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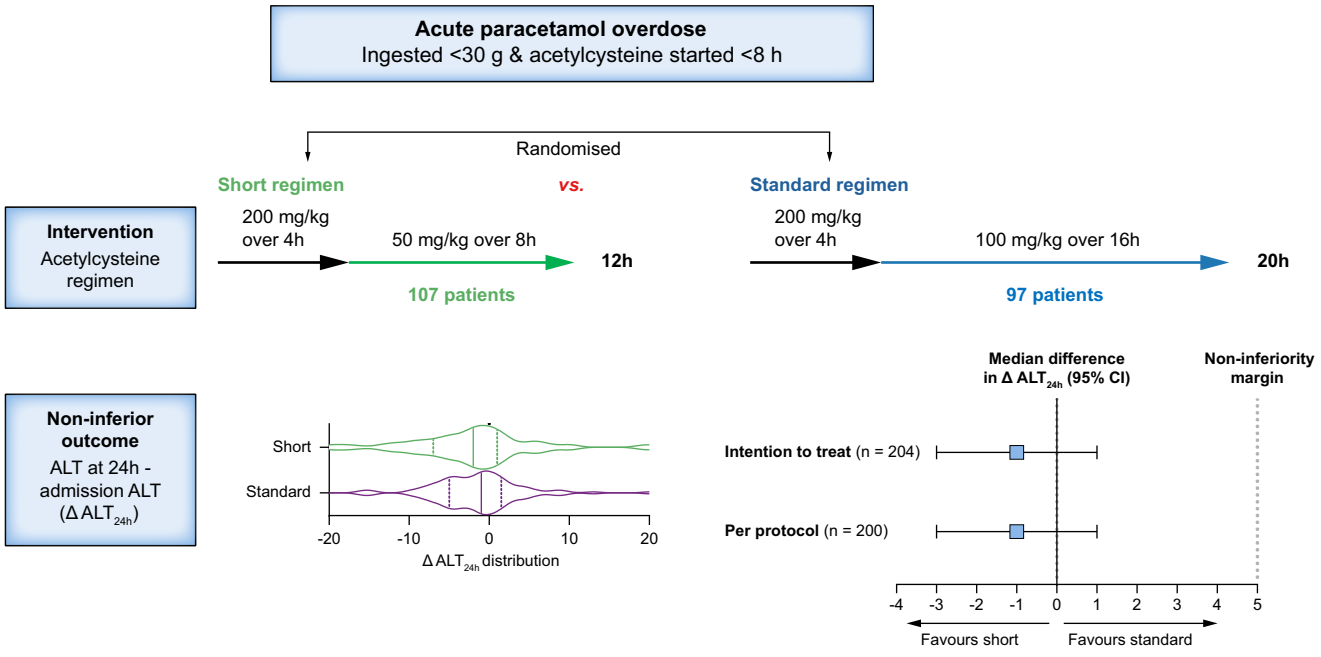
Graphical abstract



Highlights

- A shorter 12 h acetylcysteine regimen was as effective as the standard 20 h regimen in paracetamol overdoses of ≤30 g.
- The shorter regimen was safe with similar adverse effect rates.
- The 12-hour regimen almost halved the length of treatment.

Impact and implications

We aimed to examine a simple and shorter strategy for the antidotal administration of acetylcysteine in patients with low-risk paracetamol overdose. The new shortened protocol of 12 hours duration is safe and effective, and applicable to about one-third of acute paracetamol overdoses. The findings will make acetylcysteine treatment easier for treating physicians, with a shortened length of stay. The protocol cannot be extended to high-risk paracetamol overdoses, including massive and staggered ingestions, without further study.

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A non-inferiority randomised controlled trial of a shorter acetylcysteine regimen for paracetamol overdose – the SARPO trial

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Background & Aims: Paracetamol is a commonly overdosed medication worldwide. Early acetylcysteine treatment can prevent hepatotoxicity. Multiple intravenous acetylcysteine regimens exist; the commonest recommending 300 mg/kg over 20 h. We investigated the effectiveness and safety of a shorter regimen in paracetamol overdoses ≤30 g.

Methods: In a multicentre, non-inferiority, randomised-controlled trial performed at three hospitals, 204 patients with acute paracetamol overdose ≤30 g, presenting within 8 h, were randomised to the standard 20 h acetylcysteine (200 mg/kg/4 h, 100 mg/kg/16 h) regimen or a short 12 h acetylcysteine (200 mg/kg/4 h, 50 mg/kg/8 h) regimen. The primary outcome was the absolute difference between alanine aminotransferase (ALT) 24 h post-ingestion and at admission (ΔALT24). Secondary outcomes included ALT >150 U/L and ≥2x admission value at 24 h, systemic hypersensitivity and gastrointestinal adverse effects.

Results: The two groups were similar in terms of age, gender, dose ingested, paracetamol concentration, baseline ALT, hospital, charcoal administration and time until acetylcysteine treatment. The shorter regimen was non-inferior to the standard regimen. The median ΔALT24 for 107 patients given the shorter regimen was -2 U/L (IQR: -7 to 1 U/L) compared to -1 U/L (IQR -5 to 1.5 U/L) for the 97 patients given the standard regimen; difference in medians of -1 U/L (95% CI -3 to 1 U/L) were less than the upper non-inferiority margin of 5. No patient receiving the shorter regimen had a 24 h ALT of ≥2x admission value and >150 U/L, compared to one receiving the standard regimen. No patient had an ALT >1,000 U/L. The frequency of systemic hypersensitivity reactions was similar between groups (9/107 [8%] for short *vs.* 10/97 [10%] for standard regimens). Gastrointestinal adverse effects occurred in 78/107 patients (73%) receiving the short *vs*. 63/97 (65%) receiving the standard regimen.

Conclusions: The shorter 12 h acetylcysteine regimen had the same effectiveness and safety as the standard 20 h regimen in acute paracetamol overdoses ≤30 g, almost halving the length of treatment required.

Trial registration: Australian New Zealand Clinical Trials Registry number ACTRN12616001617459.

Introduction

Paracetamol (acetaminophen) is one of the commonest medications taken in overdose worldwide and is also the major cause of acute liver failure in the United States and Europe.[1–3] Prior to the introduction of specific antidotes, the rate of severe liver damage was over 50%.[4] The antidote acetylcysteine has been used since the 1970s and now hepatotoxicity and mortality secondary to paracetamol toxicity are rare in those treated within 8 h of ingestion.[4,5] However, the intravenous acetylcysteine regimen developed in the 1970s by Prescott was never subjected to a randomised-controlled trial (RCT) or any dose-ranging studies.[6,7] Recently the intravenous regimen has been simplified from a three-bag regimen to a two-bag regimen in many parts of the world, which has reduced the early very high concentrations and therefore adverse reaction rate.[8] In addition, recommended doses have been increased for 'massive' and modified-release paracetamol overdoses.[9,10]

The rationale for acetylcysteine dosing regimens is to provide sufficient acetylcysteine to restore liver glutathione levels (if depleted) and then maintain them to replace excessive glutathione turnover while paracetamol is still present.[7] Thus, ingested paracetamol dose and concentrations are a major factor in

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determining the amount of acetylcysteine required. Higher ingested doses increase the levels of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) and the amount of glutathione required for detoxification. Clinical evidence reinforcing this concept comes from three recent studies of large or massive paracetamol ingestions, which describe hepatotoxicity occurring despite early (<8 h) administration of standard doses of acetylcysteine.[9–11] It is now accepted that the patient weight-based standard regimen will not be effective for all patients, and an individualised approach to therapy should be based on the amount of paracetamol ingested.[7] This may also mean that patients ingesting smaller doses of paracetamol with normal liver function could be given acetylcysteine for a shorter duration.[5]

The only RCT published to date that has examined shorter acetylcysteine regimens compared the traditional three-bag regimen (20.25 h) with a 12 h modified regimen (100 mg/kg over 2 h followed by 200 mg/kg over 10 h; SNAP).[12] The study was primarily designed to examine adverse effects of acetylcysteine, which were reduced with the 12 h regimen. A 50% increase in alanine aminotransferase (ALT) was observed in a similar proportion of patients on the two regimens, suggesting similar effectiveness, although this was a secondary outcome.[12] The authors suggested that patients with no change in their ALT and paracetamol concentrations <20 mg/L could be discharged at 12 h, but a larger study is required to confirm this. Since this publication, there have been cohort studies supporting the effectiveness of SNAP in widespread use.[13,14] There has also been a small non-randomised cohort study investigating stopping the standard acetylcysteine regimen at 12 h when blood tests are normal, but this has not changed clinical practice in Australia because of the wide confidence intervals around the point estimate of difference in liver injury between arms.[15]

Editorials in both the United Kingdom[16] and Australia[17] have argued for a shorter total duration for patients deemed to be at low risk of hepatotoxicity. The shorter SNAP protocol is now used across the United Kingdom for patients treated within 8 h of ingestion. The acetylcysteine infusion is only stopped at 12 h if paracetamol concentrations are <20 mg/L, international normalised ratio is ≤1.3, and ALT is <100 U/L and <2x the admission value at the end of a 12 h regimen.[13]

There is a significant clinical advantage in using a shorter acetylcysteine regimen, because it will allow many patients with low-risk paracetamol overdoses to be discharged 12 h post-treatment, shortening length of hospital stay.[14] However, it should be noted that the United Kingdom guidelines use a much lower treatment nomogram line and therefore these cohorts include many patients who would not receive any treatment in most countries, including the United States, Europe and Australia.

Our study was designed to examine an even simpler strategy for the majority of patients. We hypothesized that stopping the standard acetylcysteine regimen at 12 h for low-risk patients would provide the same protection as the standard 20 h regimen. We aimed to investigate the effectiveness and safety of this shortened regimen in acute overdoses of ≤30 g presenting within 8 h of ingestion.

Patients and methods

Study design and setting

The study design was a multicentre non-inferiority unblinded RCT of a 20 h *vs.* a 12 h regimen of acetylcysteine in patients with low-risk paracetamol overdoses. The primary outcome was the absolute difference between the ALT on admission and the ALT 24 h post-ingestion (ΔALT24). The study was approved by the South Metro Human Research Ethics Committees (HREC/16/QPAH/801), with site-specific approval at the three hospital sites. The study was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12616001617459. Informed consent was obtained from all patients.

The study was undertaken in three Australian hospitals with dedicated clinical toxicology services. Trained clinical toxicologists treat all poisoned patients presenting to their respective hospitals. The Princess Alexandra Hospital is located in Brisbane, Queensland. Its clinical toxicology unit is based in a tertiary referral adult (>15 years of age) hospital with an emergency department that has approximately 70,000 presentations each year. The Calvary Mater Newcastle hospital is located in Newcastle, New South Wales. Its clinical toxicology unit admits all overdoses or poisonings either as primary presentations or hospital referrals (>15 years of age) from a population of over 500,000 people. The Prince of Wales Hospital is located in Sydney, New South Wales. Its clinical toxicology unit is based within an emergency department that has approximately 60,000 presentations each year. It also admits and takes referrals from nearby hospitals of overdose or poisoned patients.

Study patients

Patients over 16 years of age were recruited from the 10th July 2017 to the 4th April 2024, if they took an acute single paracetamol overdose ≤30 g, presented within 8 h and had an initial paracetamol concentration above but less than twice the nomogram line (paracetamol ratio 1 to 2; Fig. S1). The paracetamol ratio is the first paracetamol concentration taken between 4 h and 16 h post-ingestion divided by the paracetamol concentration on the 150 mg/L at 4 h standard nomogram line, at the same time point. We excluded any staggered or repeated supratherapeutic ingestions, ingestion of the modified-release formulation, and patients aged 16 years or less.

Treatment protocol

Patients were identified on admission by nursing or medical staff. All eligible patients with a paracetamol concentration above the nomogram line (Fig. S1) were commenced on the 20 h regimen used at the three participating hospitals based on a previous study:[8] 200 mg/kg of acetylcysteine over 4 h followed by 100 mg/kg acetylcysteine over 16 h. Once commenced on acetylcysteine and informed consent was obtained, patients were randomised to receive either the full 20 h acetylcysteine (standard treatment arm, 300 mg/kg) or the first 12 h of the 20 h acetylcysteine regimen (experimental treatment arm, 250 mg/kg). Randomisation could occur at any time up to the point when the patient has received 12 h of acetylcysteine. Those randomised to receive 12 h of acetylcysteine had their second treatment bag (16 h infusion of acetylcysteine) ceased at 8 h and were then commenced on the equivalent volume of 5% glucose over 8 h.

ALT and paracetamol concentrations were measured 12 h after commencement of acetylcysteine (when the infusion was ceased for patients randomised to the experimental arm) and 24 h post-ingestion. If the ALT was >50 IU/L and ≥2x the admission value at 12 h after the commencement of

acetylcysteine, the acetylcysteine infusion was continued or restarted for the experimental arm.

Recruitment, randomisation and blinding

Emergency department medical staff were informed and educated on the study and the clinical toxicologists on call at the three participating hospitals identified suitable patients. Once identified, patients were enrolled by contacting the investigator at each study site. The treating doctor obtained consent and randomisation was done on a secure online website, using the biased coin design, including minimisation in the algorithm.

Randomisation was minimised by paracetamol ratio (≤1.5 and >1.5, equivalent to ≤225 mg/L and >225 mg/L at 4 h) and by hospital site (Princess Alexandra Hospital, Calvary Mater Newcastle Hospital, Prince of Wales Hospital). Minimisation by the paracetamol ratio was required to ensure a similar distribution of paracetamol concentrations in each arm. Site minimisation was to account for any differences in the outcome measure analysis by the three hospital laboratories. Patients could receive activated charcoal but this factor was not included in the minimisation strategy. The potential impact of activated charcoal was examined in a *post hoc* analysis.

To randomise each patient the online website would generate a random number between 0 and 10,000 and allocation to either arm of the study was dependent on whether the generated number was greater than or less than a set-point equal to X_i, where i = 1 to 6 based on the six subgroups the patient was in according to hospital and paracetamol ratio, and was initially 5,000. If any of the subgroups were imbalanced then the set-point was decreased or increased to 4,000 or 6,000, respectively, to reduce the chance that the next patient was randomised to the larger group. Adjustments were made by a blinded author (NB).

There was blinded allocation and once randomisation was completed, this was recorded online and could not be changed. Blinding of the patient, treating clinician or investigator to treatment received was not possible. This would have been unlikely to be effective, given the protocol required changes in the duration of regimen based on laboratory results. We thus pre-specified an objective laboratory-based primary outcome to reduce the risk of recording or analytical bias.

Data collection

A data collection form was used which recorded study site, basic demographics, paracetamol dose and ingestion time, paracetamol concentration and ratio, activated charcoal use, and acetylcysteine commencement details. Laboratory results: 12 h after acetylcysteine commencement and 24 h post-ingestion paracetamol and ALT were also recorded. An acetylcysteine adverse reaction observation table was used to record all adverse effects on the data collection form. This was recorded at regular intervals, including baseline and for the first 12 h, the heart rate, blood pressure, gastrointestinal symptoms (nausea and vomiting), skin reaction (rash, flushing and itch), and respiratory symptoms (shortness of breath and/or wheeze). The acetylcysteine adverse reaction data sheet has been previously used and published.[18] All data were entered into a purpose designed Microsoft Excel™ datasheet and were de-identified. Each patient had a study code designated at randomisation, which was stored separately. The study code was used to identify the patient to retrieve missing or additional data.

Adverse events and data monitoring

All adverse events were monitored, recorded and managed by clinical staff, consistent with standard clinical and quality assurance processes. All patients involved had their liver enzymes closely monitored by the respective site investigator and reported to the lead investigator (CP then GI) and to a Data and Safety Monitoring Committee. Any major adverse events were reported to the ethics committee after each review. In the event that the research team and the data monitoring committee felt that the rate of hepatotoxicity in the experimental arm (12 h) was not consistent with a non-inferior treatment, the study could be ceased.

Study outcomes

The primary outcome was the absolute difference between the ALT 24 h post-ingestion and the admission ALT (ΔALT24), a positive number indicating an increase in the ALT and hepatotoxicity. The secondary outcomes were the proportion of patients with a 50% increase in ALT over the admission ALT at 24 h post-ingestion, the proportion of patients with an ALT >150 U/L and ≥2x admission value at 24 h, the proportion of patients in each arm with an ALT >1,000 IU/L at any time post-ingestion, the proportion of patients with systemic hypersensitivity reactions within 12 h of treatment, and the proportion of patients with gastrointestinal adverse effects within 12 h of treatment. A systemic hypersensitivity reaction was defined as either skin only hypersensitivity reaction or non-immune-mediated anaphylaxis, if they met NIAID-FAAN consensus criteria.[19]

Analysis

A statistical equivalence boundary (non-inferiority margin) was used for the sample size calculation,[20] and was based on previous data for current acetylcysteine treatment (20 h regimen) effect, to which the new alternative treatment was to be compared. The non-inferiority margin or difference between the two treatment effects being compared should be no more than half of the upper limit of the 95% CI of the standard treatment effect.[20]

The ALT data from 121 paracetamol overdoses (single ingestion of <30 g within 1 h and treated with the 20 h acetylcysteine regimen within 8 h of ingestion) from the three hospitals participating in the study was collected, prior to the study commencing (Fig. S2). The mean difference between admission and 24 h ALT was 0.2 IU/L with a standard deviation of 10.9 and 95% CIs of -21.2 to 21.6 IU/L. Half the 95% CI (21.4) is 10.7 hence the non-inferiority margin had to be ≤10. An even tighter margin of 5 IU/L was chosen, as we felt clinicians were unlikely to accept any increased risk. Therefore, a mean difference in ALT (between baseline and 24 h post-ingestion, ΔALT24) of <5.2 (0.2 + 5) in the new treatment arm (12 h regimen) would be considered a non-inferior treatment for paracetamol toxicity.

This is a one-sided test and the alpha level was set at 0.025. With a power of 90% (higher power to minimise the risk of a non-inferior treatment being missed due to chance) and a standard deviation of 10.9 with a non-inferiority limit of 5, the total sample size required was 200 patients – 100 in each arm. Allowing for a 10% margin for failure to adhere to the study protocol, we aimed to recruit 220 patients.

Statistical analysis

The continuous ΔALT24 data was tested for normality by the Kolmogorov-Smirnov test and was found not to be normal, so non-parametric methods were used for the analysis. For the analysis of the primary outcome, non-inferiority was established if the upper limit of the 95% CI of the difference in the medians of the ΔALT24 between the shorter regimen and the standard regimen was below the pre-defined non-inferiority margin of 5. The difference in medians was calculated in PRISM using the Hodges-Lehmann estimate and 95% CIs were calculated based on the Hodges-Lehmann method.[21] Secondary outcomes were similarly compared by calculating the 95% CIs in PRISM using the Newcombe/Wilson method with continuity correction.[22] All analyses were performed in GraphPad Prism version 10.3.0 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results

There were 3,664 patients with paracetamol poisoning that presented to the three hospitals over the 6 years and 9 months of the study. Of these, 204 patient admissions met the inclusion criteria, were recruited to the study and randomised (Fig. 1); 190 were recruited once, four were recruited twice and two were recruited three times. No patients were excluded for a paracetamol ratio >2. One hundred and seven patients were randomised to receive the shorter 12 h regimen, but two of these patients received the standard 20 h regimen and one 17 h of acetylcysteine, so only 104 patients were included in the per-protocol analysis (Fig. 1). There were 97 patients randomised to receive the standard 20 h regimen; one patient received a smaller loading dose (50 mg/kg over 4 h, in error) so was removed from the per-protocol analysis.

The two groups were similar in terms of age, sex, dose ingested, paracetamol concentration and paracetamol ratio, baseline ALT, hospital recruited, charcoal administration and time until acetylcysteine commenced (Table 1). One patient in the standard treatment arm had further acetylcysteine due to ingestion of 35 g (paracetamol ratio <2) and an increase of the 12 h ALT after commencing acetylcysteine to 87 U/L from 13 U/L, which decreased at 24 h post-ingestion to 71 U/L. One patient in the shorter regimen took 37 g (paracetamol ratio <1.5), but their ALT peaked at 11 U/L. Both patients were recruited

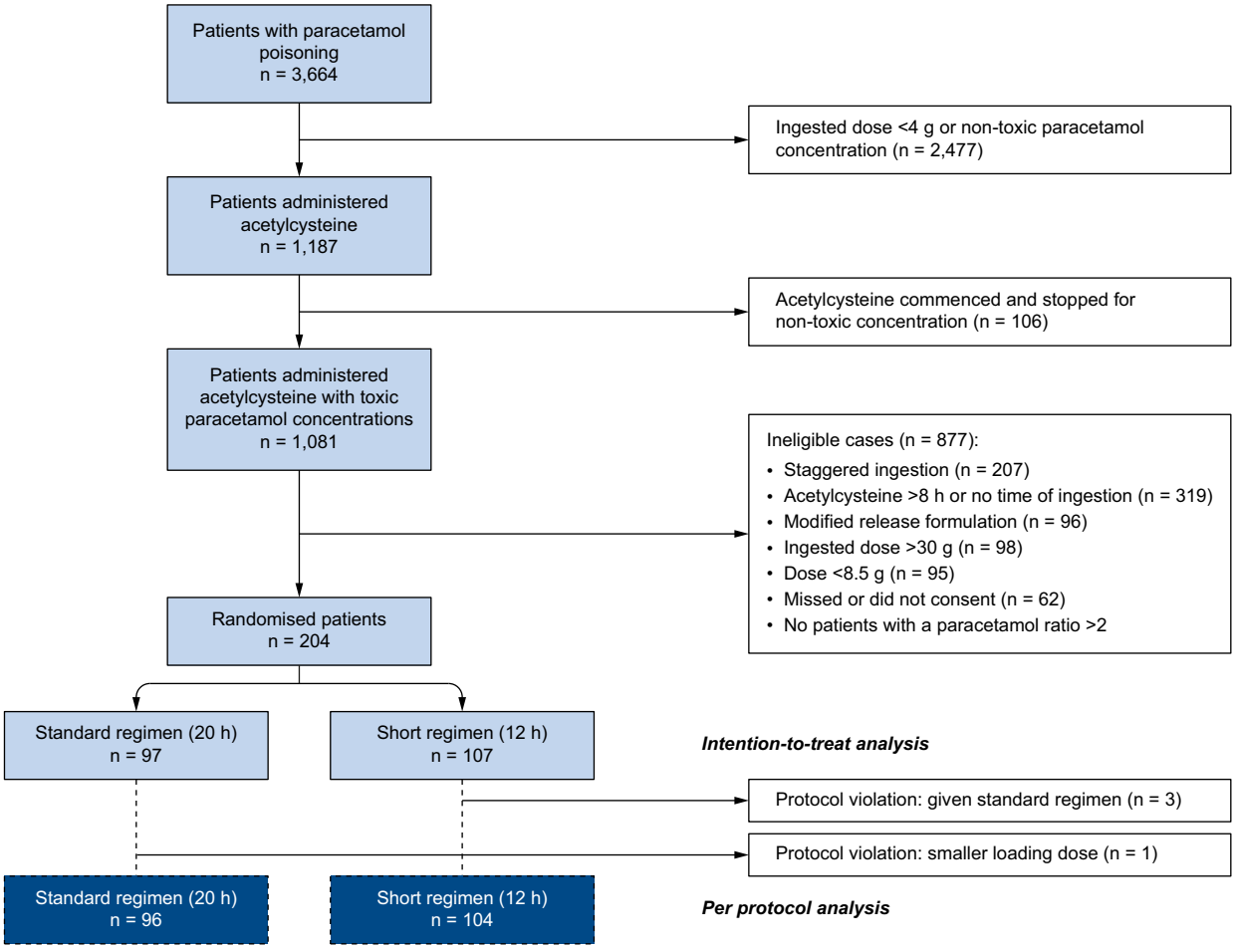

Fig. 1. Flow diagram and patients with paracetamol poisoning, those eligible for the study and exclusions, randomised patients and four trial violations.

Table 1. Baseline demographics, paracetamol dose and concentration, hospital and treatments.

Baseline characteristics	Standard (n = 97)	Short (n = 107)
Age (years)	25 (21–32)	24 (19–38)
Female	85 (87%)	93 (87%)
Dose (g)*	15 (12–20; 8.5–35)	15 (13–20; 5–37)
Paracetamol concentration (mg/L)	182 (148–219)	179 (152–228)
Paracetamol ratio	1.3 (1.1–1.5)	1.3 (1.1–1.5)
Paracetamol ratio >1.5	26 (27%)	32 (30%)
Baseline alanine aminotransferase (U/L)*	18 (13–24; 5–108)	22 (15–35; 5–169)
Hospital		
Princess Alexandra	66 (68%)	74 (69%)
Calvary Mater Newcastle	26 (27%)	29 (27%)
Prince of Wales	5 (5%)	4 (4%)
Activated charcoal	13 (13%)	17 (16%)
Time to acetylcysteine (hours)	6.2 (5.5–6.8)	6.2 (5.7–7.2)

NB: Data shown are median (IQR) or n (%), except.
*median (IQR; range).

based on an initial history of <30 g being ingested. All other patients received the correct duration of acetylcysteine based on their study allocation and acetylcysteine was not stopped early in any patient.

Outcomes

In an intention-to-treat analysis, non-inferiority was demonstrated in the difference between the ΔALT24 for 107 patients randomised to the shorter regimen (median of -2 U/L; IQR -7 to 1 U/L) compared to 97 patients randomised to the standard regimen (median -1 U/L; IQR -5 to 1.5 U/L); difference in medians of -1 U/L (95% CI -3 to 1 U/L) were less than the upper non-inferiority margin of 5 (Fig. 2). The per-protocol analysis (104 *vs*. 96 patients) also confirmed non-inferiority on the primary outcome, and no significant differences in any secondary outcomes (Table S1). There was no difference between the medians for all subgroups for the primary outcome, including those with a paracetamol ratio >1.5, those given activated charcoal, those given acetylcysteine >6 h post-ingestion *vs*. those given it <6 h, and those ingesting >20 g (Fig. 3, Table S2).

No patients receiving the shorter regimen had an ALT at 24 h ≥2x the admission value and >150 U/L, compared to one (1%) patient receiving the standard regimen, and a similar proportion of patients in each group had a 50% increase in ALT over the admission ALT at 24 hours post-ingestion (Table 2). No patient had an ALT >1,000 U/L. There were five patients with an ALT >50 IU/L and ≥2x the admission value at 12 h after the infusion commenced. One received the shorter regimen, but did not have acetylcysteine recommenced and the ALT decreased 24 h post-ingestion. Four patients received the regular regimen, and in three the ALT decreased 24 h post-ingestion. A further 22 patients had a 12-hour post-infusion ALT >50 IU/L, but not ≥2x their admission ALT (Fig. S3).

Systemic hypersensitivity reactions were similar between groups: 9/107 (8%) for the short regimen *vs.* 10/97 (10%) in the standard regimen (absolute difference 2%; 95% CI -7% to 11%; Table 2). Gastrointestinal adverse effects occurred in 78 (73%) patients receiving the shorter regimen compared to 63 patients (65%) receiving the standard regimen (absolute difference 8%; 95% CI -5% to 21%; Table 2).

Discussion

We have demonstrated that acetylcysteine given for 12 h is not inferior to the standard 20 h regimen for patients ingesting an acute immediate release overdose of ≤30 g, treated within 8 h of ingestion. Outcomes were similar for patients more likely to

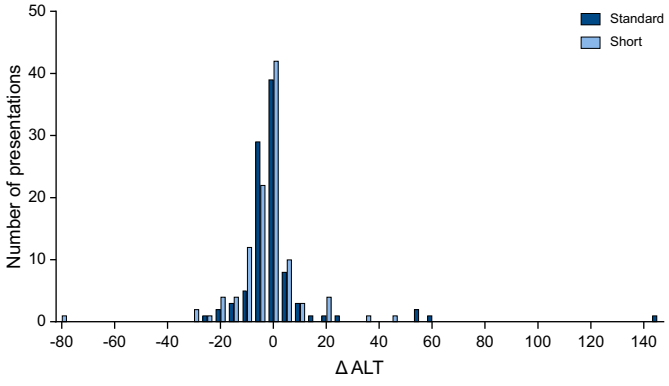

Fig. 2. Frequency histogram of the delta ALT (24 h ALT – admission ALT) for patients given the short regimen (12 h; light blue) *vs*. patients given the standard regimen (20 h; dark blue). ALT, alanine aminotransferase.

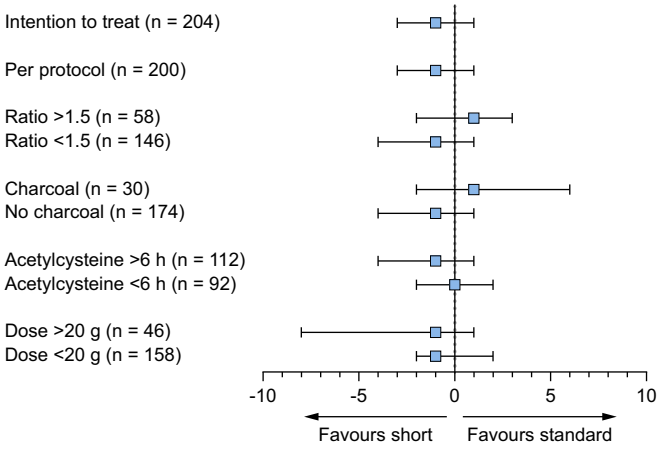

Fig. 3. Forest plot of the difference between the median (with 95% CIs) for the primary outcome of absolute difference between the ALT on admission and the ALT 24 h post-ingestion, in those having the standard regimen (20 h) *vs.* those having the shorter regimen (12 h). ALT, alanine aminotransferase.

Table 2. Primary and secondary outcomes for the standard *vs.* short regimens for the intention-to-treat analysis, with medians (primary outcome) or proportions (secondary outcomes) and 95% CIs in parentheses.

Outcome	Standard (n = 97)	Short (n = 107)	Difference
ΔALT24	-1 (-5 to 1.8)	-2 (-7 to 1.8)	-1 (-3 to 1)
ΔALT24 >50%	8 (8.2%)	8 (7.5%)	0.8% (-8 to 9%)
ALT24 >150 U/L and ≥2x ALT_0	1 (1%)	0	1% (-4 to 5%)
Peak ALT >1,000 U/L	0	0	-
Adverse effects			
Systemic hypersensitivity	10 (10%)	9 (8%)	2% (-7 to 11%)
Gastrointestinal effects	61 (63%)	77 (72%)	9% (-4% to 22%)

ALT, alanine aminotransferase; ΔALT24, delta ALT24, difference between the ALT at 24 h and the ALT on admission.

have toxicity; ingesting doses >20 g (and/or paracetamol ratios >1.5), further supporting the similar effectiveness of the shorter 12 h regimen. No patients had an ALT >1,000 U/L and hypersensitivity reactions were similar between groups.

Our study was designed specifically to look at shortening the duration of the acetylcysteine regimen from 20 h to 12 h, which is accompanied by a decrease in the dose. Although this does not include all patients with paracetamol toxicity, such as those with staggered ingestions and presenting to hospital after 8 h, it constitutes between 20% and 35% of patients (Fig. 1).

Based on our understanding, the historical evidence behind the original acetylcysteine regimen was empirically derived to administer a large loading dose (patients thought to be glutathione depleted on presentation) and a 20 h infusion (5x a theoretical 4 h half-life of paracetamol).[4,7] More recent evidence has suggested a "one size fits all" approach is not suitable for all patients.[6] Currently we manage most paracetamol overdoses with a patient weight-based acetylcysteine dose (300 mg/kg) and not based on paracetamol (NAPQI) body burden. In our study we demonstrated that acetylcysteine could be adjusted (250 mg/kg over 12 h *vs*. 300 mg/kg over 20 h) based on the amount of paracetamol ingested (≤*vs*. >30 g), if the patient presents within 8 h and the paracetamol ratio is <2. This builds on the principle of individualising acetylcysteine therapy for paracetamol overdoses, as increased doses (400 mg/kg over 20 h) are already recommended for larger ingestions with a paracetamol ratio >2 and hence more NAPQI.[9] In lower risk patients, selective use of 12 h acetylcysteine regimens will significantly shorten the average patient's length of stay in hospital.[14]

To establish non-inferiority in effectiveness, we used a difference in ALT based on historical data taken from the three toxicology units involved in the study (Fig. 2 and S1). This has allowed us to choose a very rigorous statistical equivalence boundary, such small changes in ALT are extremely sensitive indicators of liver injury, much less than those that would indicate clinically significant liver toxicity.[23] The trial was designed to detect an increased risk of even very small increases in ALT. However, the increases in ALT we used as an outcome in this trial were mostly not clinically important or even enough to justify any change in management (*e.g.* further observation in hospital).

We found a high rate of gastrointestinal adverse effects, which may be due to additional gastrointestinal effects of paracetamol toxicity, but alternatively due to better recording of adverse effects in a prospective clinical trial. A recent systematic review found that gastrointestinal side effects ranged from <1% to 76%.[24] Higher rates tended to be from prospective studies, whereas lower rates likely resulted from underreporting in retrospective studies.[24] In the SNAP clinical trial, the standard regimen was associated with similarly high rates of vomiting of 60-65% as in our study, while the experimental SNAP protocol (with half the loading dose of acetylcysteine) was associated with lower rates of vomiting.[12] Therefore, the higher rates of gastrointestinal effects may be associated with the acetylcysteine loading dose, which was the same in both arms of our study.

The shorter acetylcysteine regimen of 12 h can be applied to any region or country currently using the standard two-bag or three-bag acetylcysteine regimen. This includes most of the world except for the United Kingdom where SNAP is the standard treatment. The main difference between many parts of the world is the criteria for the administration of acetylcysteine, with different risk assessment tools, such as lower nomogram lines. However, it is important that the shorter regimen is only applied to the same group included in our study: acute ingestions of immediate release paracetamol <30 g presenting with 8 h of ingestion.

There are some important limitations to note. We had strict inclusion criteria (Fig. 1), and these results cannot necessarily be generalised to the many people who present with unclear timing of the overdose. Nor can immediate release overdoses >30 g or modified-release paracetamol ingestions be treated based on our results. There is a very slight possibility that patients were not included in the study because they had a paracetamol ratio close to 2. This is unlikely because all patients were discussed with the clinical toxicologist and there were only a small number of missed patients, almost always due to late notification to the investigators. Finally, there was an imbalance in the two study arms. This was because attempting to balance allocation for six subgroups using a biased coin randomisation, with a study of 204 patients, led to an overall imbalance. We opted for randomisation to be balanced for each subgroup (three hospitals and two paracetamol ratio groups >1.5 or <1.5; Table 1), rather than overall.

In conclusion, a shorter 12 h regimen of acetylcysteine had the same effectiveness and safety as the standard 20 h regime in moderate paracetamol overdoses (≤30 g), almost halving the length of treatment required and therefore duration of hospital admission.

Affiliations

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Abbreviations

ALT, alanine aminotransferase; ΔALT24, delta ALT24, difference between the ALT at 24 h and the ALT on admission; RCT, randomised-controlled trial.

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Conflict of interest

The authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

CP and GI designed the study and wrote the protocol. NB, AC and KI reviewed the protocol and all authors contributed to the final design of the study. GI, IB, MD, CP, KI and AC recruited patients. GI and NB analysed the data. CP and GI drafted this manuscript. All authors read and approved the final manuscript. GI is guarantor of the paper.

Data availability

All data generated or analysed during this study will be included in the published article (and supplementary information files if required). The dataset used to design this study *i.e.* sample size calculation, are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.05.008.

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Supplemental information

A non-inferiority randomised controlled trial of a shorter acetylcysteine regimen for paracetamol overdose – the SARPO trial

Geoffrey Isbister, Angela Chiew, Nicholas Buckley, Keith Harris, Ingrid Berling, Michael Downes, Colin Page, and Katherine Isoardi

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Geoffrey Isbister, Angela Chiew, Nicholas Buckley, Keith Harris, Ingrid Berling, Michael Downes, Colin Page, Katherine Isoardi

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Trial Protocol 1

Study Full Title: A non-inferiority randomised controlled trial of a Shorter Acetylcysteine Regimen for Paracetamol Overdose – the SARPO trial.

Study Short Title: SARPO Trial

Background:

Paracetamol is one of the commonest medications taken in overdose worldwide and is the leading cause of acute liver failure in the United States and Europe[1]. Locally it accounts for 18% of overdose patients presenting to the Princess Alexandra Hospital (PAH) who are managed by the clinical toxicology unit. The antidote acetylcysteine was developed in the 1970's[2] and has decreased both the rates of hepatotoxicity and mortality secondary to paracetamol toxicity. The regimen developed at the time was never subjected to either a randomised controlled trial (RCT) or any dose ranging studies and has remained unchanged until recently[3]. The conventional "3 bag" regimen has been used for decades and is as follows:

1. 150mg/kg NAC over 15-60 minutes
2. 50mg/kg NAC over 4 hours
3. 100mg/kg NAC over 16 hours

From its early clinical use it was recognised that acetylcysteine had adverse effects, which were due to the high initial peak concentration of acetylcysteine attained with the first infusion (150mg/kg) and was anaphylactoid in nature. Since this time a number of studies have been published that have altered the timing of the loading dose and have shown a reduction in adverse effects[3]. One of the largest of these studies undertaken at the PAH and Calvary Mater Hospital (CMN) in Newcastle New South Wales in 2012-2014, recruited 654 patients and combined the first two infusions (200mg/kg) of the three infusion regimen and administered this over a variable time period of four to nine hours depending on the time of presentation post ingestion[4]. The rate of anaphylactoid reactions was reduced from reported rates of 30-40% to 10% with a 4-hour infusion of 200mg/kg followed by an unchanged 16-hour infusion of 100mg/kg. Although the rate of hepatotoxicity was similar to the traditional regimen, neither this study nor any of the other studies looking at adverse effects were designed or powered to show non-inferiority. This regimen is now used in both toxicology units.

With the development of safer regimens for the administration of acetylcysteine, attention has now been drawn to the original dosing regimen and the evidence behind its dose and duration of administration. The original dosage regimen for acetylcysteine was unpublished but was developed on the following principles[2,5].

1. Patients were presenting with paracetamol hepatotoxicity and were glutathione deficient (70% glutathione depletion required to develop necrosis)[6] and therefore a large loading dose of acetylcysteine as a source of glutathione was required. Glutathione binds to the toxic metabolite of paracetamol *N*-acetyl-*p*-

benzoquinone imine (NAPQI). Since these patients had a high rate of morbidity and mortality, high rates of adverse effects were considered acceptable. This contrasts to the current era where nearly all patients with paracetamol overdose present soon after paracetamol ingestion, do not have hepatotoxicity, are not glutathione deficient and acetylcysteine is administered within eight hours of ingestion.

2. Once the liver had been replenished with glutathione, 6.25mg/kg/hr of acetylcysteine was sufficient based on liver glutathione turnover to maintain glutathione levels[5,7]. In fact this dose "gives a therapeutic excess of acetylcysteine in virtually all cases"[5].

3. The duration of the regimen (20.25 to 21 hours) was set empirically but based on five 4-hour half-lives of a therapeutic dose of paracetamol i.e. acetylcysteine was administered for the duration of time that paracetamol would still be present. This explains the third bag of the acetylcysteine regimen of 100mg/kg/16 hours (6.25mg/kg/hour), which followed the previous two bags given over 4.25 hours. This is despite a half-life of two hours (1.5 to 2.5 hours) when paracetamol is taken therapeutically and 2.9 hours in patients taking a paracetamol overdose who do not have liver damage[8,9]. Longer half-lives are usually only seen in patients with liver damage. More recent evidence of this short half-life comes from PAH clinical toxicology unit patients with paracetamol overdose. In 35 patients ingesting 30g of paracetamol or less with toxic levels, all had paracetamol levels <20mg/L (therapeutic range 10-30mg/L) after 12 hours of acetylcysteine.

The principles of the original acetylcysteine regimen suggest that the management of paracetamol toxicity could be based on ingested dose and half-life of paracetamol (proportional to degree of liver damage) and that one standard regimen should not be used for all patients[5]. Enough acetylcysteine should be given to restore liver glutathione levels and then acetylcysteine should be given while paracetamol is still present. Therefore patients with smaller ingestions and normal livers may require acetylcysteine for less than 20 hours[5]. Patients with liver damage or larger ingestions (prone to prolonged absorption) may require larger doses of acetylcysteine (>6.25mg/kg/hr) for longer than 20 hours since paracetamol will be present for a longer period[5]. Recommendations for larger ingestions have recently been incorporated in the Australia and New Zealand guidelines for paracetamol poisoning[10].

The only study to date that has looked at a shorter regimen was a RCT comparing the traditional regimen with a 12-hour regimen (100mg/kg over 2 hours followed by 200mg/kg over 10 hours)[11]. This study was primarily designed to look at acetylcysteine adverse effects, which were less with the 12-hour regimen. The 12-hour regimen was based on pharmacokinetic modelling that demonstrated a maximum concentration of acetylcysteine (Cmax) that was approximately 20% of the traditional regimen and a acetylcysteine concentration at 20.25 hours being similar to the traditional regimen. The later was subsequently proven to be incorrect[3] when the correct pharmacokinetic model for acetylcysteine was used. It showed the concentration of acetylcysteine to be approximately half the concentration of the traditional regimen at 20.25 hours. Despite

this lower acetylcysteine concentration at 20.25 hours, the two regimens had a similar rate of a 50% increase in ALT suggesting similar effectiveness although the study was not sufficiently powered to show non-inferiority.

The authors of the RCT in their discussion state[11]:

"We identified a large proportion of patients with no change in the amount of alanine aminotransferase and with paracetamol concentrations less than 20 mg/L at 12 h. We believe this patient group could be discharged early, if findings of a larger study confirm the absence of inferiority."

Since this publication, there has been discussion in both the United Kingdom[12] and Australia[13] suggesting that low risk patients defined as patients treated within eight hours of ingestion and whose paracetamol concentration is below 20mg/L at the end of a 12-hour acetylcysteine regimen could be safely discharged.

Based on previous research, recent commentary and our understanding of acetylcysteine in paracetamol toxicity, it is proposed to undertake a RCT of two different duration regimens of acetylcysteine. This will provide evidence for the further development of patient tailored regimens of acetylcysteine in paracetamol toxicity.

Aims:

The aims of the study are:

1. To investigate if a shortened 12-hour regimen compared to a 20 hour regimen of acetylcysteine provides the same protection against liver damage from paracetamol overdose in patients taking 30g or less of paracetamol and with an initial paracetamol concentration of less than twice the nomogram line (paracetamol ratio <2) who commence acetylcysteine within eight hours of ingestion.

2. To assess the adverse reaction rate to acetylcysteine in the first 12 hours.

Hypothesis:

1. That a shortened 12-hour regimen of acetylcysteine in paracetamol overdose will provide the same protection as a 20-hour regimen of acetylcysteine.

2. The rate of acetylcysteine reactions will be similar to previous studies that have utilised an initial 4-hour acetylcysteine infusion of 200mg/kg.

Research Plan:

Study Group:

Colin Page	Clinical Toxicologist and Emergency Physician (PAH)
Angela Chiew	Clinical Toxicologist and Emergency Physician

	(Prince of Wales Hospital, Sydney, NSW)
Geoff Isbister	Clinical Toxicologist and Emergency Physician (Calvary Mater Newcastle, Newcastle, NSW)

Study design and setting:

This will be a multicentre non inferiority per protocol unblinded RCT of a 20 hour versus a 12 hour regimen of acetylcysteine in paracetamol overdose. The study will be undertaken at the PAH, CMN and Prince of Wales hospitals. All three hospitals have established clinical toxicology units, managed by trained clinical toxicologists, which care for all poisoned patients presenting to their respective hospitals. Ethics approval for the three participating sites will be through the Metro South Human Research Ethics Committee located at the PAH. Site specific applications will be through the three respective hospitals involved in the study. Informed consent will be obtained.

Patient recruitment:

Inclusion criteria:

All patients 16 years and above who fulfil the following criteria:

1. Single immediate release paracetamol overdoses of 30g or less with an initial paracetamol concentration above but less than twice the nomogram line (paracetamol ratio <2)
2. Acetylcysteine can be safely commenced within 8 hours of ingestion.
3. Informed consent can be obtained.

Exclusion criteria

1. Staggered or repeated immediate release paracetamol overdoses.
2. Single, staggered or repeated overdoses of sustained release paracetamol.
3. Repeated supratherapeutic ingestion of paracetamol.
4. Late presentation i.e. >8 hours since ingestion time[a].
5. >30g paracetamol[b] or paracetamol ratio >2.

a. Evidence from published studies of reduced acetylcysteine effectiveness when administered more than 8 hours after paracetamol ingestion[14-16].

b. Recent increasing evidence that ingested paracetamol doses >30g need an increase dose and duration of acetylcysteine[10].

Protocol:

All patients will be commenced on the current 20 hour regimen used at the participating hospitals based on the previous study undertaken at PAH and CMN[4]. That is:

200mg/kg of acetylcysteine in 500mL of 5% glucose over four hours followed by 100mg/kg of acetylcysteine in 1L of 5% glucose over 16 hours (6.25mg/kg/hr).

Once commenced on acetylcysteine and informed consent has been obtained, patients will be randomised to receive either the full 20 hours of acetylcysteine (standard treatment arm) or the first 12 hours (experimental arm) of the 20 hour acetylcysteine regimen. Randomisation can occur at any time up to the point where the patient has received 12 hours of acetylcysteine. Those randomised to receive 12 hours of acetylcysteine only will have their 16 hour infusion of acetylcysteine ceased at eight hours (250mg/kg acetylcysteine) and then be commenced on the equivalent fluid and volume but not acetylcysteine for the remaining eight hours i.e. 500mL of 5% glucose over 8 hours.

Liver function tests will be taken 24 hours post ingestion, which will be approximately two hours prior to the end of the infusion. An additional sample will be taken 12 hours after commencement of acetylcysteine (when the infusion will be ceased in patients randomised to the short protocol). Patients with acute liver injury defined as ALT >150IU/L and double the admission value[17] will have their acetylcysteine continued or recommenced depending on randomisation arm. Patients randomised to the standard arm (20 hours) will continue acetylcysteine at 100mg/kg over 16 hours until the patient is clinically improving, ALT levels are decreasing, the international normalised ratio (INR) is improving and less than 2[10]. Patients randomised to the experimental arm (12 hours) will receive 100mg/kg over 8 hours to catch up and then continue at 100mg/kg over 16 hours. The criteria for ceasing acetylcysteine will be as above.

Enrolment, randomisation and blinding:

Emergency department medical staff will be informed and educated on the study and the clinical toxicologists on call will identify suitable patients from the three clinical toxicology units. Enrolment will require contacting the lead investigator (CP) or one of the other investigators (GI or AC) if CP is unavailable. The lead investigator will keep a record of all prospective enrolments. Once contacted and informed consent has been confirmed randomisation will be done by a secure on line website.

Randomisation will be stratified by paracetamol ratio (<1.5 and >1.5) and also by site. Dose stratification is required so that by chance a similar distribution of overdose amounts is achieved in each acetylcysteine arm. Site stratification will also allow for any differences in the outcome measure analysis by the three hospital laboratories.

Patient's who receive activated charcoal are eligible to be included in the study but they will not be stratified by its use for randomisation. As only a small number of patients currently receive activated charcoal, any effect of charcoal will likely be underpowered, but this will still be examined as a post hoc analysis.

Apart from acetylcysteine adverse effects the primary and secondary outcomes measures are objective and laboratory based i.e. liver function tests. Blinding of patient, treating clinician or investigator is not required. However, there will be blinded allocation and once randomisation is done this is recorded online and can't be changed. The acetylcysteine reaction rates are recorded for the first 12 hours only and should be unaffected by treatment arm randomisation and lack of blinding.

Data collection:

A data collection form will be employed at all three sites. The form will include basic demographics, acetylcysteine allocation arm (12 or 20 hours), overdose details including dose and ingestion time, baseline and 24 hour post ingestion liver function tests. An acetylcysteine observation table to record adverse effects will also be part of the form.

Study Outcomes:

Primary outcome:

The primary outcome will be a comparison between the standard and the experimental arm of the absolute difference between the alanine aminotransferase (ALT) on admission and 24 hours post ingestion.

Secondary outcomes:

1. Proportion of patients with a 50% increase in ALT over the admission ALT at 24 hours post ingestion[11].
2. Proportion of patients with an ALT >150IU/L and double the admission value (acute liver injury) at 24 hours post ingestion[17].
3. Proportion of patients with an ALT >1000IU/L (hepatotoxicity) at any time post ingestion[17] assuming it did not rise to >1000 if no change after 24 hours.
4. Differences in other biomarkers apart from ALT. Specifically miRNA-122 and INR at 24 hours post ingestion.
5. Proportion of patients with systemic hypersensitivity reactions in the first 12 hours of treatment with acetylcysteine.
6. Proportion of patients with gastrointestinal adverse effects in the first 12 hours of treatment with acetylcysteine.

Secondary outcomes 5 and 6 are included to enlarge our data set on patients receiving 200mg/kg acetylcysteine over fours hours. Both arms of this study will receive 200mg/kg over four hours

Post-hoc sub group analysis (a priori)

1. Proportion of patients with an ALT > 150IU/L and double the admission value (acute liver injury) OR paracetamol concentration > 20mg/L after 12 hours of acetylcysteine.

Sample size calculation and statistical analysis:

There are two methods for setting the equivalence boundary or minimally significant effect size for sample size calculation in a non-inferiority trial – clinical and statistical[18,19]. A clinical equivalence boundary is when the researchers and/or a group of clinicians choose the smallest or minimum clinically important difference that they think is important. There are no validated rules for calculating this margin and hence is prone to an arbitrary decision, which is open to differences in interpretation and possible disagreement. A statistical equivalence boundary is based on previous data of

the existing treatment effect that the new alternative treatment is to be compared. The non-inferiority margin should be no more than half of the lower limit of the 95% confidence interval of the standard treatment (20 hours acetylcysteine) effect[18].

ALT data from 121 paracetamol overdoses (single ingestion, 30g or less and treated with 20 hour acetylcysteine regimen within 8 hours of ingestion) from the three participating hospitals has been collected. The mean difference between admission and 24 hour ALT is 0.2IU/L with a standard deviation of 10.9 and 95% confidence interval of -21.2 to 21.6 IU/L. Half the lower limit of the 95% confidence interval is 10.7 hence 10 or less should be chosen as the non inferiority margin. A margin of 5 has been chosen which is also satisfactory for a clinical significance boundary. Therefore a mean difference in ALT (between baseline and 24 hours post ingestion) of -4.8 to 5.2 (0.2 +/- 5) in the new treatment arm (12 hour acetylcysteine regimen) would be considered as a non-inferior treatment of paracetamol toxicity.

A non-inferiority study aims to show that one treatment is not significantly worse than another treatment. Therefore this is a one sided test and the significance or alpha level is set at 0.025. With a power of 90% (higher power to minimize the risk of a non-inferior treatment being missed due to chance) and a standard deviation of 10.9 with a non-inferiority limit of 5, the total sample size required is 200 or 100 in each arm[20]. Allowing for a 10% margin for failure to adhere to the study protocol, we aim to recruit 220 patients in total.

The continuous primary outcome of ALT difference between the two-acetylcysteine regimens will be analysed per protocol by student's t-test or non-parametric equivalent depending on the distribution of the data. Secondary outcomes will be analysed using Chi-square or Fisher's exact test, whichever is appropriate.

Study Monitoring

All patients involved in the study will have their liver enzymes closely monitored by the lead investigator or the respective site investigator (GI - CMN and AC - POW) and a Data Monitoring Committee. The committee chair will be Professor Andrew Dawson a clinical pharmacologist and toxicologist from the Royal Prince Alfred (RPA) Hospital (Sydney). There will be three other members. Professor Peter Pillans, clinical pharmacologist from PAH, Professor Tony Brown, emergency physician from Royal Brisbane Woman's Hospital and Dr Joel Oedema, clinical pharmacologist and general physician from Redlands Hospital. The committee will meet six monthly or more urgently if required. A report will be supplied to the ethics committee after each review. In the event that the research team and the data monitoring committee feel that the rate of hepatotoxicity in the experimental arm is not consistent with a non-inferior treatment the study may be ceased.

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Trial Protocol 2

Study Full Title: A non-inferiority randomised controlled trial of a Shorter Acetylcysteine Regimen for Paracetamol Overdose – the SARPO trial.

Study Short Title: SARPO Trial

Background:

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2. Once the liver had been replenished with glutathione, 6.25mg/kg/hr of acetylcysteine was sufficient based on liver glutathione turnover to maintain glutathione levels[5,7]. In fact this dose "gives a therapeutic excess of acetylcysteine in virtually all cases"[5].

3. The duration of the regimen (20.25 to 21 hours) was set empirically but based on five 4-hour half-lives of a therapeutic dose of paracetamol i.e. acetylcysteine was administered for the duration of time that paracetamol would still be present. This explains the third bag of the acetylcysteine regimen of 100mg/kg/16 hours (6.25mg/kg/hour), which followed the previous two bags given over 4.25 hours. This is despite a half-life of two hours (1.5 to 2.5 hours) when paracetamol is taken therapeutically and 2.9 hours in patients taking a paracetamol overdose who do not have liver damage[8,9]. Longer half-lives are usually only seen in patients with liver damage. More recent evidence of this short half-life comes from PAH clinical toxicology unit patients with paracetamol overdose. In 35 patients ingesting 30g of paracetamol or less with toxic levels, all had paracetamol levels <20mg/L (therapeutic range 1030mg/L) after 12 hours of acetylcysteine.

The principles of the original acetylcysteine regimen suggest that the management of paracetamol toxicity could be based on ingested dose and half-life of paracetamol (proportional to degree of liver damage) and that one standard regimen should not be used for all patients[5]. Enough acetylcysteine should be given to restore liver glutathione levels and then acetylcysteine should be given while paracetamol is still present. Therefore patients with smaller ingestions and normal livers may require acetylcysteine for less than 20 hours[5]. Patients with liver damage or larger ingestions (prone to prolonged absorption) may require larger doses of acetylcysteine (>6.25mg/kg/hr) for longer than 20 hours since paracetamol will be present for a longer period[5]. Recommendations for larger

ingestions have recently been incorporated in the Australia and New Zealand guidelines for paracetamol poisoning[10].

The only study to date that has looked at a shorter regimen was a RCT comparing the traditional regimen with a 12-hour regimen (100mg/kg over 2 hours followed by 200mg/kg over 10 hours)[11]. This study was primarily designed to look at acetylcysteine adverse effects, which were less with the 12-hour regimen. The 12-hour regimen was based on pharmacokinetic modelling that demonstrated a maximum concentration of acetylcysteine (Cmax) that was approximately 20% of the traditional regimen and a acetylcysteine concentration at 20.25 hours being similar to the traditional regimen. The later was subsequently proven to be incorrect[3] when the correct pharmacokinetic model for acetylcysteine was used. It showed the concentration of acetylcysteine to be approximately half the concentration of the traditional regimen at 20.25 hours. Despite this lower acetylcysteine concentration at 20.25 hours, the two regimens had a similar rate of a 50% increase in ALT suggesting similar effectiveness although the study was not sufficiently powered to show non-inferiority.

The authors of the RCT in their discussion state[11]:

"We identified a large proportion of patients with no change in the amount of alanine aminotransferase and with paracetamol concentrations less than 20 mg/L at 12 h. We believe this patient group could be discharged early, if findings of a larger study confirm the absence of inferiority."

Since this publication, there has been discussion in both the United Kingdom[12] and Australia[13] suggesting that low risk patients defined as patients treated within eight hours of ingestion and whose paracetamol concentration is below 20mg/L at the end of a 12-hour acetylcysteine regimen could be safely discharged.

Based on previous research, recent commentary and our understanding of acetylcysteine in paracetamol toxicity, it is proposed to undertake a RCT of two different duration regimens of acetylcysteine. This will provide evidence for the further development of patient tailored regimens of acetylcysteine in paracetamol toxicity.

Aims:

The aims of the study are:

1. To investigate if a shortened 12-hour regimen compared to a 20-hour regimen of acetylcysteine provides the same protection against liver damage from paracetamol overdose in patients taking 30g or less of paracetamol and with an initial paracetamol concentration of less than twice the nomogram line (paracetamol ratio <2 – see below) who commence acetylcysteine within eight hours of ingestion.

2. To assess the adverse reaction rate to acetylcysteine in the first 12 hours.

Hypothesis:

1. That a shortened 12-hour regimen of acetylcysteine in paracetamol overdose will provide the same protection as a 20-hour regimen of acetylcysteine.

2. The rate of acetylcysteine reactions will be similar to previous studies that have utilised an initial 4-hour acetylcysteine infusion of 200mg/kg.

The paracetamol ratio is the first paracetamol concentration taken between four and 16 hours post ingestion divided by the paracetamol concentration on the 150mg/L at fourhour standard nomogram line at the same time point.

Research Plan:

Study Group:

Colin Page	Clinical Toxicologist and Emergency Physician (PAH)
Angela Chiew	Clinical Toxicologist and Emergency Physician (Prince of Wales Hospital, Sydney, NSW)
Nicole Ryan	Post Doctoral Research Fellow (NHMRC ECF) Clinical Toxicology Research Group University of Newcastle
Geoff Isbister	Clinical Toxicologist and Emergency Physician (Calvary Mater Newcastle, Newcastle, NSW)

Study design and setting:

This will be a multicentre non inferiority per protocol unblinded RCT of a 20 hour versus a 12 hour regimen of acetylcysteine in paracetamol overdose. The study will be undertaken at the PAH, CMN and Prince of Wales hospitals. All three hospitals have established clinical toxicology units, managed by trained clinical toxicologists, which care for all poisoned patients presenting to their respective hospitals. Ethics approval for the three participating sites will be through the Metro South Human Research Ethics Committee located at the PAH. Site specific applications will be through the three respective hospitals involved in the study.

Informed consent will be obtained. The study will be registered with the Australian New Zealand Clinical Trials Registry (ANZCTR).

Patient recruitment:

Inclusion criteria:

All patients 16 years and above who fulfil the following criteria:

1. Single immediate release paracetamol overdoses of 30g or less with an initial paracetamol concentration above but less than twice the nomogram line (paracetamol ratio <2)
2. Acetylcysteine can be safely commenced within 8 hours of ingestion.
3. Informed consent can be obtained.

Exclusion criteria

1. Staggered or repeated immediate release paracetamol overdoses.
2. Single, staggered or repeated overdoses of sustained release paracetamol.
3. Repeated supratherapeutic ingestion of paracetamol.
4. Late presentation i.e. >8 hours since ingestion time[a].
5. >30g paracetamol[b] or paracetamol ratio >2.

a. Evidence from published studies of reduced acetylcysteine effectiveness when administered more than 8 hours after paracetamol ingestion[14-16].

b. Recent increasing evidence that ingested paracetamol doses >30g need an increase dose and duration of acetylcysteine[10].

Protocol:

All patients will be commenced on the current 20 hour regimen used at the participating hospitals based on the previous study undertaken at PAH and CMN[4]. That is:
200mg/kg of acetylcysteine in 500mL of 5% glucose over four hours followed by 100mg/kg of acetylcysteine in 1L of 5% glucose over 16 hours (6.25mg/kg/hr).

Once commenced on acetylcysteine and informed consent has been obtained, patients will be randomised to receive either the full 20 hours of acetylcysteine (standard treatment arm) or the first 12 hours (experimental arm) of the 20 hour acetylcysteine regimen. Randomisation can occur at any time up to the point where the patient has received 12 hours of acetylcysteine. Those randomised to receive 12 hours of acetylcysteine only will have their 16 hour infusion of

acetylcysteine ceased at eight hours (250mg/kg acetylcysteine) and then be commenced on the equivalent fluid and volume but not acetylcysteine for the remaining eight hours i.e. 500mL of 5% glucose over 8 hours.

Liver function tests will be taken 24 hours post ingestion, which will be approximately two hours prior to the end of the infusion. An additional sample will be taken 12 hours after commencement of acetylcysteine (when the infusion will be ceased in patients randomised to the experimental arm). Patients with acute liver injury defined as ALT >50IU/L and double the admission value[10] at 24 hours post ingestion will have their acetylcysteine continued or recommenced depending on randomisation arm. Patients randomised to the standard arm (20 hours) will continue acetylcysteine at 100mg/kg over 16 hours until the patient is clinically improving, ALT levels are decreasing, the international normalised ratio (INR) is improving and less than 2[10]. Patients randomised to the experimental arm (12 hours) will receive 100mg/kg over 8 hours to catch up and then continue at 100mg/kg over 16 hours. The criteria for ceasing acetylcysteine in the experimental arm will be the same as the standard arm..

Investigations:

1. Paracetamol level and LFT's between four and eight hours post ingestion
2. Paracetamol level and LFT's 12 hours post commencement of acetylcysteine.
3. Paracetamol level, LFT's, INR and miRNA-122 at 24 hours post paracetamol ingestion.

Enrolment, randomisation and blinding:

Emergency department medical staff will be informed and educated on the study and the clinical toxicologists on call will identify suitable patients from the three clinical toxicology units. Enrolment will require contacting the lead investigator (CP) or one of the other investigators (GI or AC) if CP is unavailable. The lead investigator will keep a record of all prospective enrolments. Once contacted and informed consent has been confirmed randomisation will be done by a secure on line website.

Randomisation will be stratified by paracetamol ratio (≤1.5 and >1.5) and also by site. Dose stratification is required so that by chance a similar distribution of overdose amounts is achieved in each acetylcysteine arm. Site stratification will also allow for any differences in the outcome measure analysis by the three hospital laboratories.

Patient's who receive activated charcoal are eligible to be included in the study but they will not be stratified by its use for randomisation. As only a small number of patients currently receive activated charcoal, any effect of charcoal will likely be underpowered, but this will still be examined as a post hoc analysis. Apart from acetylcysteine adverse effects the primary and secondary outcomes

measures are objective and laboratory based i.e. liver function tests. Blinding of patient, treating clinician or investigator is not required. However, there will be blinded allocation and once randomisation is done this is recorded online and can't be changed. The acetylcysteine reaction rates are recorded for the first 12 hours only and should be unaffected by treatment arm randomisation and lack of blinding.

Data collection:

A data collection form will be employed at all three sites. The form will include basic demographics, acetylcysteine allocation arm (12 or 20 hours), overdose details including dose and ingestion time, baseline and 24 hour post ingestion liver function tests. An acetylcysteine observation table to record adverse effects will also be part of the form.

Study Outcomes:

Primary outcome:

The primary outcome will be a comparison between the standard and the experimental arm of the absolute difference between the alanine aminotransferase (ALT) on admission and 24 hours post ingestion.

Secondary outcomes:

1. Proportion of patients with a 50% increase in ALT over the admission ALT at 24 hours post ingestion[11].

2. Proportion of patients with an ALT >150IU/L and double the admission value (acute liver injury) at 24 hours post ingestion[17].

3. Proportion of patients with an ALT >1000IU/L (hepatotoxicity) at any time post ingestion[17] assuming it did not rise to >1000 if no change after 24 hours.

4. Differences in other biomarkers apart from ALT. Specifically miRNA-122 and INR at 24 hours post ingestion.

5. Proportion of patients with systemic hypersensitivity reactions in the first 12 hours of treatment with acetylcysteine.

6. Proportion of patients with gastrointestinal adverse effects in the first 12 hours of treatment with acetylcysteine.

Secondary outcomes 5 and 6 are included to enlarge our data set on patients receiving 200mg/kg acetylcysteine over fours hours. Both arms of this study will receive 200mg/kg over four hours.

Post-hoc sub group analysis (a priori)

1. Proportion of patients with an ALT > 50IU/L and double the admission value (acute liver injury) OR paracetamol concentration > 20mg/L after 12 hours of acetylcysteine.

Sample size calculation and statistical analysis:

There are two methods for setting the equivalence boundary or minimally significant effect size for sample size calculation in a non-inferiority trial – clinical and statistical[18,19]. A clinical equivalence boundary is when the researchers and/or a group of clinicians choose the smallest or minimum clinically important difference that they think is important. There are no validated rules for calculating this margin and hence is prone to an arbitrary decision, which is open to differences in interpretation and possible disagreement. A statistical equivalence boundary is based on previous data of the existing treatment effect that the new alternative treatment is to be compared. The non-inferiority margin should be no more than half of the lower limit of the 95% confidence interval of the standard treatment (20 hours acetylcysteine) effect[18].

ALT data from 121 paracetamol overdoses (single ingestion, 30g or less and treated with 20 hour acetylcysteine regimen within 8 hours of ingestion) from the three participating hospitals has been collected. The mean difference between admission and 24 hour ALT is 0.2IU/L with a standard deviation of 10.9 and 95% confidence interval of -21.2 to 21.6 IU/L. Half the lower limit of the 95% confidence interval is 10.7 hence 10 or less should be chosen as the non inferiority margin. A margin of 5 has been chosen which is also satisfactory for a clinical significance boundary. Therefore a mean difference in ALT (between baseline and 24 hours post ingestion) of -4.8 to 5.2 (0.2 +/- 5) in the new treatment arm (12 hour acetylcysteine regimen) would be considered as a non-inferior treatment of paracetamol toxicity.

A non-inferiority study aims to show that one treatment is not significantly worse than another treatment. Therefore this is a one sided test and the significance or alpha level is set at 0.025. With a power of 90% (higher power to minimize the risk of a noninferior treatment being missed due to chance) and a standard deviation of 10.9 with a non-inferiority limit of 5, the total sample size required is 200 or 100 in each arm[20]. Allowing for a 10% margin for failure to adhere to the study protocol, we aim to recruit 220 patients in total.

The continuous primary outcome of ALT difference between the two-acetylcysteine regimens will be analysed per protocol by student's t-test or non-parametric equivalent depending on the distribution of the data. Secondary

outcomes will be analysed using Chi-square or Fisher's exact test, whichever is appropriate.

Study Monitoring

All patients involved in the study will have their liver enzymes closely monitored by the lead investigator and/or the respective site investigator (CP-PAH, GI - CMN and AC - POW) and a Data and Safety Monitoring Board. The committee chair will be
Professor Andrew Dawson a clinical pharmacologist and toxicologist from the Royal
Prince Alfred (RPA) Hospital (Sydney). There will be three other members. Professor Peter Pillans, clinical pharmacologist from PAH, Professor Tony Brown, emergency physician from Royal Brisbane Woman's Hospital and Dr Joel Oedema, clinical pharmacologist and general physician from Redlands Hospital. The board will meet six monthly or more urgently if required. A report will be supplied to the ethics committee after each review. In the event that the research team and the data monitoring committee feel that the rate of hepatotoxicity in the experimental arm is not consistent with a non-inferior treatment the study may be ceased.

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Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3,4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6,7
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8,9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			

Partic[CONSORT]low (a diagra[CONSORT]trongly recom[CONSORT]ed)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	10
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10,11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10,11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10,11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	2,5
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Table S1. Primary and secondary outcomes for the standard versus short regimens for the per protocol analysis, with medians (primary outcome) or proportions (secondary outcomes) and 95% confidence intervals in parentheses.

Outcome	Standard (96)	Short (104)	Difference
ΔALT24	-1 (-5 to 1.8)	-2 (-7 to 1.8)	-1 (-3 to 1)
ΔALT24 > 50%	8 (8.3%)	8 (7.7%)	0.6% (-8 to 9%)
ALT_{24} > 150U/L and double ALT_0	1 (1%)	0	1% (-4 to 6%)
Peak ALT > 1000 U/L	0	0	-
Adverse Effects			
Systemic hypersensitivity	10 (10%)	8 (8%)	3% (-7 to 12%)
Gastrointestinal effects	60 (63%)	77 (73%)	11% (-3% to 24%)

ALT – alanine transaminase; ΔALT24 – delta ALT24, difference between the ALT at 24 h and the ALT on admission.

Table S2. Difference in the medians with 95% confidence intervals for the primary outcome for the standard versus short regimens, for all subgroups, including those with a paracetamol ratio > 1.5, those given activated charcoal, those given acetylcysteine > 6 h post ingestion versus those given it < 6 h, and those ingesting > 20 g.

Outcome	Difference in medians
Ratio > 1.5 (n=58)	1 (-2 to 3)
Ratio < 1.5 (n=146)	-1 (-4 to 1)
Charcoal (n=30)	1 (-2 to 6)
No Charcoal (n=174)	-1 (-4 to 1)
Acetylcysteine > 6 h (n=112)	-1 (-4 to 1)
Acetylcysteine < 6 h (n=92)	0 (-2 to 2)
Dose > 20 g (n=46)	-1 (-8 to 1)
Dose < 20 g (n=158)	-1 (-2 to 2)

Fig. S1. Paracetamol nomogram with the normal treatment line (black) and the double treatment line (red). Paracetamol concentrations less than the treatment line (light blue) were not treated with acetylcysteine, paracetamol concentration above the treatment but below the double treatment line (green; 1 < PR < 2) were recruited to the study and randomised to either standard acetylcysteine (200 mg/kg over 4 h; 100 mg/kg over 16 h) or short acetylcysteine (200 mg/kg over 4 h; 50 mg/kg over 8 h), and paracetamol concentrations above the double treatment line (orange; PR>2) were excluded but treated with double acetylcysteine (200 mg/kg over 4 h; 200 mg/kg over 16 h).

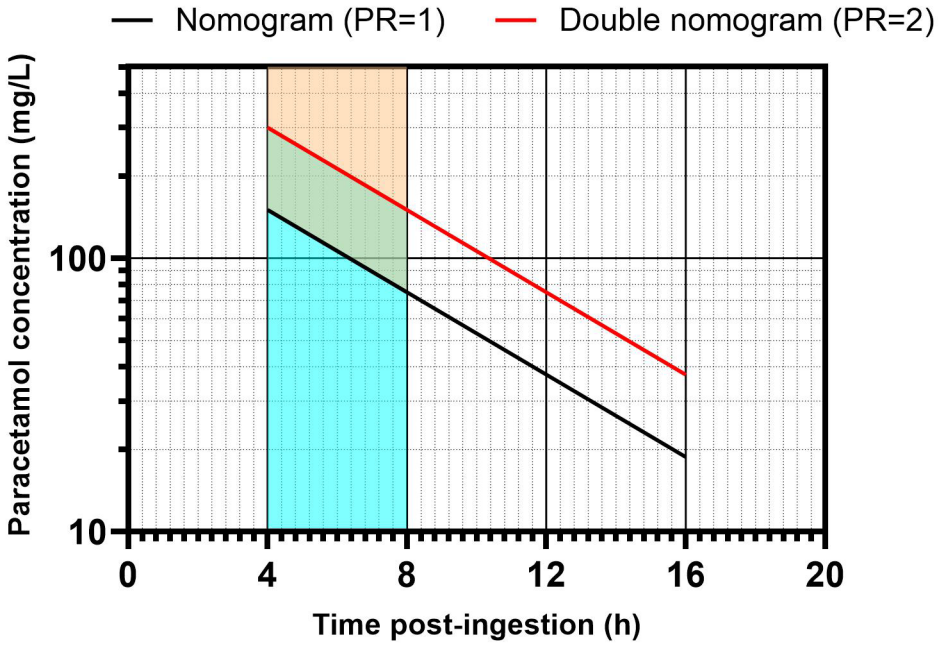

Fig. S2. Frequency histogram of the delta ALT for 121 acetaminophen overdoses (single ingestion of < 30 g within 1 h, and treated with the 20 h acetylcysteine regimen within 8 h of ingestion) from the three hospitals participating in the study was collected, prior to the study.

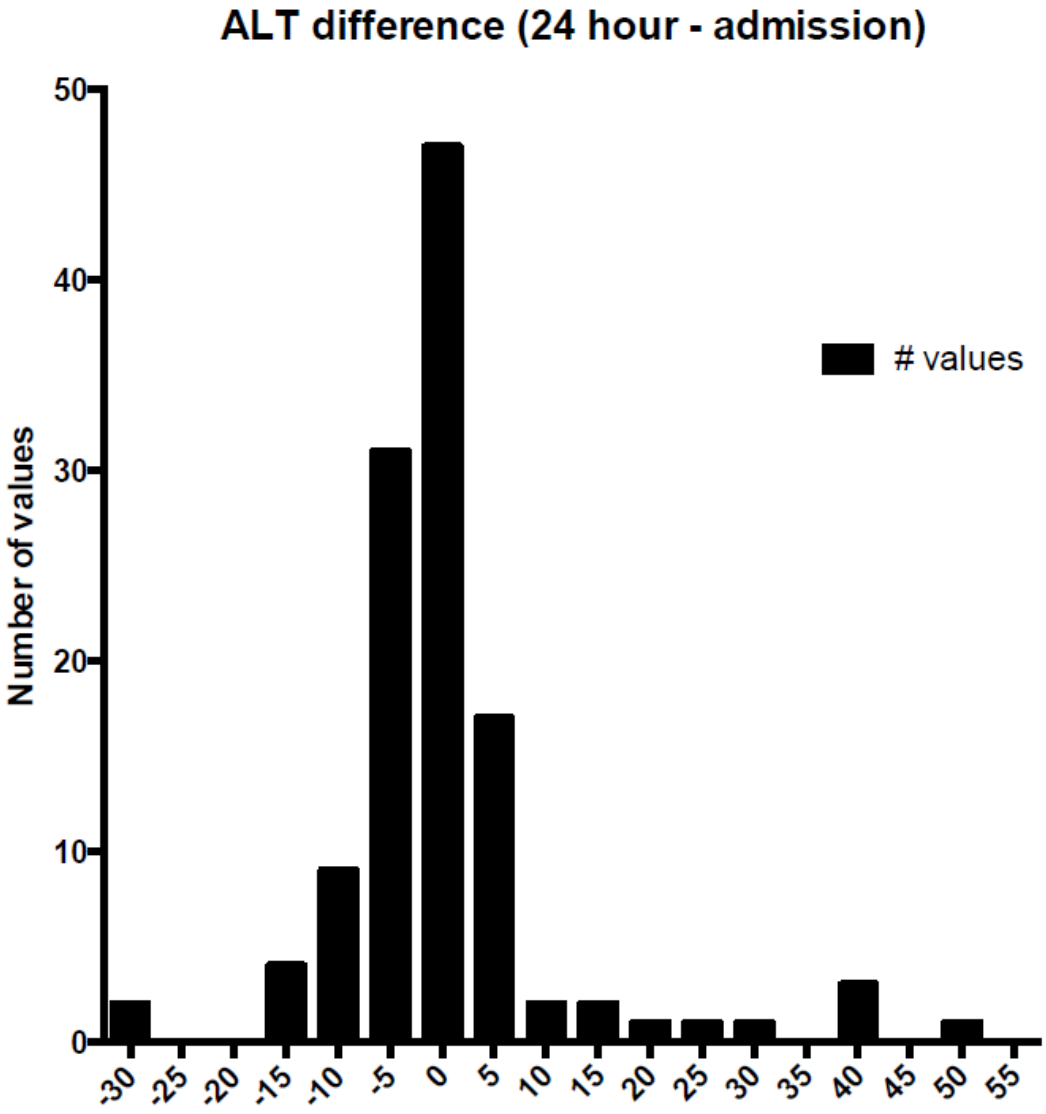

Fig. S3. Twenty seven patients in which the 12 hour ALT was greater than 50 IU/L. In twenty two patients the 12 hour ALT was not double the admission ALT or decreased from admission (open circles; dashed lines), in four patients it was also double the admission ALT but decreased at 24 hours post-ingestion (black filled circles; black line) and one in which it was double the admission ALT and increased (filled red circle; red line).