

# Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial



D Nicholas Bateman, James W Dear, H K Ruben Thanacoody, Simon H L Thomas, Michael Eddleston, Euan A Sandilands, Judy Coyle, Jamie G Cooper, Aryelly Rodriguez, Isabella Butcher, Steff C Lewis, A D Bastiaan Vliegthart, Aravindan Veiraiah, David J Webb, Alasdair Gray



## Summary

**Background** Paracetamol poisoning is common worldwide. It is treated with intravenous acetylcysteine, but the standard regimen is complex and associated with frequent adverse effects related to concentration, which can cause treatment interruption. We aimed to ascertain whether adverse effects could be reduced with either a shorter modified acetylcysteine schedule, antiemetic pretreatment, or both.

**Methods** We undertook a double-blind, randomised factorial study at three UK hospitals, between Sept 6, 2010, and Dec 31, 2012. We randomly allocated patients with acute paracetamol overdose to either the standard intravenous acetylcysteine regimen (duration 20·25 h) or a shorter (12 h) modified protocol, with or without intravenous ondansetron pretreatment (4 mg). Masking was achieved by infusion of 5% dextrose (during acetylcysteine delivery) or saline (for antiemetic pretreatment). Randomisation was done via the internet and included a minimisation procedure by prognostic factors. The primary outcome was absence of vomiting, retching, or need for rescue antiemetic treatment at 2 h. Prespecified secondary outcomes included a greater than 50% increase in alanine aminotransferase activity over the admission value. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov (identifier NCT01050270).

**Findings** Of 222 patients who underwent randomisation, 217 were assessable 2 h after the start of acetylcysteine treatment. Vomiting, retching, or need for rescue antiemetic treatment at 2 h was reported in 39 of 108 patients assigned to the shorter modified protocol compared with 71 of 109 allocated to the standard acetylcysteine regimen (adjusted odds ratio 0·26, 97·5% CI 0·13–0·52;  $p < 0·0001$ ), and in 45 of 109 patients who received ondansetron compared with 65 of 108 allocated placebo (0·41, 0·20–0·80;  $p = 0·003$ ). Severe anaphylactoid reactions were recorded in five patients assigned to the shorter modified acetylcysteine regimen versus 31 who were allocated to the standard protocol (adjusted common odds ratio 0·23, 97·5% CI 0·12–0·43;  $p < 0·0001$ ). The proportion of patients with a 50% increase in alanine aminotransferase activity did not differ between the standard (13/101) and shorter modified (9/100) regimens (adjusted odds ratio 0·60, 97·5% CI 0·20–1·83); however, the proportion was higher with ondansetron (16/100) than with placebo (6/101; 3·30, 1·01–10·72;  $p = 0·024$ ).

**Interpretation** In patients with paracetamol poisoning, a 12 h modified acetylcysteine regimen resulted in less vomiting, fewer anaphylactoid reactions, and reduced need for treatment interruption. This study was not powered to detect non-inferiority of the shorter protocol versus the standard approach; therefore, further research is needed to confirm the efficacy of the 12 h modified acetylcysteine regimen.

**Funding** Chief Scientist Office of the Scottish Government.

## Introduction

Overdose of paracetamol (acetaminophen) is common, and the drug is the most frequent cause of acute liver failure in Europe and North America.<sup>1,2</sup> During 2011–12, more than 38 000 admissions for paracetamol poisoning were recorded in England<sup>3</sup> and, in 2011, at least 137 000 enquiries were made to US poisons centres about paracetamol exposure.<sup>4</sup> The toxic mechanisms of paracetamol—understood for more than 40 years—enabled development of a specific antidote, acetylcysteine, in the 1970s.<sup>5–7</sup> Intravenous regimens<sup>5</sup> are now in widespread use, with between 18 000 and 40 000 treatment courses administered in the UK annually.<sup>8</sup> However, these regimens have never

undergone formal dose-ranging studies.<sup>9</sup> In particular, little attention has been paid to the initial dose regimen, which might cause dose-related vomiting in up to 60% of patients and anaphylactoid reactions leading to treatment interruption and refusal in a further 20%.<sup>10–12</sup>

The acetylcysteine regimen, although slightly variable worldwide, is universally complex; it includes three, separate, weight-related infusions over different timeframes, with a resultant high risk of medication error.<sup>13–15</sup> Until September, 2012, the standard regimen for acetylcysteine used in the UK delivered 50% of the total dose over the first 15 min, rather than over a period of 1 h as with the US dosing schedule (panel 1).<sup>16</sup> Although a higher frequency of dose-related adverse reactions might

Lancet 2014; 383: 697–704

Published Online  
November 28, 2013  
[http://dx.doi.org/10.1016/S0140-6736\(13\)62062-0](http://dx.doi.org/10.1016/S0140-6736(13)62062-0)

This online publication has been corrected. The corrected version first appeared at [thelancet.com](http://thelancet.com) on December 9, 2013. The second corrected version first appeared at [thelancet.com](http://thelancet.com) on May 5, 2015

See [Comment](#) page 672

Copyright © Bateman et al. Open Access article distributed under the terms of CC BY

National Poisons Information Service, Royal Infirmary of Edinburgh, Edinburgh, UK (D N Bateman MD, J W Dear PhD, M Eddleston PhD, E A Sandilands MB, A Veiraiah MB); British Heart Foundation Centre for Cardiovascular Science, Edinburgh University, Edinburgh, UK (J W Dear, M Eddleston, A D B Vliegthart BSc, Prof D J Webb DSc); Institute of Cellular Medicine, Newcastle University, and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK (H K R Thanacoody MD, S H L Thomas MD); Emergency Medicine Research Group, Department of Emergency Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK (J Coyle BSc, A Gray MD); Emergency Department, Aberdeen Royal Infirmary, Aberdeen, UK (J G Cooper MB); and Edinburgh Clinical Trials Unit (A Rodriguez MSc), and Centre for Population Health Sciences (I Butcher PhD, S C Lewis PhD), University of Edinburgh, Edinburgh, UK

Correspondence to: Prof D Nicholas Bateman, National Poisons Information Service, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, UK [spib@luht.scot.nhs.uk](mailto:spib@luht.scot.nhs.uk)

**Panel 1: Acetylcysteine regimens used in the study****UK standard schedule (duration 20-25 h)<sup>16</sup>**

- 150 mg/kg in 200 mL, over 15 min
- 50 mg/kg in 0.5 L, over 4 h
- 100 mg/kg in 1 L, over 16 h

**Modified (shorter) protocol (duration 12 h)**

- 100 mg/kg in 200 mL, over 2 h
- 200 mg/kg in 1 L, over 10 h
- 0.5 L of 5% dextrose, to 20-25 h

Acetylcysteine is administered in 5% dextrose.

be expected with this faster infusion rate, no differences have been noted between these two initial doses.<sup>17</sup> The total duration of the infusion is between 20·25 h and 21 h for these regimens.

We postulated that the incidence of adverse effects reported with acetylcysteine treatment could be reduced with a simpler regimen that delivers the same total dose but over a shorter (12 h) period and with a lower, slower initial infusion dose (panel 1).<sup>16</sup> Monte Carlo modelling based on published data from patients indicates that acetylcysteine concentrations at 20·25 h would be similar with the two regimens.<sup>18,19</sup> Therefore, we did a factorial study to compare the rates of adverse reactions—with and without antiemetic pretreatment—between the standard acetylcysteine protocol and a shorter (12 h) modified schedule.

## Methods

### Participants

The study methods have been reported in full elsewhere.<sup>19</sup> In summary, we did a double-blind, randomised controlled trial at three acute clinical units in the UK, initially at the Royal Infirmary in Edinburgh and the Royal Victoria Infirmary, Newcastle, and subsequently at Aberdeen Royal Infirmary, to ensure adequate recruitment within the funding timeframe. Recruitment started on Sept 6, 2010, and ended on Dec 31, 2012. Patients were eligible for the study if they presented after an acute paracetamol overdose and needed treatment with acetylcysteine, on the basis of standard UK guidance for management.<sup>16,19</sup> Exclusion criteria are shown in figure 1 and described elsewhere.<sup>19</sup> We obtained ethics and regulatory approval for the study. Trained clinician recruiters obtained informed consent from all patients before trial entry.

### Procedures

We treated patients who presented within 8 h of paracetamol ingestion on the basis of their measured paracetamol concentration in plasma. Individuals who presented more than 8 h after ingestion were managed initially according to the history of the ingested dose, but subsequently we withdrew them from the study if measured concentrations of paracetamol in plasma were

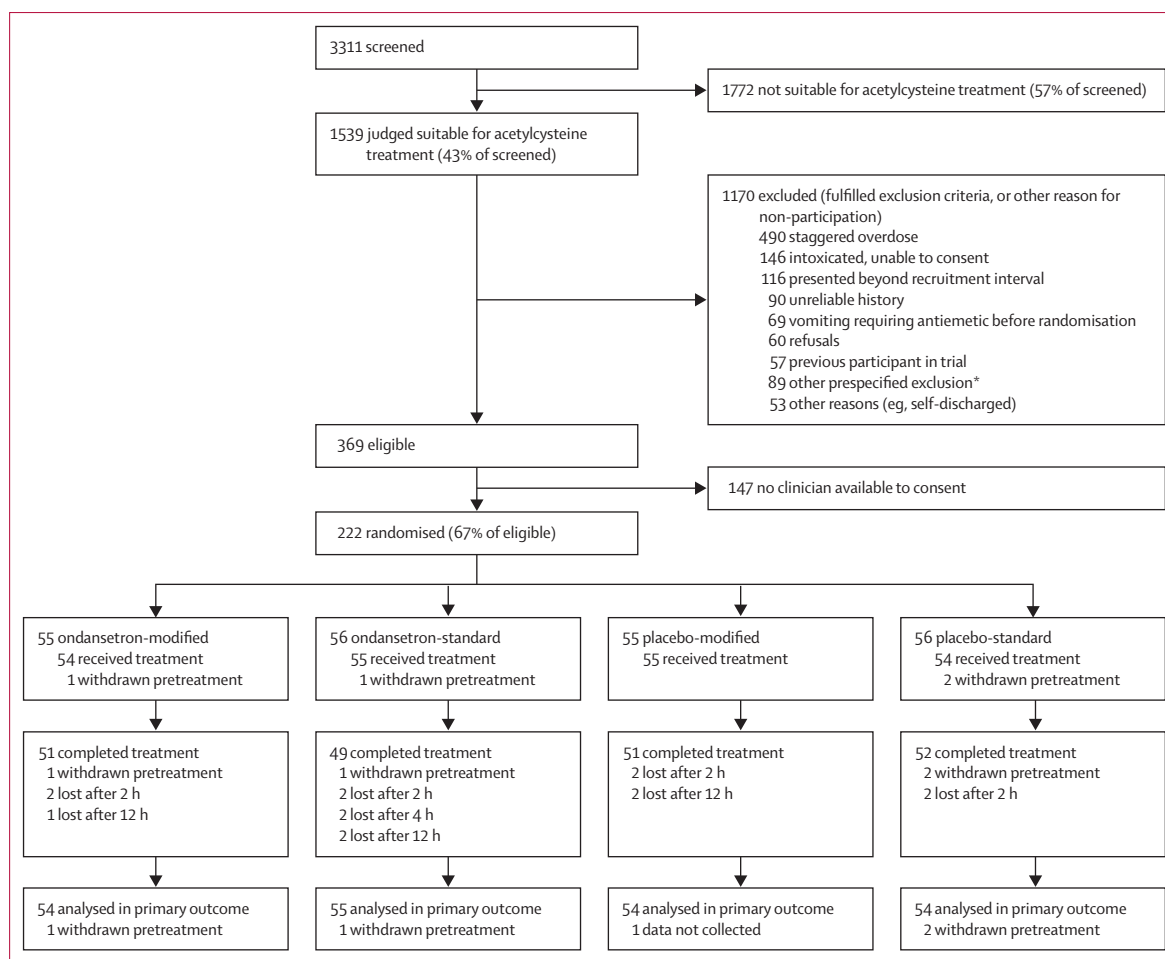
below standard UK treatment lines (200 mg/L or 100 mg/L at 4 h, depending on risk assessment). When clinically indicated, we administered further doses of acetylcysteine after completion of the initial schedule, according to standard UK practice.<sup>16</sup> We pretreated all patients with either intravenous ondansetron (4 mg) or a matched placebo (saline), then we administered either the UK standard acetylcysteine regimen or the shorter (12 h) version (panel 1).<sup>16</sup>

We recorded adverse events in the patient's clinical record and extracted data to the case report form. We also noted the use and timing of rescue drugs; we used intravenous cyclizine as antiemetic rescue and, initially, intravenous chlorphenamine for anaphylactoid symptoms. We allowed use of other treatments when clinically indicated, and we recorded these in the clinical record. The research team gathered outcome and survival data via the electronic system at every hospital and clinical notes, and they recorded this information in the case report form. We also obtained data from a sample of patients to assess acetylcysteine concentrations in the two regimens, and these will be reported separately.

We made two major protocol amendments. First, we extended the time allowed for ingestion of paracetamol from 1 h to 2 h to assist recruitment, because in practice many patients were found to ingest large single overdoses over a period up to 2 h. Second, after new UK guidance was issued in September, 2012,<sup>19,20</sup> we used the 100 mg/L paracetamol nomogram line for recruitment of all patients. We established a data monitoring committee that met about every 6 months; they were aware of and supported all protocol modifications and made no other changes to the study.

### Randomisation and masking

We used a 2x2 factorial trial design, which included four parallel groups: ondansetron pretreatment and the shorter acetylcysteine regimen (ondansetron-modified); ondansetron and the standard schedule (ondansetron-standard); placebo and the shorter acetylcysteine protocol (placebo-modified); and placebo and the standard regimen (placebo-standard). We did randomisation by minimisation to achieve balance (1:1:1:1 allocation), according to the following prognostic factors: reported paracetamol dose (<16 g or ≥16 g); risk factors for paracetamol-induced hepatic toxic effects; and time to presentation (<8 h or ≥8 h).<sup>16</sup> We used an online program for the randomisation, which was provided by the Edinburgh Clinical Trials Unit, thus ensuring allocation concealment. To achieve masking, ondansetron and saline placebo ampoules were identical in appearance, but because of ethical and practical concerns, we could not mask the administering team to the acetylcysteine regimen. Patients allocated to the shorter modified acetylcysteine regimen received intravenous 5% dextrose after the full acetylcysteine dose was given, to ensure the total infusion time was the same in both groups.



**Figure 1: Trial profile**

One patient had incomplete data at 2 h but completed the trial. \*Other reasons for exclusion: unlikely to complete treatment (n=27), life-threatening illness (17), detained under the Mental Health Act (15), permanent cognitive impairment (9), pregnant (6), on anticoagulants (5); non-English speaking (4), unable to complete questionnaires (3), and history of hypersensitivity to serotonin antagonists (3).

### Outcome measures

The primary outcome, defined a priori, was the proportion of patients who did not vomit or retch and did not need rescue antiemetic drugs—as assessed by clinical case records and patients' self-reporting—within 2 h of initiation of acetylcysteine.<sup>19</sup> For clarity, this outcome measure is reported in terms of treatment benefit (ie, symptom presence, need to treat, or both).

We assessed secondary outcomes up to 12 h after the start of treatment. Secondary outcomes were: the proportion of patients without nausea (Likert scale <5 of 11), vomiting, or retching up to 12 h after initiation of acetylcysteine treatment (for clarity, expressed as treatment benefit); and occurrence of anaphylactoid reactions, which was judged by the need for treatment or acetylcysteine interruption for an anaphylactoid response, by self-reported flushing, itchy skin, skin rash, chest pain, breathlessness, wheeze, and tongue or lip swelling (all assessed on Likert scales,

>4 of 11), and by recorded changes in blood pressure (fall of systolic >20 mm Hg) and pulse rate (rise of >20 bpm). We categorised the severity of anaphylactoid reactions on a predefined three-grade severity scale.<sup>19,21</sup> Grade 1 reactions (mild) were defined either as a positive response in one of the domains on the Likert scales or as a change in blood pressure or pulse rate (as described). Grade 2 reactions (moderate) fulfilled either two or more positive symptom domains on the Likert scales, cardiovascular changes (blood pressure or pulse), or both, but with no requirement for specific treatment or stopping acetylcysteine treatment. Grade 3 reactions (severe) included patients who either had acetylcysteine treatment interrupted, an intervention with an anti-allergy drug, or both.

We prespecified other analyses to assess the frequency of hepatic toxic effects at the end of treatment (derived from case records), including a greater than 50% increase

in alanine aminotransferase activity over the admission value and activity of alanine aminotransferase greater than 1000 IU/L. We also recorded, at 20·25 h after initiation of acetylcysteine, when the international normalised ratio rose to more than 1·3, although this measurement can potentially be confounded by acetylcysteine.<sup>11,22</sup> Finally, in a subset of Edinburgh patients, we did a post-hoc analysis of microRNA miR-122, which is a sensitive and specific marker of hepatic injury.<sup>23,24</sup>

### Statistical analysis

To achieve at least 80% power to detect a relative risk of 0·6 for the proportion of patients with vomiting within 2 h (from 60% in the placebo group to 36% in the treated group), we needed to enrol 91 patients on ondansetron and 91 on placebo ( $p=0\cdot025$ ). This number was increased to allow for dropouts and to ensure we included 50 patients in each of the four groups in the factorial study.<sup>19</sup> To account for the factorial design, we used a

significance level of 2·5%, and we calculated 97·5% CIs. All applicable statistical tests were two-sided.

The analysis was done according to randomised treatment group, irrespective of adherence to treatment (intention to treat). Because of the trial design and the need to recruit late-presenting patients before data for paracetamol concentration were available, we subsequently excluded some individuals (figure 1); data collection and follow-up were stopped after treatment discontinuation for any reason. If patients had missing data for an outcome variable, we removed them from formal statistical analysis at that timepoint.

We analysed binary variables (including the primary outcome) with logistic regression, adjusting for prognostic factors included in the minimisation algorithm and for centre. Because we did a factorial trial, we entered the main effect for both treatment comparisons into the model concurrently. We derived Kaplan-Meier plots for use of antiemetic or anaphylactic rescue medication from the start of the first infusion, by regimen and treatment.

	Acetylcysteine regimen		Ondansetron pretreatment		Ondansetron-modified (n=55)	Ondansetron-standard (n=56)	Placebo-modified (n=55)	Placebo-standard (n=56)
	Modified (n=110)	Standard (n=112)	Active (n=111)	Placebo (n=111)				
<b>Demographics</b>								
Centre								
Edinburgh	75 (68%)	75 (67%)	74 (67%)	76 (68%)	37 (67%)	37 (66%)	38 (69%)	38 (68%)
Newcastle	26 (24%)	28 (25%)	27 (24%)	27 (24%)	13 (24%)	14 (25%)	13 (24%)	14 (25%)
Aberdeen	9 (8%)	9 (8%)	10 (9%)	8 (7%)	5 (9%)	5 (9%)	4 (7%)	4 (7%)
Median (IQR) age (years)	32 (22–47)	32 (22–45)	30 (21–44)	35 (26–47)	29 (20–44)	32 (22–45)	36 (25–49)	33 (27–46)
Median (IQR) weight (kg)	70 (60–84)	68 (60–80)	68 (57–83)	70 (62–80)	70 (55–86)	68 (60–81)	70 (63–83)	70 (60–80)
Women	64 (58%)	67 (60%)	65 (59%)	66 (59%)	31 (56%)	34 (61%)	33 (60%)	33 (59%)
<b>Clinical characteristics</b>								
Time from ingestion to treatment, <8 h	64 (58%)	64 (57%)	65 (59%)	63 (57%)	32 (58%)	33 (59%)	32 (58%)	31 (55%)
Median (IQR) ingested paracetamol (mg/kg)	229 (167–328)	244 (184–357)	224 (167–327)	243 (169–353)	224 (168–333)	233 (184–312)	233 (169–308)	264 (182–417)
Ingested paracetamol $\geq 16$ g	58 (53%)	58 (52%)	57 (51%)	59 (53%)	28 (51%)	29 (52%)	30 (55%)	29 (52%)
Nomogram at 4 h*								
100–149 mg/L	22 (20%)	26 (23%)	28 (25%)	20 (18%)	12 (22%)	16 (29%)	10 (18%)	10 (18%)
150–199 mg/L	19 (17%)	18 (16%)	22 (20%)	15 (14%)	11 (20%)	11 (20%)	8 (15%)	7 (13%)
$\geq 200$ mg/L	35 (32%)	41 (37%)	41 (37%)	35 (32%)	21 (38%)	20 (36%)	14 (25%)	21 (38%)
Alcohol ingested	52 (47%)	59 (53%)	58 (52%)	53 (48%)	28 (51%)	30 (54%)	24 (44%)	29 (52%)
Other drugs ingested								
Opiates	11	21	12	20	4	8	7	13
Antihistamines	4	1	3	2	3	0	1	1
Nutritional deficiency	15 (14%)	15 (13%)	17 (15%)	13 (12%)	8 (15%)	9 (16%)	7 (13%)	6 (11%)
Debilitating disease	3 (3%)	3 (3%)	2 (2%)	4 (4%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Chronic alcohol use	37 (34%)	39 (35%)	35 (32%)	41 (37%)	16 (29%)	19 (34%)	21 (38%)	20 (36%)
Identified as high risk†	51 (46%)	52 (46%)	50 (45%)	53 (48%)	24 (44%)	26 (46%)	27 (49%)	26 (46%)
Median (IQR) alanine aminotransferase (IU/L)	20 (14–30)	20 (14–29)	21 (14–34)	19 (14–26)	21 (14–37)	21 (14–30)	19 (14–26)	19 (14–26)

Data are number of patients (%) or median (IQR). \*Nomogram assessments are from the paracetamol risk nomogram for patients with paracetamol samples between 4 h and 24 h after ingestion. †According to the British National Formulary, 2009;<sup>16</sup> no patients were taking enzyme-inducing drugs.

Table 1: Baseline characteristics

We analysed grade of anaphylaxis with proportional odds logistic regression. We also did sensitivity analyses, unadjusted analyses, and analyses adjusting for the interaction between treatment groups, but none of these affected the conclusions. For the microRNA analysis, we did two-way analysis of variance on log-transformed data.

This trial is registered with the European Clinical Trials Database (EudraCT number 2009-017800-10) and ClinicalTrials.gov (identifier NCT01050270).

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all study data and the corresponding author had responsibility for the decision to submit for publication.

### Results

Between Sept 6, 2010, and Dec 31, 2012, 3311 patients presented with paracetamol overdose and were screened for inclusion in the study; 1539 were judged potentially suitable for acetylcysteine treatment, 369 were eligible for inclusion, and 222 underwent randomisation (figure 1). Table 1 shows the number of patients at each participating centre and their baseline demographic features, according to treatment allocation. Groups were well balanced at baseline with respect to age, sex, weight, ingested paracetamol dose, paracetamol nomogram band, other risk factors for paracetamol hepatic toxic effects, and other ingested agents (including opiates and antihistamines) or regular prescribed drugs. Of 19 patients who withdrew from the study before completion of treatment (figure 1), 14 were below treatment lines and five refused to complete the study. No emergency unmasking took place.

Table 2 presents available outcome data for patients who had vomiting or retching or used rescue medication within 2 h of acetylcysteine initiation. This primary outcome was significantly less frequent in patients who received the shorter modified acetylcysteine regimen compared with those allocated to the standard schedule (adjusted odds ratio 0.26, 97.5% CI 0.13–0.52;  $p < 0.0001$ ) and in those treated with ondansetron versus placebo (0.41, 0.20–0.80;  $p = 0.003$ ). No interaction was noted between the two treatment comparisons ( $p = 0.69$ ).

The secondary outcome of nausea (Likert  $> 4$  of 11), vomiting, or retching up to 12 h after the start of treatment was less common in patients who received the shorter modified acetylcysteine regimen compared with those who were allocated the standard protocol (adjusted odds ratio 0.37, 97.5% CI 0.18–0.79;  $p = 0.003$ ). Similarly, the treatment difference was significant for those pretreated with ondansetron versus individuals who received placebo (0.35, 0.17–0.74;  $p = 0.002$ ). The Kaplan-Meier plot for time to antiemetic rescue is shown in figure 2.

	Number with outcome	Total	Adjusted data*		Unadjusted data†	
			Odds ratio (97.5% CI)	p	Odds ratio (97.5% CI)	p
<b>Primary outcome‡</b>						
Acetylcysteine regimen						
Modified	39	108	0.26 (0.13–0.52)	<0.0001	0.29 (0.15–0.55)	<0.0001
Standard	71	109	..	..	..	..
Ondansetron pretreatment						
Active	45	109	0.41 (0.20–0.80)	0.003	0.43 (0.22–0.82)	0.004
Placebo	65	108	..	..	..	..
<b>Secondary outcome§</b>						
Acetylcysteine regimen						
Modified	60	101	0.37 (0.18–0.79)	0.003	0.39 (0.19–0.80)	0.004
Standard	80	102	..	..	..	..
Ondansetron pretreatment						
Active	58	99	0.35 (0.17–0.74)	0.002	0.37 (0.18–0.76)	0.002
Placebo	82	104	..	..	..	..

\*Adjusted by the variables in the minimisation algorithm, and centre. †Obtained with a model in which only treatment and regimen were included. ‡Patients with vomiting or retching or given rescue medication, from 0 h to 2 h. §Patients with vomiting or retching or nausea, from 0 h to 12 h.

Table 2: Primary and secondary nausea and vomiting outcomes

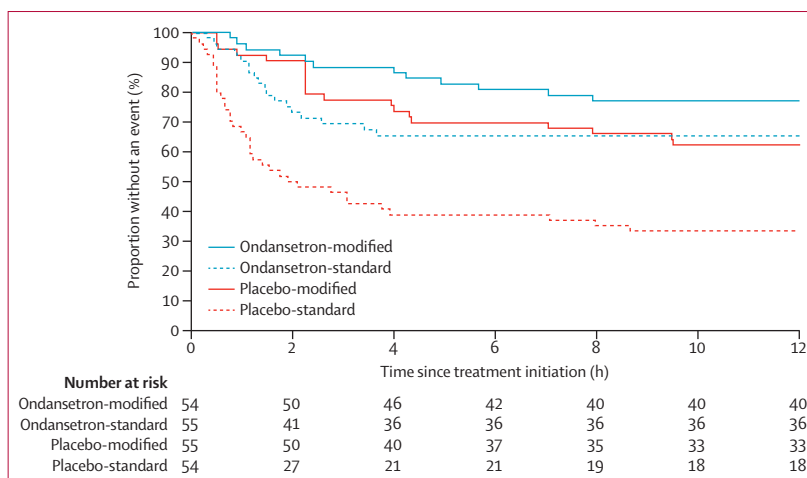


Figure 2: Kaplan-Meier plot of patients who did not need antiemetic rescue for 0–12 h, by treatment regimen

Anaphylactoid symptoms were recorded in 133 (64%) of 208 patients overall, and these were classified as mild in 79 (38%), moderate in 18 (9%), and severe in 36 (17%). Anaphylactoid symptoms were absent in 50 (46%) of 108 patients allocated to the shorter modified acetylcysteine regimen and 25 (25%) of 100 who received the standard treatment. Fewer patients allocated to the shorter modified acetylcysteine regimen had clinically relevant grade 3 (severe) reactions needing either drug treatment or interruption of the acetylcysteine infusion (five of 108, five treated, two interrupted) compared with those assigned to the standard regimen (31 of 100, 31 treated, 26 interrupted; adjusted common odds ratio

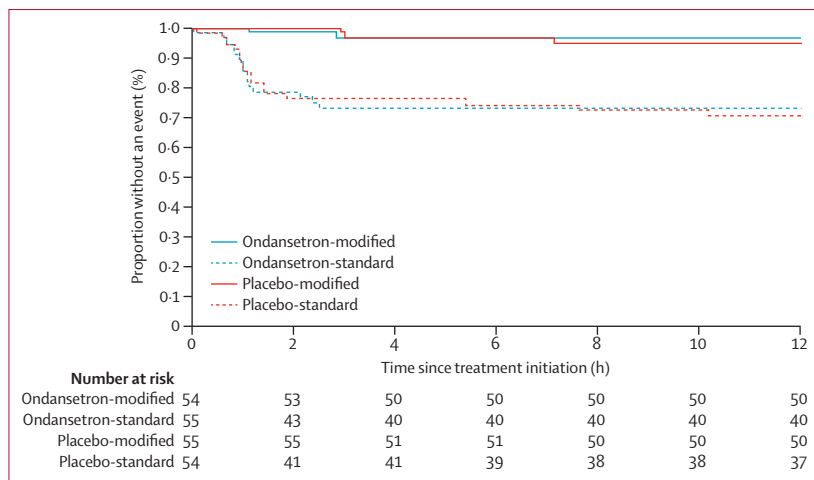


Figure 3: Kaplan-Meier plot of patients who did not need treatment for anaphylactoid reactions for 0–12 h, by treatment regimen

0.23, 97.5% CI 0.12–0.43;  $p < 0.0001$ ); this finding was not affected by ondansetron pretreatment (17 of 103 vs 19 of 105 on placebo; 1.40, 0.78–2.53;  $p = 0.198$ ). The Kaplan-Meier plot for time to anaphylactoid rescue is shown in figure 3.

A 50% increase in activity of alanine aminotransferase 20.25 h after initiation of the acetylcysteine infusion was recorded in 22 (11%) of 201 patients, 13 who were allocated to the standard acetylcysteine regimen and nine of those assigned to the shorter modified schedule (adjusted odds ratio 0.60, 97.5% CI 0.20–1.83). This escalation in activity of alanine aminotransferase was more frequent in patients pretreated with ondansetron (16 of 100) compared with those receiving placebo (six of 101; 3.30, 1.01–10.72;  $p = 0.024$ ; appendix p 1). An increased frequency in the doubling of alanine aminotransferase (post-hoc analysis) was noted in patients pretreated with ondansetron (14 of 100) compared with those given placebo (five of 101; adjusted odds ratio 3.47, 97.5% CI 0.95–12.66;  $p = 0.031$ ). At the end of acetylcysteine infusion, five of 202 patients had activity of alanine aminotransferase greater than 1000 IU/L (two ondansetron-modified, one ondansetron-standard, two placebo-standard) and 25 of 201 people had an international normalised ratio higher than 1.3 (seven ondansetron-modified, seven ondansetron-standard, two placebo-modified, nine placebo-standard); no difference was recorded between treatment allocations (appendix p 1). Six (6%) patients allocated to the shorter modified acetylcysteine regimen received additional acetylcysteine infusions (post-hoc analysis) compared with 11 (10%) of those allocated to the standard schedule (adjusted odds ratio 0.46, 97.5% CI 0.13–1.68;  $p = 0.180$ ); 12 (11%) patients assigned to ondansetron pretreatment received additional infusions of acetylcysteine compared with five (5%) of those who received placebo beforehand (2.82, 0.76–10.53;  $p = 0.077$ ). No patients developed acute kidney injury.

See Online for appendix

In a post-hoc analysis of miR-122 (normalised for hsa-let-7d-5p) in 124 patients from Edinburgh, no difference was apparent at the end of either of the acetylcysteine regimens (standard, median  $\Delta\Delta Ct$  0.5 [IQR 0.2–3.4] vs modified,  $\Delta\Delta Ct$  1.1 [0.4–2.4];  $p = 0.79$ ). However, miR-122 was higher in patients pretreated with ondansetron than those who received placebo ( $\Delta\Delta Ct$  1.3 [0.4–3.4] vs  $\Delta\Delta Ct$  0.6 [0.2–2.0];  $p = 0.03$ ).

A total of 174 adverse events were reported by 170 participants across all groups. Most of these were expected reactions: 92 gastrointestinal and 13 hepatobiliary. One patient died, an elderly man, who recovered from paracetamol overdose but died 20 days after the end of treatment from previously diagnosed malignant disease.

## Discussion

The findings of our study show that a shorter (12 h) modified acetylcysteine regimen substantially reduces the frequency of both vomiting and serious anaphylactoid reactions when compared with the standard schedule for acetylcysteine administration (duration 20.25 h). The shorter duration of acetylcysteine infusion offers simpler administration, a probable reduction in administration errors, and a potential decrease in the length of the hospital stay. However, further clinical trials and studies of novel<sup>23</sup> and traditional<sup>25</sup> biomarkers are needed to confirm the efficacy and safety of the modified regimen before widespread adoption into clinical practice.

Vomiting was reduced by pretreatment with ondansetron, thus increasing the antiemetic benefit of the modified regimen, but this fall was associated with an unexpected increase in activity of aminotransferase. Potential mechanisms include either alterations in paracetamol metabolism or glutathione synthesis or a direct effect of ondansetron on a stressed liver, although a type 1 error is possible. Although these effects did not seem to be clinically important, further research is needed before ondansetron is used routinely for this indication.

Our study findings confirm that symptomatic adverse effects, particularly vomiting and anaphylactoid reactions (panel 2), are associated commonly with the standard UK regimen for acetylcysteine administration. These events are unpleasant, result in treatment interruption and delay, and can cause patients to refuse or even be denied treatment in subsequent presentations.<sup>1</sup> Such effects can be severe, with 28 (13%) patients in our trial having their treatment interrupted. Anaphylactoid reactions occur most commonly at lower concentrations of paracetamol and, thus, are more likely to be seen in patients now treated under new UK guidance.<sup>8,12,29,30</sup>

Not all patients eligible for treatment with acetylcysteine were included in our study (figure 1), mostly because of a staggered overdose, alcohol intoxication, or drowsiness. These exclusions are unlikely to affect our main findings.

**Panel 2: Research in context****Systematic review**

We searched PubMed and the Cochrane Database for clinical trials and systematic reviews of acetylcysteine treatment for paracetamol overdose and antiemetic pretreatment published between January, 1975, and December, 2008, with the terms “paracetamol”, “acetaminophen”, “overdose”, “acetylcysteine”, and “anti-emetic”. In 2006, the Cochrane Collaboration published a systematic review of evidence for management of paracetamol overdose.<sup>26</sup> The efficacy of different oral and intravenous acetylcysteine regimens did not differ with respect to prevention of hepatotoxic effects but these drugs were associated with adverse events such as vomiting and anaphylactoid reactions. The conclusion stated that the best method of administration of acetylcysteine and the most beneficial dose had not been reported. No published trials were identified of antiemetic prophylaxis before administration of intravenous acetylcysteine treatment. Although high-dose metoclopramide was effective at prevention of emesis before oral acetylcysteine in one small study,<sup>27</sup> this drug was associated with a high incidence of extrapyramidal adverse effects in young adults, making it unsuitable for this patient group. For prophylaxis of nausea and vomiting in other settings (eg, postoperative), more trial evidence was available for efficacy of ondansetron than for other antiemetics, in a Cochrane Collaboration systematic review.<sup>28</sup> Our search did not identify any studies that have addressed the need for treatment interruption because of adverse events.

**Interpretation**

We have shown in our study that a 12 h intravenous regimen of acetylcysteine, with an initial loading dose over 2 h, is effective at reducing the incidence of vomiting and anaphylactoid reactions, compared with the standard 20-25 h intravenous acetylcysteine schedule. Our trial was not powered to assess non-inferiority of the modified protocol, but no difference in efficacy was recorded between groups. Ondansetron pretreatment was effective at reducing vomiting but had no effect on anaphylactoid reactions and was associated with a rise in the amount of aminotransferase. Other key advantages of the 12 h regimen include simplicity and substantial reductions in the need to treat anaphylactoid reactions and to interrupt the acetylcysteine infusion because of adverse effects, both of which complicate and prolong hospital care. This shorter and simpler protocol, if proven to be non-inferior to the conventional acetylcysteine regimen, has considerable potential to reduce adverse effects and length of hospital stay in patients requiring acetylcysteine treatment after a paracetamol overdose.

However, efficacy and safety of the modified acetylcysteine regimen in staggered overdoses will need to be assessed.

Some patients who were included in our study initially were withdrawn later when paracetamol concentrations showed they did not need acetylcysteine. These individuals featured in the analysis if they were still

receiving acetylcysteine at the time of primary outcome assessment. These factors are unlikely to affect the generalisability of our results.

In view of the complexity of the standard acetylcysteine regimen, a double-blind comparison with the shorter modified protocol was not feasible. The potential regimens are complex, requiring either five infusions in the standard procedure (for 15 min, 1 h 45 min, 2 h 15 min, 7 h 45 min, and 8 h 15 min) or two concurrent infusion regimens for every patient.

The open nature of the comparison might have led to observer bias in the assessment of adverse drug reactions. However, the primary outcome—the noted absence of vomiting, retching, and use of antiemetic rescue treatment—is objective, as is the measurement of concentrations of aminotransferases. Assessment of anaphylactoid reactions was made as objective as possible by use of a detailed scoring system, including patient self-rating at prespecified times.

Although our trial is, to our knowledge, the largest randomised controlled trial of paracetamol poisoning ever undertaken, it was not sufficiently powered to show non-inferiority of the modified acetylcysteine regimen for prevention of hepatotoxic effects. We used a 50% increase in alanine aminotransferase concentration as a surrogate marker of liver damage, because more severe liver dysfunction is rare (although rises in the international normalised ratio and activity of alanine aminotransferase >1000 IU/L were also measured). Doubling of alanine aminotransferase and miR-122 findings were similar for both acetylcysteine regimens, but both measurements were more frequently abnormal in patients administered ondansetron. 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 (appendix p 1). We believe this patient group could be discharged early, if findings of a larger study confirm the absence of inferiority.

The shorter modified acetylcysteine regimen caused significantly less nausea, vomiting, and anaphylactoid reactions, with diminished requirement for rescue treatment. This approach offers potentially major advantages for patients, staff, and health-care institutions. Further research in larger numbers of patients is needed to confirm the efficacy of the shorter acetylcysteine regimen.

**Contributors**

HKRT, DNB, and SHLT had the idea for the trial and produced the initial draft. ME, JWD, AG, SCL, and DJW developed the protocol. HKRT, DNB, SHLT, DJW, ME, JWD, EAS, AV, JGC, and AG recruited patients and collected data. JC was trial manager and AR, IB and SCL were the trial's statisticians. AR and SCL analysed the final trial results and produced the figures. ADBV and JWD analysed miR-122 samples. DNB drafted the report, and all authors contributed to the final version.

**Conflicts of interest**

DJW has been a member of the Agency Board at MHRA since Sept 1, 2013. SHLT is a member of the UK Commission on Human Medicines. All other authors declare that they have no conflicts of interest.

**Acknowledgments**

We thank our colleagues in the treating hospitals who assisted with recruitment and patients' management, the Data Monitoring Committee (R E Ferner, J E Gray, and K Simpson), and the programmers in the Edinburgh Clinical Trials Unit. The trial was funded by Chief Scientist Office, Scotland (award CZB/4/722).

**References**

- 1 Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. *BMJ* 2011; **342**: d2218.
- 2 Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 2008; **359**: 285–92.
- 3 Health and Social Care Information Centre. Hospital episode statistics, admitted patient care—England 2011–12: primary diagnosis, 4 characters table [xls]. Nov 1, 2012. <http://www.hscic.gov.uk/catalogue/PUB08288> (accessed May 13, 2013).
- 4 Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. *Clin Toxicol* 2012; **50**: 911–1164.
- 5 Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979; **2**: 1097–100.
- 6 Prescott LF, Ballantyne A, Park J, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. *Lancet* 1977; **310**: 432–34.
- 7 Smilkstein MJ, Knapp JL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose: analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988; **319**: 1557–62.
- 8 Commission on Human Medicines Paracetamol Expert Group. Benefit risk profile of acetylcysteine in the management of paracetamol overdose. April 25, 2013. <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con184709.pdf> (accessed May 13, 2013).
- 9 Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. *Clin Toxicol* 2012; **50**: 91–98.
- 10 Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* 2004; **12**: 10–15.
- 11 Pakravan N, Waring WS, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. *Clin Toxicol* 2008; **46**: 697–702.
- 12 Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol* 2009; **47**: 81–88.
- 13 Ferner RE, Langford NJ, Anton C, Hutchings A, Bateman DN, Routledge PA. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions using acetylcysteine as an example. *Br J Clin Pharmacol* 2001; **52**: 573–77.
- 14 Hayes BD, Klein-Schwartz W, Doyon S. Frequency of medication errors with 21-hour acetylcysteine for acetaminophen overdose. *Ann Pharmacother* 2008; **42**: 766–70.
- 15 Fathalla S, Hill S, Hodson K, Salih IS, Thomas SHL. Inaccuracies in acetylcysteine dose calculation or infusion rates in patients with and without anaphylactoid reactions. *Clin Toxicol* 2008; **46**: 401–02.
- 16 British Medical Association and the Royal Pharmaceutical Society. British National Formulary, 58th edn. London: BMJ Group and RPS publishing, 2009.
- 17 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**: 402–08.
- 18 Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT. The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdose. *Eur J Clin Pharmacol* 1989; **37**: 501–06.
- 19 Thanacoody HKR, Gray A, Dear JA, et al. Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning study (SNAP). *BMC Clin Pharmacol* 2013; **14**: 20.
- 20 British Medical Association and the Royal Pharmaceutical Society. British National Formulary, 64th edn. London: BMJ Group and RPS publishing, 2012.
- 21 Simons FER, Arduoso LRF, Bilò MB, et al, for the World Allergy Organization. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011; **4**: 13–36.
- 22 Whyte IM, Buckley NA, Reith DM, Goodhew I, Seldon M, Dawson AH. Acetaminophen causes an increased international normalized ratio by reducing functional factor VII. *Ther Drug Monit* 2000; **22**: 742–48.
- 23 Antoine DJ, Dear JW, Starkey Lewis PJ, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. *Hepatology* 2013; **58**: 777–87.
- 24 Starkey Lewis PJ, Dear J, Platt V, et al. Circulating microRNAs as potential markers of human drug-induced liver injury. *Hepatology* 2011; **54**: 1767–76.
- 25 Al-Hourani K, Mansi R, Pettie J, Dow M, Bateman DN, Dear JW. The predictive value of hospital admission serum alanine transaminase activity in patients treated for paracetamol overdose. *QJM* 2013; **106**: 541–46.
- 26 Brok J, Buckley NA, Gluud C. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev* 2006; **2**: CD003328.
- 27 Wright RO, Anderson AC, Lesko SL, Woolf AD, Linakis JG, Lewander WJ. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. *J Toxicol Clin Toxicol* 1999; **37**: 35–42.
- 28 Carlisle J, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006; **3**: CD004125.
- 29 Waring WS, Pettie JM, Dow MA, Bateman DN. Paracetamol appears to protect against N-acetylcysteine-induced anaphylactoid reactions. *Clin Toxicol* 2006; **44**: 441–42.
- 30 Schmidt LE. Identification of patients at risk of anaphylactoid reactions to N-acetylcysteine in the treatment of paracetamol overdose. *Clin Toxicol* 2013; **51**: 467–72.