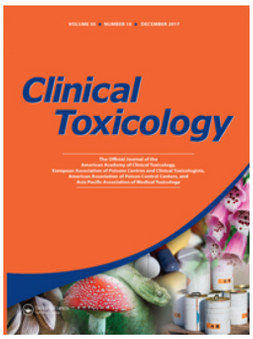

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CLINICAL RESEARCH

Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2)

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ABSTRACT

Context: Paracetamol is commonly taken in overdose, with increasing concerns that those taking "massive" overdoses have higher rates of hepatotoxicity and may require higher doses of acetylcysteine. The objective was to describe the clinical characteristics and outcomes of "massive" (≥ 40 g) paracetamol overdoses.

Methods: Patients were identified through the Australian Paracetamol Project, a prospective observational study through Poisons Information Centres in NSW and Queensland, over 3 and 1.5 years, respectively, and retrospectively from three clinical toxicology unit databases (over 2.5 to 20 years). Included were immediate-release paracetamol overdoses ≥ 40 g ingested over ≤ 8 h. Outcomes measured included paracetamol ratio[defined as the ratio of the first paracetamol concentration taken 4–16 h post-ingestion to the standard (150 mg/L at 4 h) nomogram line at that time] and hepatotoxicity (ALT >1000 U/L).

Results: Two hundred paracetamol overdoses were analysed, reported median dose ingested was 50 g (interquartile range (IQR): 45–60 g) and median paracetamol ratio 1.9 (IQR: 1.4–2.9, $n = 173$). One hundred and ninety-three received acetylcysteine at median time of 6.3 h (IQR: 4–9.3 h) post-ingestion. Twenty-eight (14%) developed hepatotoxicity, including six treated within 8 h of ingestion. Activated charcoal was administered to 49(25%), at median of 2 h post-ingestion (IQR:1.5-5 h). Those receiving activated charcoal (within 4 h of ingestion), had significantly lower paracetamol ratio versus those who did not: 1.4 ($n = 33$, IQR: 1.1–1.6) versus 2.2 ($n = 140$, IQR: 1.5–3.0) ($p < .0001$) (paracetamol concentration measured ≥ 1 h after charcoal). Furthermore, they had lower rates of hepatotoxicity [unadjusted OR: 0.12 (95% CI: <0.001–0.91); adjusted for time to acetylcysteine OR: 0.20 (95%CI: 0.002–1.74)].
Seventy-nine had a paracetamol ratio ≥2, 43 received an increased dose of acetylcysteine in the first 21 h; most commonly a double dose in the last bag (100 to 200 mg/kg/16 h). Those receiving increased acetylcysteine had a significant decrease risk of hepatotoxicity [OR:0.27 (95% CI: 0.08–0.94)]. The OR remained similar after adjustment for time to acetylcysteine and paracetamol ratio.

Conclusion: Massive paracetamol overdose can result in hepatotoxicity despite early treatment. Paracetamol concentrations were markedly reduced in those receiving activated charcoal within 4 h. In those with high paracetamol concentrations, treatment with increased acetylcysteine dose within 21 h was associated with a significant reduction in hepatotoxicity.

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Paracetamol; acetylcysteine; overdose; activated charcoal; hepatotoxicity

Introduction

Paracetamol is one of the commonest drugs taken in overdose and a significant cause of acute liver injury in developed countries [1,2]. The major risk factor for developing acute liver injury following paracetamol ingestion is delayed time to treatment with acetylcysteine. Beyond 8 h post-ingestion, the effectiveness of acetylcysteine rapidly decreases. Rates of hepatotoxicity reported in those receiving treatment within 8 h range from 0% to 6% compared with those treated >8–10 h post-ingestion of 8–50% [3–5].

In Australia and many other countries, the standard dose of intravenous acetylcysteine is 300 mg/kg over 20–21 h given as either a 2 or 3 bag infusion [6]. Although this regimen is sufficient for the majority of overdoses, questions remain as to whether this regimen is optimal in patients with high paracetamol concentrations [7]. Furthermore, serum paracetamol concentration has a dose dependent relationship with hepatotoxicity, regardless of time to treatment with acetylcysteine [8,9].

The practice of increasing acetylcysteine dose varies globally. The 2015 Australia and New Zealand paracetamol

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Supplemental data for this article can be accessed here.

guidelines now recommends an increase in acetylcysteine dose, in those with an initial paracetamol concentration more than twice the 150 mg/L at 4 h nomogram line [6]. An international survey of clinical toxicologists and poison centres found that 61% of the 164 respondents would increase the dose of acetylcysteine in the third infusion, in those with high paracetamol concentrations. However, the paracetamol concentration at which the dose would be increased varied widely between respondents, with 33% nominating triple the nomogram line [10]. Despite this widespread practice, no supporting evidence for any threshold has been published.

Activated charcoal is recommended following paracetamol ingestion within 1–4 h of ingestion, with recommendations also varying around the world. The evidence for the use of charcoal is based mainly on non-randomised trials and studies in healthy volunteers. Activated charcoal given within 2 h of ingestion appeared to reduce the absorption of paracetamol and need for acetylcysteine [11,12]. However, it is not known if it improves clinical outcomes such as rates of acute liver injury. The use of activated charcoal following all overdoses has declined over the last 20 years, with the American Association of Poison Control Centres reporting activated charcoal administration decreasing from 7.7% of all exposures in 1995, to 2.3% in 2013 [13]. There is little data on the rate of activated charcoal use following paracetamol ingestion and whether there is a benefit in large overdoses.

There is no set definition of "massive" paracetamol overdose; in Australia, the majority of patients ingest less than 20 g of paracetamol and present within 8 h of ingestion, with less than half requiring treatment with acetylcysteine [12,14]. Of those that have toxic paracetamol concentrations the majority are just above the standard (150 mg/L at 4 h) treatment nomogram line. Only a small percentage of patients take overdoses greater than 40–50 g [12]. The objective of this study was to describe clinical characteristics, treatments and outcomes of "massive" paracetamol overdose and whether treatments such as activated charcoal or increased acetylcysteine dose were associated with an altered outcome. We arbitrarily used a definition of $\geq$40 g of paracetamol, which is over four times the generally regarded potentially toxic dose [6,15].

Methods

Design and setting

This was an observational study using four data sources. One was the Australian Paracetamol Project (APP) which is an arm of the Australian TOxicology Monitoring (ATOM) Study. APP is an observational study that recruits patients prospectively through four toxicology units in Australia and through calls to the New South Wales (NSW) and Queensland Poisons Information Centres (PIC). The ATOM study has ethical approval by Human Research and Ethics Committees in NSW and QLD to cover all involved institutions and PICs.

The other three data sources were clinical toxicology unit databases from the Hunter Area Toxicology Service (HATS), South Eastern Area (Sydney) Toxicology Service (SEATs), and Princess Alexandria Hospital (PAH). These clinical toxicology units prospectively collect data on all toxicology patients, and enter this data into purpose-built databases. These units are based in NSW and Queensland and treat approximately 800–2000 toxicology patients per year. The SEATs and PAH clinical databases have ethical approval from their respective local ethics committees. While the HATS database has been granted exemption by the local Human Research Ethics Committee to use de-identified patient information as an audit.

Selection of participants

Patients were included who ingested $\geq$40 g of immediate release paracetamol over less than 8 h. APP recruited patients $\geq$14 years prospectively from NSW from September 2013 until November 2016 and from QLD from April 2015 to November 2016. The three toxicology unit databases collected data over varying time periods from 2.5 to 20 years (Supplementary Table 1), with no age restriction.

Methods and measurements

Data collected from all sources included demographic information, overdose exposure (time and dose ingested), co-ingestions including ethanol, laboratory investigations, treatments, and outcomes. Patients recruited through APP had preformatted clinical data sheets collected. The same data was extracted from the toxicology unit databases. If there was any missing data, this was obtained from medical records.

Outcomes

Outcomes recorded included acute liver injury, liver transplant, and death. There are various cut-offs for acute liver injury, traditionally the main outcome measure is hepatotoxicity, defined as a peak ALT >1000 U/L [16]. However, as varying definitions are used for acute liver injury, these were also considered and reported in supplementary data, including ALT >50 U/L (the Australian indication, for continuing acetylcysteine therapy after completion of the initial regimen) [6] and ALT >150 U/L (the UK indication for continuing acetylcysteine therapy after completion of the initial regimen) [17].

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 [16,18].

In patients who had more than one paracetamol concentration taken ≥4 h post-ingestion, the slope of the paracetamol concentration versus time of overdose was calculated. Slopes were calculated by GraphPad Prism (version 7©2017 GraphPad Software Inc., San Diego, CA) using a semi-log line of best fit. Slopes were compared in all those patients who received charcoal within 4 h of ingestion, to indicate if there was an effect of activated charcoal on subsequent paracetamol concentrations. From negative slope data, a corresponding half-life was estimated.

Statistical analysis

Age, dose, paracetamol ratio, and weight were treated as continuous variables. Missing weights ($n=6$) were replaced with the median weight for Australians with the same age and sex [19]. If ALT was not measured around 24 h or later, the ALT was assumed to remain unchanged. There were 24 patients with missing ALT data of which 14 had a paracetamol concentration below the nomogram line. Hence, they were predominantly patients with low concentrations who did not require acetylcysteine and rates of hepatotoxicity are low in this group (<1%) [20].

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 and categorical variables were compared using Fisher's exact test.

Multivariable analyses were performed to estimate the effect of activated charcoal on the initial paracetamol ratio, the risk of hepatotoxicity, and the effect of increased acetylcysteine dose on risk of hepatotoxicity.

For both activated charcoal analyses, patients were divided into those receiving activated charcoal within 4 h post-ingestion, and those not receiving charcoal or receiving charcoal later. To assess the association of activated charcoal administration with initial paracetamol ratio, we used generalized linear models within the log-link and Poisson family so that the point estimates for the explanatory variables could be interpreted as factor changes in paracetamol ratio. Patients were only included in the activated charcoal arm if there was greater than 1 h between activated charcoal administration and initial paracetamol ratio. Variables adjusted for included age, sex, weight, and dose ingested.

Logistic regression models were used to assess whether activated charcoal within 4 h of ingestion was associated with decreased risk of hepatotoxicity. We excluded those treated >16 h post-ingestion, as this group has a very high risk (≈45%) of hepatotoxicity, even with treatment [18,20]. Covariates considered for entry into the model included time to acetylcysteine, age, sex, weight, co-ingestion of ethanol, and paracetamol ratio. These were first analysed 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 1–2 variables were included in each model. Firth exact logistic regression was used where there was separation in the data.

Increased acetylcysteine infusion doses are largely confined to those with high paracetamol concentrations (usually paracetamol ratio of ≥2) [6,10]. In these patients, logistic regression analysis was performed to determine if increased acetylcysteine reduced the risk of acute liver injury. Multivariable analysis adjusted for time to acetylcysteine, age, sex, weight, co-ingestion of ethanol, and paracetamol ratio. These were first analysed using bivariable models; variables with $p<.10$ were assessed in the multivariable models and because of the small number of adverse outcomes only one covariate was adjusted for at a time.

Statistical analyses were performed using Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.), SAS Software (Version 9.4 Copyright©2013 SAS Institute Inc., Cary, NC), and GraphPad Prism (version 7©2017 GraphPad Software Inc., San Diego, CA).

Results

Demographics

Two hundred cases were identified, 123(62%) were female, median age of 29 years (IQR: 20–41). The median time to presentation was 3.5 h (IQR: 1.8–7.8 h), with a median dose ingested of 50 g (IQR: 45–60 g). Patient demographic data, co-ingestions and treatments are shown in Table 1. Data from the four different sites were comparable (Supplementary Table 1). One hundred and seventy-three (87%) patients had a paracetamol concentration between 4 and 16 h post-ingestion, with a median paracetamol ratio of 1.9 (IQR: 1.4–2.9). Of these, 79(40%) had an initial paracetamol concentration more than double the 150 mg/l at 4 h nomogram line.

Outcomes

Twenty-eight (14%) patients developed hepatotoxicity, with a further 9(5%) having a peak ALT between 150 and <1000 U/L. Those who developed hepatotoxicity had a significantly longer time to treatment than those who did not, 13.9 h ($n=28$, IQR: 9.1–23.9 h) versus 6 h ($n=165$, IQR: 3.8–7.6) ($p=<.0010$). Six patients (3%) who developed hepatotoxicity had treatment commenced within 8 h of ingestion, their paracetamol ratios were 2.7, 3.3, 3.4, 3.5, 3.5, and 5.8. Four of these six had acetylcysteine commenced within 4 h of ingestion. One patient required a liver transplant, despite acetylcysteine being commenced 2.5 h post-ingestion. There was one death which was unrelated to paracetamol ingestion.

Activated charcoal

Activated charcoal was administered in 49(25%), of which 13 had charcoal >4 h post-ingestion. Five patients received activated charcoal greater than 24 h post-ingestion because of a delayed or double paracetamol peak. Median time to

Table 1. Patient demographic ingestion and treatment data.

	All patients ($n = 200$)
% Females	123 (62%)
Median Age (years) (IQR)	29 years (20–41)
Median weight (kg) (IQR)	70 kg (60–89) ($n = 193$)
Median Dose ingested (grams) (IQR)	50 g (45–60)
Median dose ingested (g/kg) (IQR)	0.7 g/kg (0.56–0.90) ($n = 193$)
Co-ingested gut slowing medications	66 (33%)
Co-ingested Ethanol	53 (27%)
Median time to presentation (hours)(IQR)	3.5 h (1.8–7.8h)
Received Activated Charcoal	49 (25%)
Median time to activated charcoal (hours)(IQR)	2 h (1.5–5.0 h)
Median Paracetamol Ratio (IQR)[b]	1.9 (1.4–2.9) ($n = 173$)
ALT at presentation not elevated (< 50 U/L or at their baseline)	171 (86%)
Commenced on acetylcysteine	193 (97%)
• Median time to acetylcysteine (hours)(IQR)	6.3 h (4–9.3 h)
• Completing at least 21 h of acetylcysteine	183 (95%)[a]
• Adjustment to standard acetylcysteine dosing in the first 21 h of treatment	59 (31%)[a]
• Prolonged acetylcysteine required beyond standard 20.5 h infusion	75 (39%)[a]

[a]Percentage of those commenced on acetylcysteine ($n = 193$).
[b]Paracetamol ratio was only calculated in those patients who had a paracetamol concentration measured between 4 and 16 h post-ingestion.

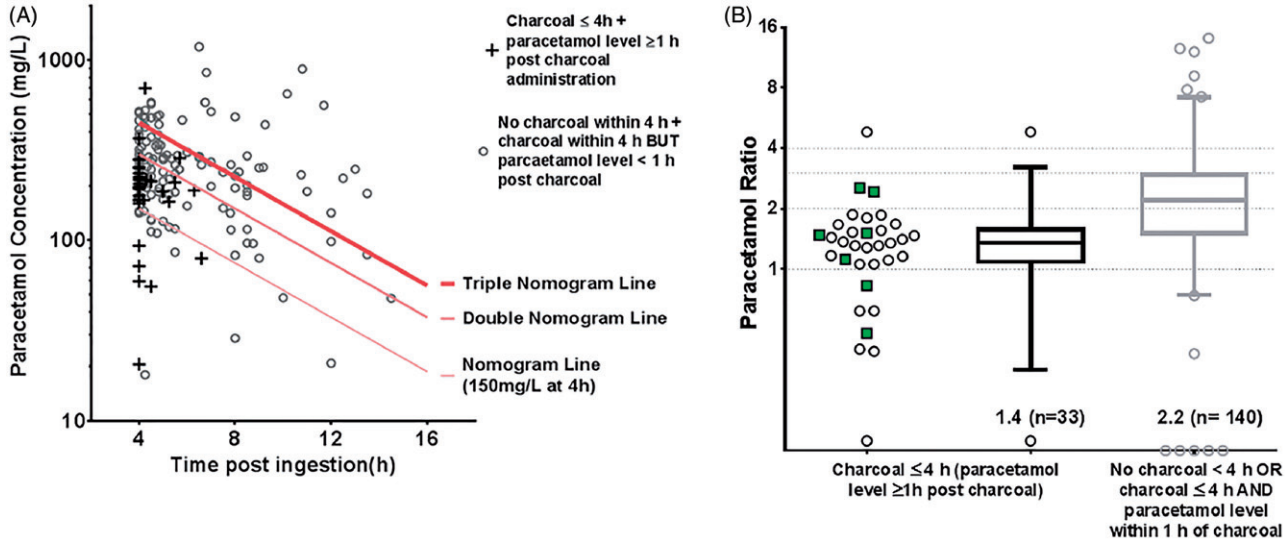


Figure 1. Effect of activated charcoal on initial paracetamol concentration. (A) Initial paracetamol concentration stratified per those who received activated charcoal ≤4 h post-ingestion and had a paracetamol concentration ≥1 h after charcoal administration versus those that did not. Note four patients whom had no activated charcoal had an initial paracetamol level <10 mg/L. (B) Box and whiskers plot comparing median paracetamol ratio in those who received activated charcoal ≤4 h post-ingestion and had a paracetamol concentration measured ≥1 h post-activated charcoal compared with all other patients who had a paracetamol concentration taken within 16 h. Activated charcoal group stratified per time activated charcoal given post-ingestion. Circles: activated charcoal ≤2 h. Squares activated charcoal between 2 and 4 h post-ingestion. (Box and whiskers plot bar is the median value, box represents the 1st and 3rd quartile, bars the 10th and 90th centiles and individual points are the outliers).

activated charcoal was 2 h (IQR: 1.5–5.0 h). Those who received activated charcoal within 4 h of ingestion subsequently had a significantly lower paracetamol ratio versus than those who did not, 1.4 ($n = 33$, IQR: 1.1–1.6) versus 2.2 ($n = 140$, IQR: 1.5–3.0) (Figure 1(A,B)).

Figure 2 shows a flowchart of numbers utilised for the multivariable analyses comparing those patients receiving or not receiving activated charcoal, looking at both paracetamol ratio and rate of hepatotoxicity. Activated charcoal and age were found to be independent risk factors affecting the paracetamol ratio (Table 2). Receiving activated charcoal within 4 h of ingestion was associated with a decrease in paracetamol ratio of 45% (adjusted risk ratio 0.55, 95% CI: 0.43–0.69, $n = 33$), after adjustment for other variables and compared with those not receiving charcoal or receiving charcoal >4 h post-ingestion.

Activated charcoal within 4 h of ingestion was associated with lower risk of hepatotoxicity; unadjusted odds ratio (OR): 0.12 (95% CI: <0.001–0.91). The effect was reduced when adjusted for time to acetylcysteine [adjusted OR was 0.20 (95% CI: 0.002–1.74)] and adjusted for paracetamol ratio [adjusted OR 0.18 (95% CI: 0.001–1.46)] (Figure 3). This suggests some but not all effects of activated charcoal were reflected in the paracetamol ratio and time to treatment. Similar results were seen for the various other cut-offs of acute liver injury (peak ALT >50 U/L and peak ALT >150 U/L) (Supplementary Figure 1).

Age, increased paracetamol ratio, and time to acetylcysteine were all associated with an increased risk of hepatotoxicity (Figure 3). Higher paracetamol ratio was associated with an increased risk of hepatotoxicity [OR: 1.30 (95% CI: 1.10–1.54)], with an adjusted OR for time to acetylcysteine

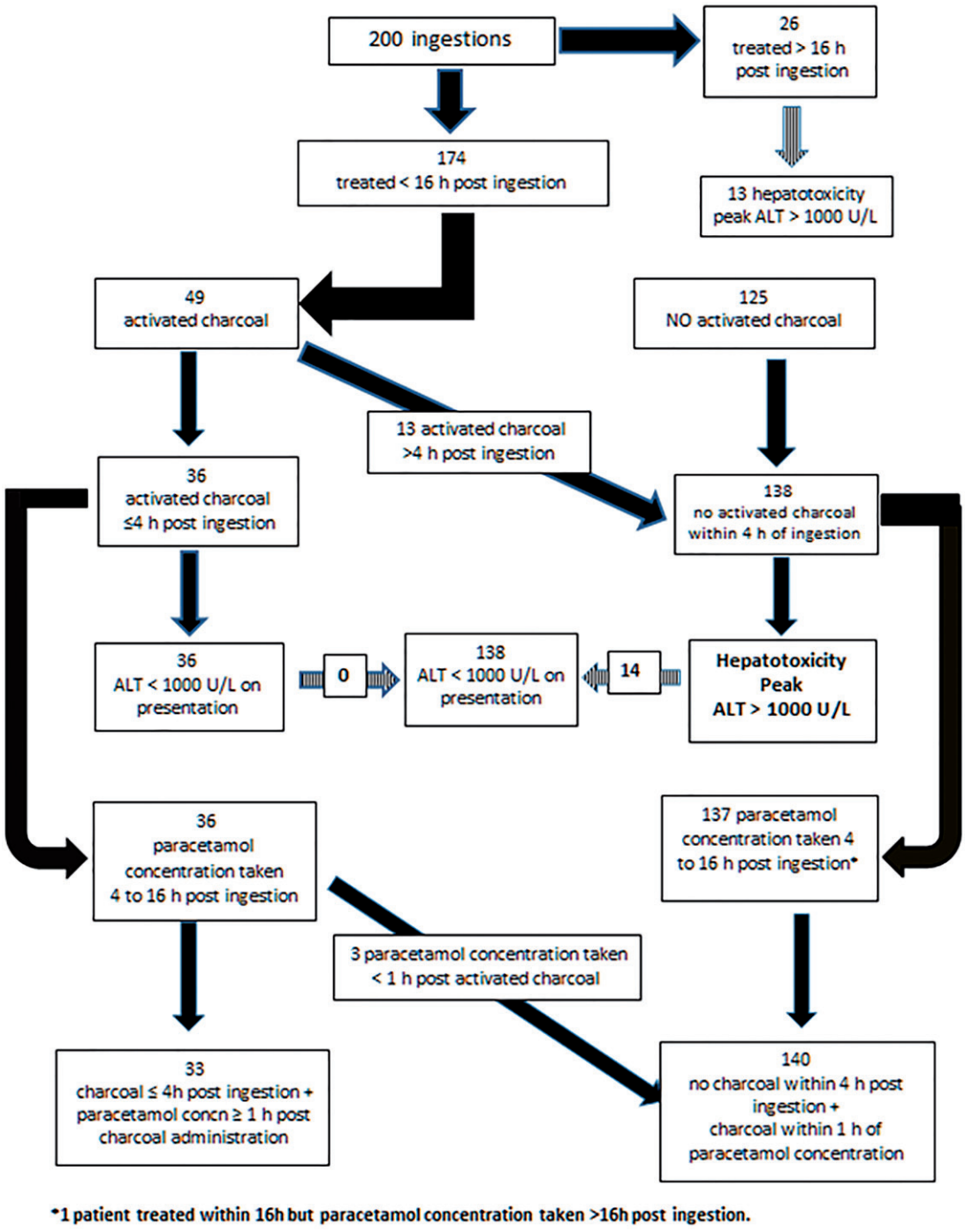


Figure 2. Flowchart of numbers utilised for activated charcoal analysis of hepatotoxicity and paracetamol ratio.

and administration of activated charcoal of 1.16 (95% CI: 0.97–1.40) (Figure 3).

The slope of the paracetamol concentration versus time post-ingestion was determined in those with more than one paracetamol concentration (Supplementary Figure 2). The median slope in those receiving activated charcoal within 4 h was significantly different −0.08 ($n = 23$) from those not receiving charcoal within 4 h of ingestion −0.06 ($n = 70$) ($p = .013$). This corresponds to a median paracetamol half-life in these two groups of 3.8 h and 5.0 h, respectively (Supplementary Figure 3).

Acetylcysteine treatment

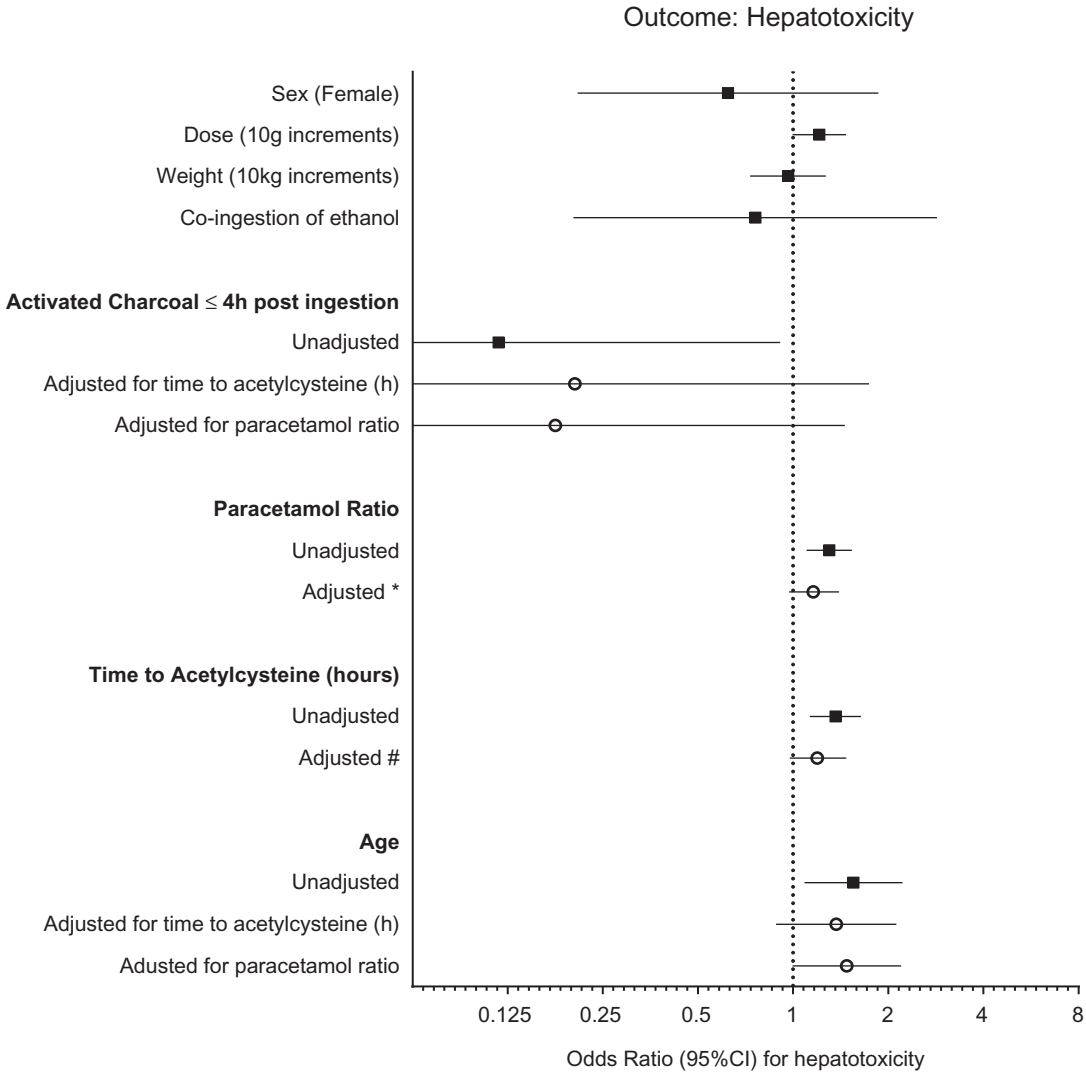
Acetylcysteine was commenced in 193(97%) patients, at a median time of 6.3 h (IQR: 4–9.3 h), with 137 (71%) treated within 8 h. One hundred and eighty-three patients completed at least a 21 h course of acetylcysteine. Of these, 59 (32%) received an increased dose of acetylcysteine within the first 21 h, most commonly a doubling of the dose in the 100 mg/kg/16 h bag to 200 mg/kg/16 h. Four patients received standard acetylcysteine for the first 21 h and had an increased dose of acetylcysteine after this time. Seventy-five (41%)

received acetylcysteine beyond 21 h, 42 because of an ALT >50 U/L (current Australian recommendations), and 33 justified by paracetamol assay results near completion of the standard 21 h acetylcysteine infusion (median paracetamol concentration of 38 mg/L (IQR: 19–167 mg/L, range: 3–1142 mg/L).

Table 2. Generalized linear model results (Poisson family and log link) for paracetamol ratio response.

Variable	Unadjusted Risk ratio (95% CI)	Adjusted Risk ratio (95% CI)
Age (10 year increments)	1.25 (1.14–1.37)	1.23 (1.13–1.33)
Dose (10 g increments)	1.03 (0.97–1.10)	1.02 (0.97–1.09)
Weight (10 kg increments)	0.96 (0.91–1.01)	0.94 (0.88–0.99)
Sex (female)	0.95 (0.71–1.25)	0.93 (0.69–1.23)
Time post-OD activated charcoal administered: (categories)		
None or >4 h	1.0 (ref)	1.0
Charcoal 0 to ≤4 h ($n = 33$)	0.50 (0.39–0.65)	0.55 (0.43–0.69)

Figure 4 shows a flowchart of those with a paracetamol ratio ≥2 (within 16 h of ingestion), comparing those who received standard versus increased acetylcysteine (within the first 21 h of treatment) and the numbers utilised for the linear logistic regression analysis looking at rates of hepatotoxicity. Figure 5 shows the initial paracetamol concentration and outcomes of those receiving the standard regimen versus an increased acetylcysteine dose. Results of the multivariable analysis are shown in Table 3; due to the small number of outcomes, adjustments were performed singularly. Increased acetylcysteine doses were associated with a significantly lower risk of hepatotoxicity [OR: 0.27 (95% CI: 0.08–0.94)] this remained similar when adjusted for time to acetylcysteine [adjusted OR: 0.27 (95% CI: 0.07–0.98)] and paracetamol ratio [adjusted OR: 0.23 (95% CI: 0.06–0.86)]). Similar results were seen for the other two cut-offs levels (peak ALT >50 U/L and peak ALT >150 U/L) (Supplementary Table 2).



Square: unadjusted odds ratio

Circle: adjusted odds ratio

*adjusted for time to acetylcysteine and charcoal administration

adjusted for paracetamol ratio and charcoal administration

Figure 3. Forest plot of odds ratio (95% CI) from the logistic regression model, for risk of hepatotoxicity.

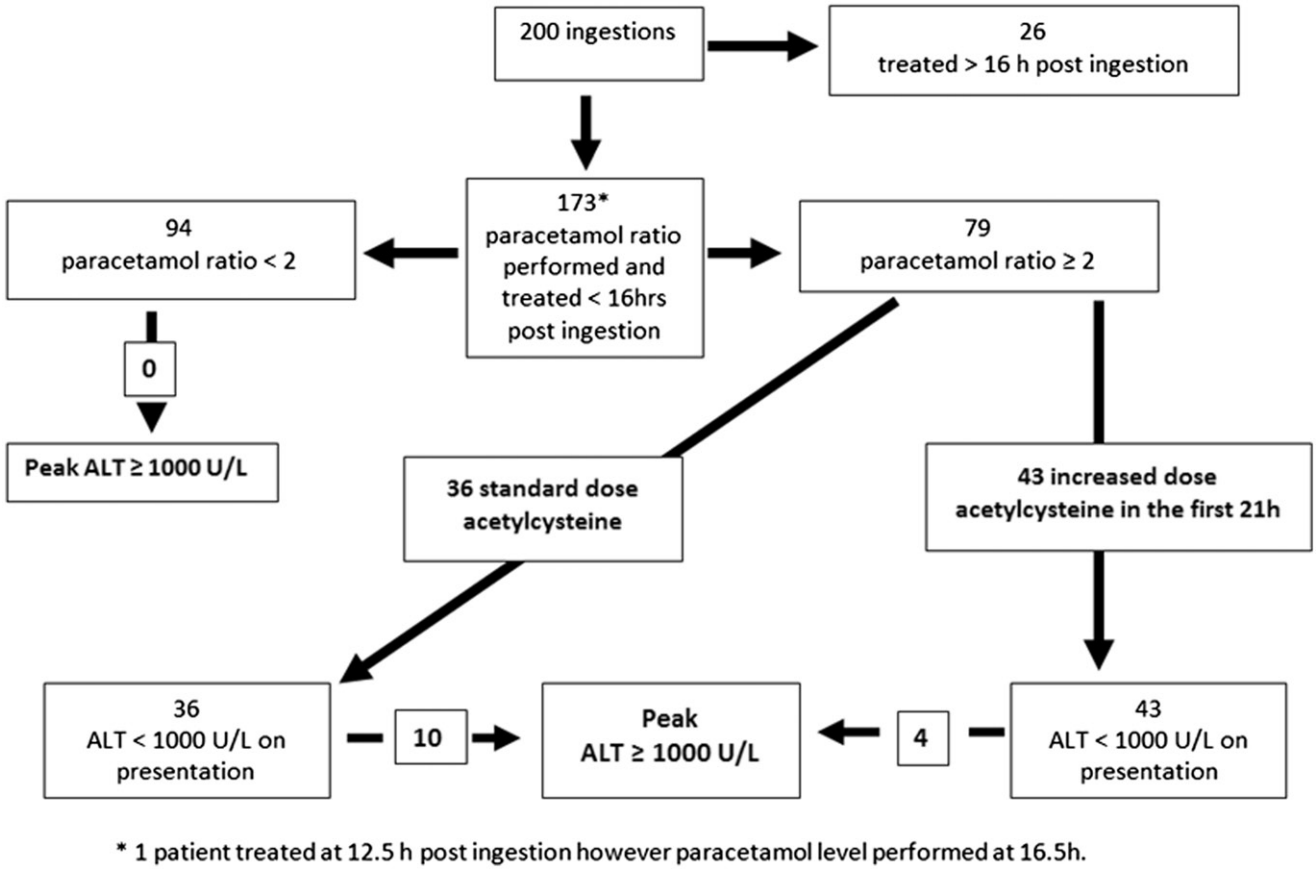


Figure 4. Flowchart of numbers utilised for increased acetylcysteine analysis.

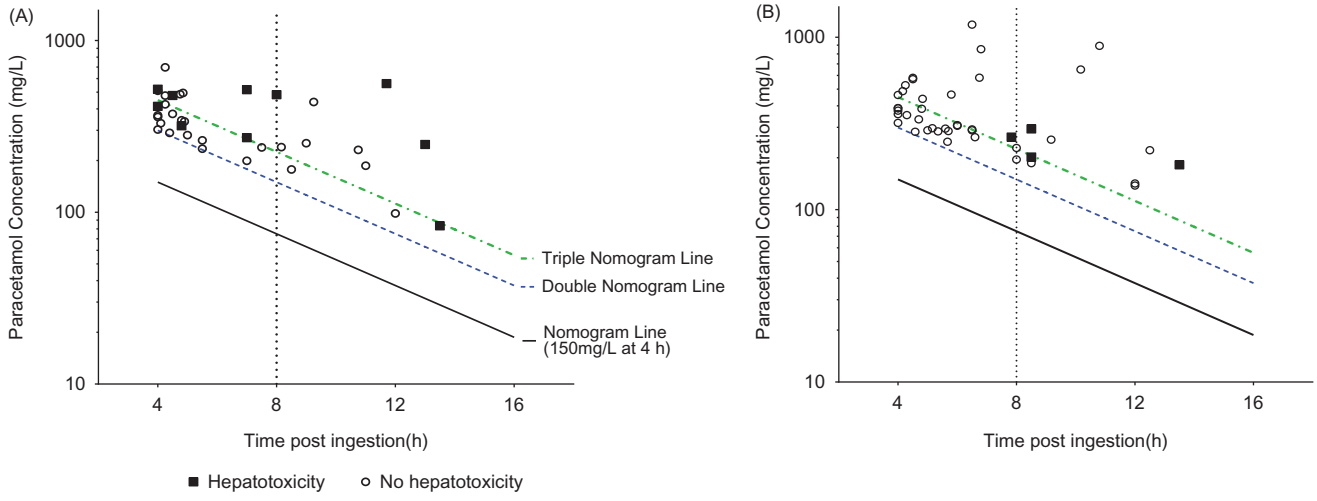


Figure 5. Paracetamol concentration versus time post-ingestion for patents presenting within 16 hours and an initial paracetamol ratio ≥2 (300 mg/L at 4 h nomogram line). (A) Standard acetylcysteine dose during initial 21 h infusion. (B) Increased acetylcysteine dose during initial 21 h infusion.

All models were re-analysed excluding the 24 patients with missing weight data and ALT at completion of treatment or after 20 h and there was no substantial change in our results or conclusions (analyses not shown).

Four patients in this study had a double paracetamol peak (Figure 6(A)) with the second peak >24 h in all four patients. Three of these patients had co-ingested opioids and the other had T4 quadriplegia. None of these patients received activated charcoal within the first 24 h post-ingestion. A further seven patients had a documented peak paracetamol concentrations >6 h post-ingestion, three had co-ingested codeine (Figure 6(B)). Only one of these patients had received activated charcoal at 5 h post-ingestion.

Three patients in this series were dialysed because of extremely elevated paracetamol concentrations with an associated lactic acidosis and a reduced level of consciousness. The decision to dialyse was made by the treating physician.

Table 3. Bivariable and multivariable logistic regression model results for those patients with a paracetamol ratio ≥2 (within 16 h of ingestion).

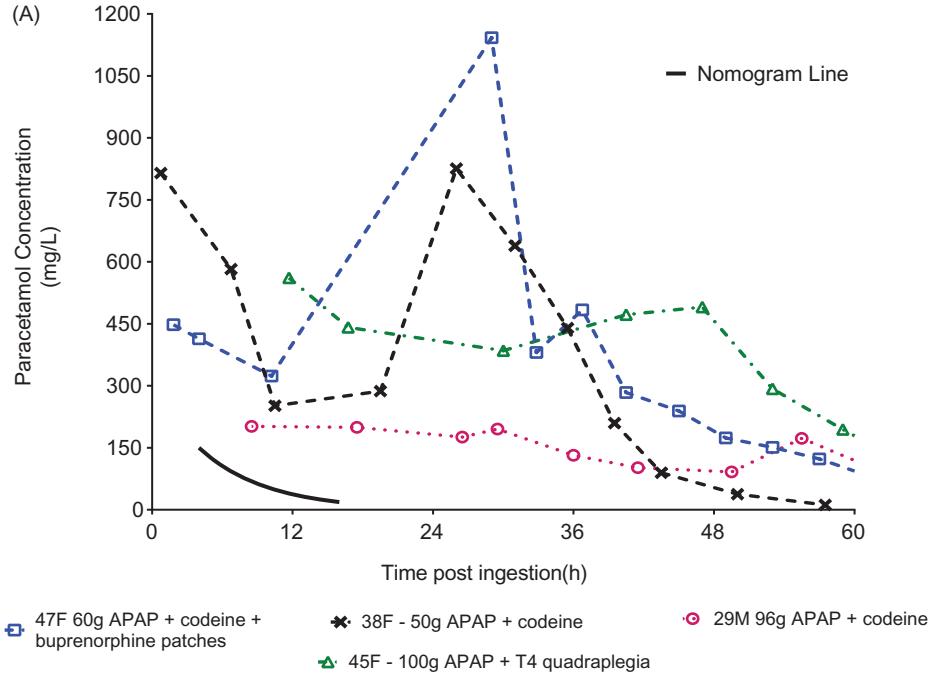
Variable	Outcome: hepatotoxicity (Peak ALT >1000)
Unadjusted odds ratio (95% CI)	
Age (10 year increments)	1.27 (0.88–1.82)
Paracetamol ratio (continuous)	1.13 (0.95–1.34)
Time to IV acetylcysteine (hours)	1.2 (1.00–1.42)
Receipt of increased acetylcysteine dose#	0.27 (0.08–0.94)
Adjusted odds ratio (95% CI)	
Increased acetylcysteine dose[a] adjusted for time to acetylcysteine	0.27 (0.07–0.98)
Increased acetylcysteine dose[a] adjusted for paracetamol ratio	0.23 (0.06–0.86)

[a]Receipt of increased acetylcysteine defined as any patient receiving greater than the standard regimen of 300 mg/kg of acetylcysteine over 21 h.

Two of these patients were dialysed because of a delayed or double paracetamol peak concentration.

Discussion

This study of "massive" paracetamol overdose highlights the prolonged absorption and persistently high concentrations in these patients. Further, some patients demonstrated altered pharmacokinetics of paracetamol with double or delayed paracetamol peak concentrations out to 60 h, suggesting pharmacobezoar formation. Activated charcoal within 4 h was associated with a large reduction in subsequent paracetamol concentrations. There were probable benefits of both



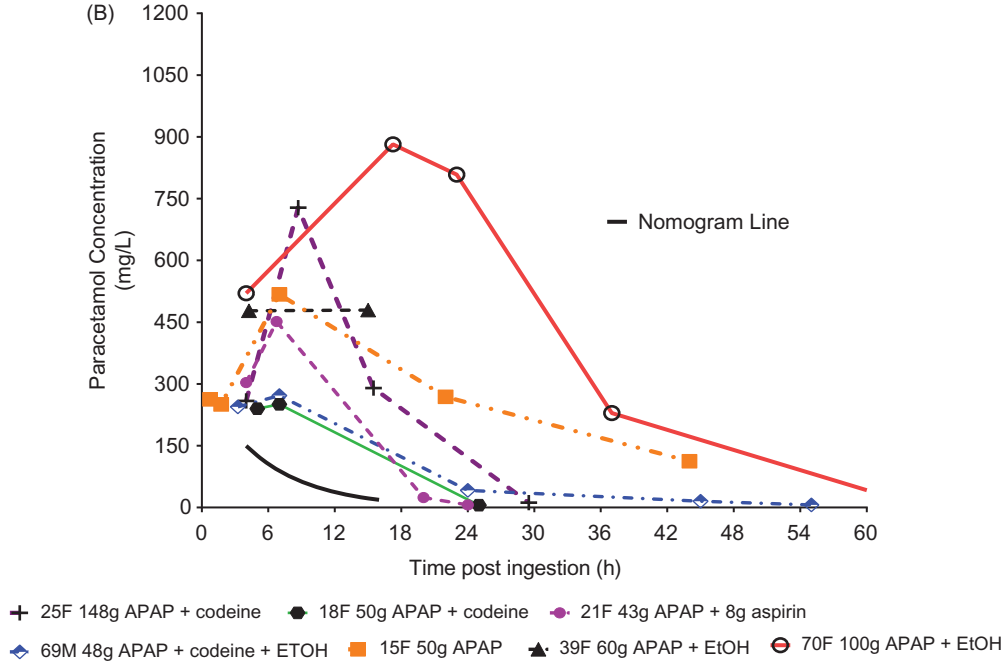


Figure 6. Paracetamol concentration versus time post-ingestion. (A) Patient with two paracetamol peak concentrations. (B) Patients with delayed paracetamol peak concentrations >6 h post-ingestion

activated charcoal and higher doses of acetylcysteine in reducing the risk of hepatotoxicity.

In our cohort, only 25% received activated charcoal. A common rationale for not giving charcoal is that charcoal in massive overdose is unlikely to decrease the ultimate need for acetylcysteine, with an underlying assumption that early acetylcysteine will be universally effective. Our data directly challenges the validity of this viewpoint. Several patients treated with acetylcysteine within hours of the overdose still developed severe liver injury. This did not occur in any patients receiving early activated charcoal. Charcoal within 4 h was associated with a significantly reduced initial paracetamol concentration and may have also interfered with subsequent absorption or increased clearance. We confirm results of others that very high early paracetamol concentrations are an independent risk factor for hepatotoxicity, even when acetylcysteine is given [8,9]. Our unadjusted and multi-variable analysis suggests charcoal also reduced hepatotoxicity, and this is the most likely explanation for that benefit.

This study complements the recent observations of both Cairney et al. and Marks et al. that quantified a concentration-dependent relationship with hepatotoxicity in early NAC-treated paracetamol poisoning. Cairney et al. observed that patients treated with acetylcysteine within 8 h of ingestion with a paracetamol ratio of 1.33–2 had a 3.6% risk of acute liver injury (ALT >150 U/L), increasing to 12.5% in those with a paracetamol ratio between 2 and 3.3 [8]. While Marks et al. looked at ingestion of ≥30 g or those with an extrapolated 4-h plasma paracetamol concentrations >250 mg/L, they similarly found that those with a paracetamol concentration greater than the 300 mg/L at 4 h nomogram line were an increased risk for liver injury even if treated within 8 h [9]. Noting our numbers were smaller, we similarly found in our selected high-dose cohort that all those patients who developed hepatotoxicity (ALT >1000 U/L) despite treatment with IV acetylcysteine within 8 h had a paracetamol ratio > than the 300 mg/L at 4 h nomogram line. Even when adjusted for time to acetylcysteine, those with a higher initial paracetamol ratio were found to be at an increased risk of hepatotoxicity (Figure 3).

Such patients have driven debate about whether the standard 300 mg/kg acetylcysteine regimen is adequate for all paracetamol overdoses [7]. The current intravenous acetylcysteine regimen is adequate to detoxify an ingested paracetamol dose of 15.9 g [7]. The current regimen has a large loading dose followed by the third infusion of 100 mg/kg over 16 h (6.25 mg/kg/h) resulting in acetylcysteine concentrations of 40 mg/L. Rumack and Bateman theoretically proposed that a patient who ingested 47.7 g of paracetamol warranted this third infusion to be increased to 17.5 mg/kg/h [7]. Even this analysis assumed standard kinetics, rather than very delayed or double peaks. Thus, there are good theoretical reasons to question whether the standard acetylcysteine dose in the third infusion is adequate to detoxify the NAPQI produced in those with prolonged high paracetamol concentrations. In our study, those receiving increased acetylcysteine had a much lower incidence of hepatotoxicity especially if treated within 8 h of ingestion (Table 3). Those patients with an initial paracetamol ratio of ≥2 who received increased acetylcysteine had a significantly decreased risk of hepatotoxicity [OR: 0.27 (95%CI: 0.08–0.94)]. The odds ratio remained similar after adjustment for time to acetylcysteine and paracetamol ratio. This has yet to be demonstrated in other studies.

Further evidence is required to more clearly identify the concentrations at which this is warranted, and to determine if doubling of NAC dose is sufficient. There is a negligible risk from modest increases in acetylcysteine dose in those with a high paracetamol ratio. The alternate risk from not changing practice while awaiting further evidence is apparent. In this study, if a patient presented within 16 h of ingesting ≥40 g paracetamol and received "standard" treatment that is, no activated charcoal and the standard acetylcysteine dose, the rate of hepatotoxicity in this group was 11% ($n = 10/87$). In comparison when you combine all those patients who received either activated charcoal or increased acetylcysteine dose, their rate of hepatotoxicity was 5% ($n = 4/87$). Hence we propose "standard" care should involve administering activated charcoal within 4 h of ingestion in eligible patients and increase acetylcysteine dose in those with an initial paracetamol concentration ≥2.

"Massive" paracetamol overdose can result in extremely high paracetamol concentrations and in many cases a delayed or double paracetamol peak. Four patients had a second paracetamol peak >24 h following ingestion. This phenomenon of a double peak has been reported previously following massive overdoses, with a second paracetamol peak occurring as late as >30 h post-ingestion in some. Furthermore, many of these patients developed hepatotoxicity, despite early acetylcysteine [21,22]. In the majority of these cases, patients had ingested large amounts of paracetamol >40 g and/or co-ingested gut slowing medications such as opioids or anti-cholinergic agents. Hence, the likely cause of this double peak is a pharmacological bezoar and/or ileus [21]. Furthermore, none of these patients received decontamination in the first 24 h. It is likely that these patients would have benefited from activated charcoal beyond 4 h post-ingestion. A concern in these cases is that the decrease in dose of acetylcysteine after the initial loading dose and/or the cessation of acetylcysteine after the standard 21 h protocol is too early and likely contributes to increased rates of hepatotoxicity [21,22]. This is further highlighted by the three patients with peak concentrations >800 mg/L around 24 h (Figure 6(A,B)), who developed a lactic acidosis, became sedated and required intubation. Patients who ingest large amounts of paracetamol and do not receive activated charcoal should be closely monitored and have paracetamol concentrations repeated before acetylcysteine is ceased.

In our study, increasing age was an independent risk for higher paracetamol ratio with an increased risk of hepatotoxicity that when adjusted for time to treatment with acetylcysteine decreased. The higher ratio does not have an obvious mechanism, and requires confirmation in other cohorts. Interestingly, there is a previous report that age >40 years increased risk of development of fulminant hepatic failure and death or liver transplant following paracetamol overdose. The authors attributed this to a higher rate of alcohol abuse

and later presentation [23]. Our data similarly suggest that later treatment is a factor; however, there may also be a pharmacokinetic explanation.

There are several limitations to this study, first it is an observational study and treatments such as activated charcoal or increased acetylcysteine dose were not randomly allocated. Hence, there are differences in baseline characteristics; care directed by the treating physician and data collected between patient groups. Furthermore, data collected in this study such as dose and time of ingestion relies on the patient's report. However, generally these are carefully recorded as they drive treatment decisions. Cases identified through poisons centres may be biased, for example towards cases with higher initial concentrations. However, the majority of these patients presented early and calls were usually before a paracetamol concentration result was available. Statistical power was limited by the small numbers of patients who develop hepatotoxicity despite early acetylcysteine treatment. This constrained the capacity to simultaneously adjust for multiple factors in the multivariable analysis, or to explore time/dose thresholds. Furthermore, it should be noted that there are limitations in interpreting the slope and half-life data. In this study, we simply compared slopes in a subset of patients; however, we did not adjust for other factors that might influence half-life such as dose ingested or acute liver injury. Using slope data to calculate half-life is an over simplification and assumes the elimination process is mono-exponential. However, by calculating the slope, it allows us to estimate the effect of activated charcoal on clearance.

Conclusion

This observational study of "massive" immediate release paracetamol overdose found that activated charcoal within 4 h of ingestion led to significantly lower paracetamol concentrations and risk of hepatotoxicity. High initial paracetamol concentrations increased risk of developing hepatotoxicity despite acetylcysteine treatment. An increased acetylcysteine dose significantly decreased the odds of developing hepatotoxicity in those with an initial paracetamol concentration more than double the nomogram line.

The evidence of benefit is limited and leaves many questions unanswered. There is uncertainty about the dose/time thresholds that justifies activated charcoal, or increased acetylcysteine dose. There is more uncertainty about the optimal increase in acetylcysteine dose and duration. These can only be resolved by further research. However, we believe that this evidence is sufficiently compelling to change standard practice in "massive" paracetamol overdose.

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Disclosure statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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References

[1] Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology (Baltimore, MD). 2005;42:1364–1372.
[2] Lancaster EM, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. Arch Toxicol. 2015;89:193–199.
[3] Kerr F, Dawson A, Whyte IM, et al. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of *N*-acetylcysteine. Ann Emerg Med. 2005;45:402–408.
[4] Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous *N*-acetylcysteine for acute acetaminophen overdose. Acad Emerg Med. 2009;16:34–39.
[5] Buckley NA, Whyte IM, O'Connell DL, et al. Oral or intravenous *N*-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? J Toxicol Clin Toxicol. 1999;37:759–767.
[6] Chiew AL, Fountain JS, Graudins A, et al. Summary statement: new guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2015;203:215–218.
[7] Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol. 2012;50:91–98.
[8] Cairney DG, Beckwith HK, Al-Hourani K, et al. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. Clin Toxicol. 2016;54:405–410.
[9] Marks DJB, Dargan PI, Archer JRH, et al. Outcomes from massive paracetamol overdose: a retrospective observational study. Br J Clin Pharmacol. 2017;83:1263–1272.
[10] Juma SA, Villeneuve E, Elliot A, Palmer RB, Gosselin S, editors. Doubling the third dose of intravenous *N*-acetylcysteine survey: an international practice perspective (abstract). XXXV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 26–29 May 2015; St Julian's, Malta: Clin Toxicol. 2015; 53:233–403.
[11] Buckley NA, Whyte IM, O'Connell DL, et al. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. J Toxicol Clin Toxicol. 1999;37:753–757.
[12] Duffull SB, Isbister GK. Predicting the requirement for *N*-acetylcysteine in paracetamol poisoning from reported dose. Clin Toxicol. 2013;51:772–776.
[13] Mowry JB, Spyker DA, Cantilena LR, et al. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol. 2014;52:1032–1283.
[14] Graudins A. Paracetamol poisoning in adolescents in an Australian setting: not quite adults. Emerg Med Austral. 2015;27:139–144.
[15] Buckley NA, Dawson AH, Isbister GK. Treatments for paracetamol poisoning. BMJ (Clin Res Ed). 2016;353:i2579.

[16] Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. British Medical Journal. 1979;2:1097–1100.
[17] Antoine DJ, Dear JW, Lewis PS, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology (Baltimore, Md). 2013;58:777–787.
[18] Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976–1985). N Engl J Med. 1988;319:1557–1562.
[19] Australian Bureau of Statistics: Height and weight 2012 [cited 2016 July]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4338.0~2011-13~Main%20Features~Height%20and%20weight~21.
[20] Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40:3–20.
[21] Hendrickson RGMN, West PL, Burke CR. Bactrian ("Double Hump") acetaminophen pharmacokinetics: a case series and review of the literature. J Med Toxicol. 2010;6:337–344.
[22] Smith SW, Howland MA, Hoffman RS, et al. Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous N-acetylcysteine therapy. Ann Pharmacother. 2008;42:1333–1339.
[23] Schmidt LE. Age and paracetamol self-poisoning. Gut. 2005;54:686–690.