdoses.

Conclusion

Following an acute overdose of MR paracetamol patients may have erratic pharmacokinetics with persistently high paracetamol concentrations, double paracetamol peaks, and ongoing absorption. Many patients required prolonged acetylcysteine treatment. Treatments such as activated charcoal and increased acetylcysteine did not appear to substantially mitigate the risk of acute liver injury in this study. Hence, research into better treatment strategies is urgently required while this product remains on the market.

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