seriously ill or not. Therefore, the bill that was approved by the Senate on Dec 12, 2013 and enacted by the Chamber of Representatives on Feb 13, 2014 makes no reference to any age limit.[16] This situation contrasts with the Dutch law,[2] which allows terminally ill children to seek euthanasia from the age of 12 years, with full parental consent required up to 16 years of age.

This bill[16] rests on the same fundamentals as the 2002 Act on Euthanasia,[3] including specifics of the request, responsibility of the physician, and the notions of serious and incurable disorder, hopeless situation, and unbearable suffering. Although it extends its application to children, it restricts its scope by excluding psychiatric disorders and, more importantly, by specifically addressing the issue of capacity for discernment, which should be assessed carefully by a multidisciplinary paediatric team, including a clinical psychologist. The parents must agree to the request. The emphasis on the child's personal competence unequivocally excludes children with altered consciousness, intellectual disability, young children, and neonates. It stands in stark contrast with the so-called Groningen protocol for newborn euthanasia,[17] a procedure used widely in the Netherlands that results in active life termination of a newborn infant with very poor prognosis or unbearable suffering, in agreement with the parents. The Belgian bill also unambiguously excludes all other proxy requests, whether placed by the parents or medical teams. It must be recognised that euthanasia does not correspond to palliative sedation treatment that aims to control refractory symptoms, which can possibly, but not deliberately, cause death.[18]

This recent societal and political move can be anticipated to fuel international debate about end-of-life decisions in children and consequently to improve palliative care further. However, it is likely to concern a very small number of clinical situations in Belgium.

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We are all invited members of the Commission on Ethics and End-of-Life of the Belgian Royal Academy of Medicine. We declare that we have no competing interests.

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Treatment of paracetamol overdose: room for improvement?

Published Online November 28, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62303-X

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Hepatic toxic effects associated with paracetamol (acetaminophen) overdose are an important clinical problem, being the commonest cause of acute liver failure in the UK and USA.[1,2] For more than 30 years, treatment with acetylcysteine has remained the cornerstone antidote for paracetamol overdose.[3,4] Clinical management in this patient group has remained largely unchanged over that time and, indeed, oral and intravenous acetylcysteine regimens have not undergone formal comparative clinical trials. Furthermore, the precise dose refinement of acetylcysteine use is supported by scant evidence. Despite the importance

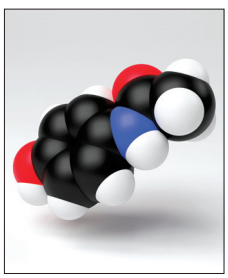
of acetylcysteine administration in a timely fashion and its undoubted effectiveness, use of the drug is hindered by frequent adverse effects related to dose and infusion rate, inaccurate administration by doctors, and poor adherence by patients.[5,6]

In *The Lancet*, Nicholas Bateman and colleagues[7] assess new regimens for administration of intravenous acetylcysteine in patients with paracetamol overdose. They did a randomised controlled trial to investigate the effects of a shorter modified acetylcysteine dosing regimen, versus the current standard protocol, on adverse events, with or without antiemetic pretreatment. The modified acetylcysteine regimen (at a shorter infusion time of 12 h *vs* 20·25 h) substantially reduced the frequency of adverse events. Vomiting, retching, and need for rescue antiemetic treatment was reported in 39 of 108 patients assigned to the shorter protocol compared with 71 of 109 allocated to the standard regimen (adjusted odds ratio 0·26, 97·5% CI 0·13–0·52). Pretreatment with the antiemetic ondansetron saw 45 of 109 patients have vomiting, retching, or need for rescue antiemetic, versus 65 of 108 who were given a placebo (0·41, 0·20–0·80). However, during the course of the trial, changes to treatment guidelines were introduced by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) that lowered the threshold for acetylcysteine treatment for paracetamol overdose.[8] Whether this change affected the efficacy of the modified acetylcysteine regimen for prevention of adverse effects is unclear and will need to be addressed in future studies.

Pretreatment with the antiemetic drug ondansetron lowered the rate of acetylcysteine-related adverse effects but was associated with higher activity of alanine aminotransferase when compared with placebo (adjusted odds ratio 3·30, 97·5% CI 1·01–10·72; p=0·024). MicroRNA analysis confirmed that the source of alanine aminotransferase was likely to be hepatic. The mechanism of this interaction between paracetamol and ondansetron is unclear. However, it highlights how cotreatment and other environmental factors can increase the risk of liver injury in patients with paracetamol overdose, underlining that we do not fully understand the mechanism of liver injury with paracetamol.

Use of a modified acetylcysteine regimen to reduce adverse events must always be balanced by the need for efficacy, and this factor is acknowledged by Bateman and colleagues. Although their trial aimed to assess the effect on acetylcysteine-related adverse events, the results are also encouraging from an efficacy perspective. According to current practice, liver injury is measured by activity of alanine aminotransferase, which has its own limitations as a biomarker of liver injury. In particular, alanine aminotransferase has a low negative predictive value in the patient population, and few data exist in relation to its formal qualification for human drug-induced liver injury versus histology. Bateman and colleagues[7] make this point and suggest that novel mechanistic biomarkers, used in parallel with current markers, could offer a route for assessment of acetylcysteine efficacy and patient discharge.[9,10] However, qualification and clinical adoption and implementation of novel biomarkers from prospective studies is a lengthy and challenging process, despite substantial efforts from large international biomarker consortia, such as SAFE-T (Safer and Faster Evidence-Based Translation) and PSTC (Predictive Safety Testing Consortium).[11] Therefore, novel endpoints are likely to retain their experimental status in the near future; the effect of a shorter modified acetylcysteine regimen on the kinetics of novel biomarkers and established indicators warrants further investigation if they are to serve as surrogates for efficacy.[12]

In conclusion, Bateman and colleagues have shown that a shorter modified acetylcysteine regimen can reduce the adverse effects associated with infusion of this drug. This work is only one part of the benefit/risk assessment of the use of acetylcysteine in paracetamol overdose. Their study needs to be followed-up with a larger randomised controlled trial designed to show not only that the modified regimen can reduce acetylcysteine-related adverse effects, but also that the shorter regimen is either non-inferior or equivalent to the current MHRA-approved acetylcysteine dosing regimen for prevention and treatment of paracetamol-associated liver injury. This additional work could provide the opportunity to address other important questions. First, is the new regimen cost effective? Second, does it reduce medication errors, clinician workload, and length of hospital stay? Finally, are new biomarkers such as miRNA-122 more sensitive and specific for detection of liver injury than are aminotransferases? In the meantime, the treatment of paracetamol overdose should follow the updated MHRA guidance.[8] Since some patients who have taken a paracetamol overdose will suffer nausea and vomiting,



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Paracetamol

which might or might not be associated with use of acetylcysteine, it could be prudent in this specific clinical setting to avoid use of ondansetron, because other antiemetics are available.

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We declare that we have no conflicts of interest.

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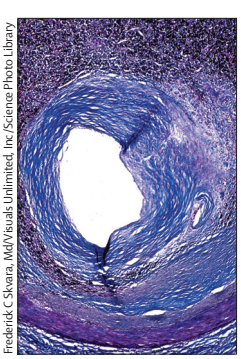
A new frontier in atherosclerotic coronary imaging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Published Online November 11, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61911-X

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Ischaemic heart disease resulting from rupture of atherosclerotic plaques is a major cause of death worldwide. Precisely why a plaque ruptures remains a mystery. However, in *The Lancet*, Nikhil Joshi and colleagues' findings[1] suggest that we are close to being able to detect when rupture is about to occur.

The simple and inexpensive ^{18}F-sodium fluoride (^{18}F-NaF) PET radioisotope, used for 30 years to image bone formation, was found to signify metabolically active calcification in the aorta by Derlin and colleagues[2] and in the coronary arteries by Beheshti,[3] Dweck,[4] and Li,[5] and their colleagues. In their landmark article, Joshi and coworkers move this nascent field much farther forward.[1] They prospectively studied 40 patients with recent myocardial infarction (mean 8 days earlier) with invasive coronary angiography, CT coronary angiography, coronary calcium scoring, and cardiac gated PET-CT with ^{18}F-NaF and ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Using invasive coronary angiography as the gold standard for determining the culprit plaque, the area of greatest ^{18}F-NaF uptake in the coronary arteries localised the plaque in 37 of 40 patients (maximum tissue-to-background ratio in the culprit plaque 1·66 [1·40–2·25] *vs* highest non-culprit plaque 1·24 [1·06–1·38]). By contrast, interpretation of ^{18}F-FDG PET-CT images in the same cohort was technically difficult because of the frequent overlap of myocardial ^{18}F-FDG uptake with the adjacent coronary arteries. Of the 55% of vascular territories that were interpretable by ^{18}F-FDG, only a weak correlation was seen with culprit plaque identification.

A second cohort of 40 patients with stable angina underwent the same imaging tests and an intracoronary ultrasound. 18 patients had one or more plaques with high ^{18}F-NaF uptake, defined as at least 25% greater than a proximal reference lesion. Intracoronary ultrasound identified that microcalcification, necrotic core size, and positive remodelling correlated strongly with plaques of high ^{18}F-NaF activity.

Histological correlation was assessed in a third cohort of nine patients who underwent carotid endarterectomy at a mean of 17 days after clinical symptoms. Ex-vivo PET-CT was done on the removed carotid atherosclerotic tissue. Macroscopic plaque rupture was present in each patient, all localised to areas of high ^{18}F-NaF uptake. Plaques with increased ^{18}F-NaF uptake had substantially larger necrotic cores, more cell death and macrophage infiltration, and, as measured by alkaline phosphatase and osteocalcin staining, more active calcification than those that did not.

With the strong in-vivo correlates of coronary plaque rupture seen on intracoronary ultrasound in patients with stable angina, and histological confirmation of

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

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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 (9/110) and shorter modified (13/112) regimens (adjusted odds ratio 0·60, 97·5% CI 0·20–1·83); however, the proportion was higher with ondansetron (16/111) than with placebo (6/111; 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.[1,2] During 2011–12, more than 38 000 admissions for paracetamol poisoning were recorded in England[3] and, in 2011, at least 137 000 enquiries were made to US poisons centres about paracetamol exposure.[4] The toxic mechanisms of paracetamol—understood for more than 40 years—enabled development of a specific antidote, acetylcysteine, in the 1970s.[5–7] Intravenous regimens[5] are now in widespread use, with between 18 000 and 40 000 treatment courses administered in the UK annually.[8] However, these regimens have never undergone formal dose-ranging studies.[9] 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%.[10–12]

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.[13–15] 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).[16] 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

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This online publication has been corrected. The corrected version first appeared at thelancet.com on December 9, 2013

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Panel 1: **Acetylcysteine regimens used in the study**

UK standard schedule (duration 20·25 h)[16]

- 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.[17] 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).[16] Monte Carlo modelling based on published data from patients indicates that acetylcysteine concentrations at 20·25 h would be similar with the two regimens.[18,19] 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.[19] 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.[16,19] Exclusion criteria are shown in figure 1 and described elsewhere.[19] 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.[16] 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).[16]

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,[19,20] 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 2×2 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).[16] 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.

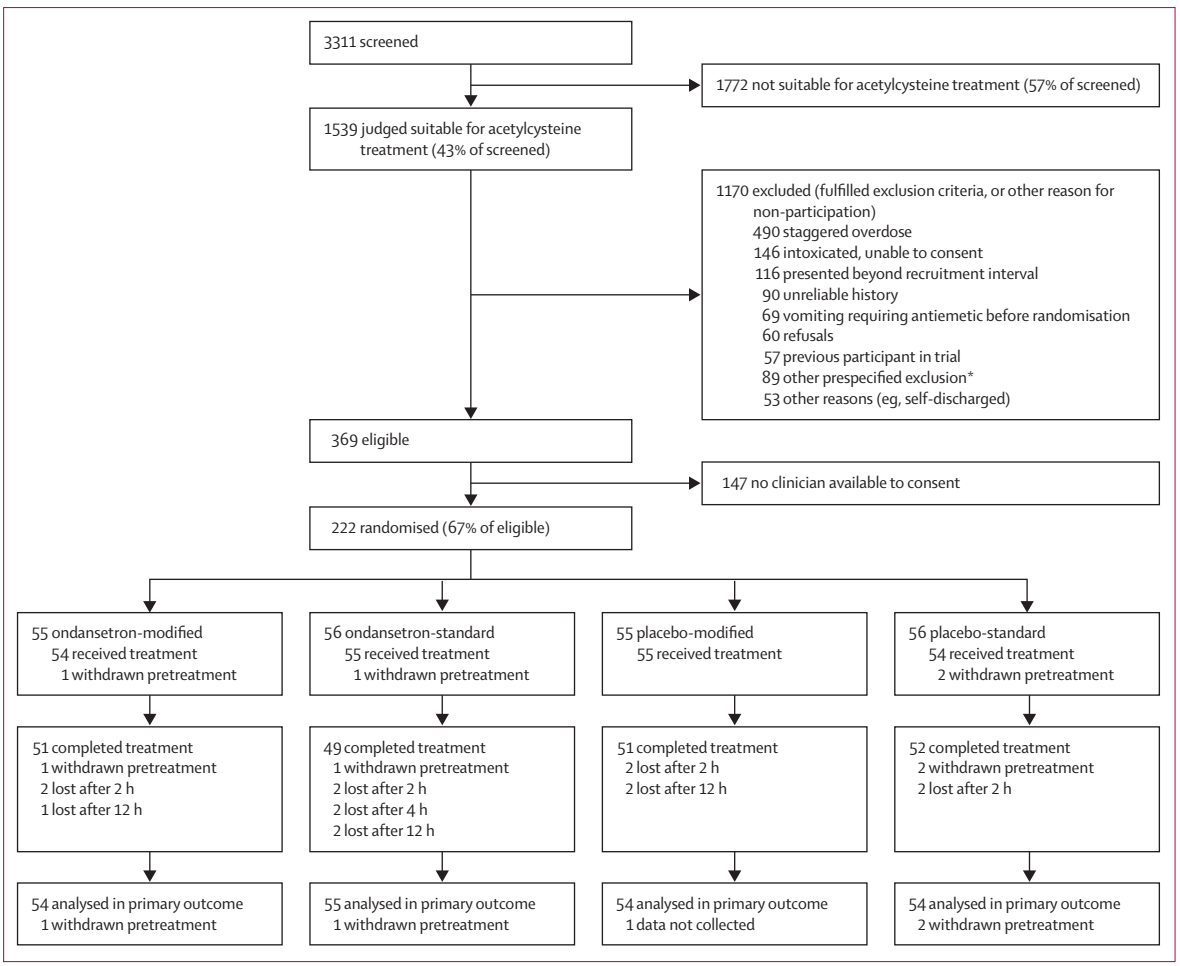

Figure 1: **Trial profile**
One patient had incomplete data at 2 h but completed the trial. *Other reasons for exclusion: unlikely to complete treatment (n=27), life-threatening illness (17), detained under the Mental Health Act (15), permanent cognitive impairment (9), pregnant (6), on anticoagulants (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.[19] 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.[19,21] 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.[11,22] 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.[23,24]

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=0·025). 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.[19] 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)				
Demographics								
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%)
Clinical characteristics								
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 ≥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%)
≥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	56 (51%)	71 (63%)	57 (51%)	70 (63%)	25 (45%)	32 (57%)	31 (56%)	39 (70%)
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;[16] 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
Primary outcome‡						
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	..	..	..	..
Secondary outcome§						
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**

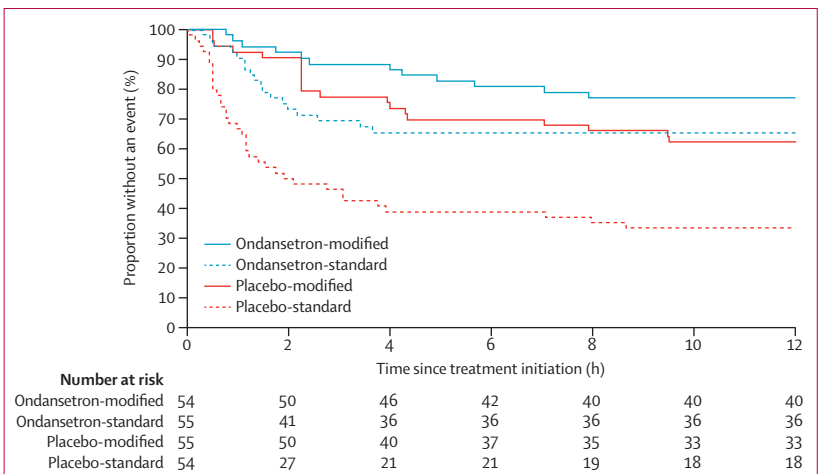

Figure 2: **Kaplan-Meier plot of patients who did not need antiemetic rescue for 0–12 h, by treatment regimen**

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

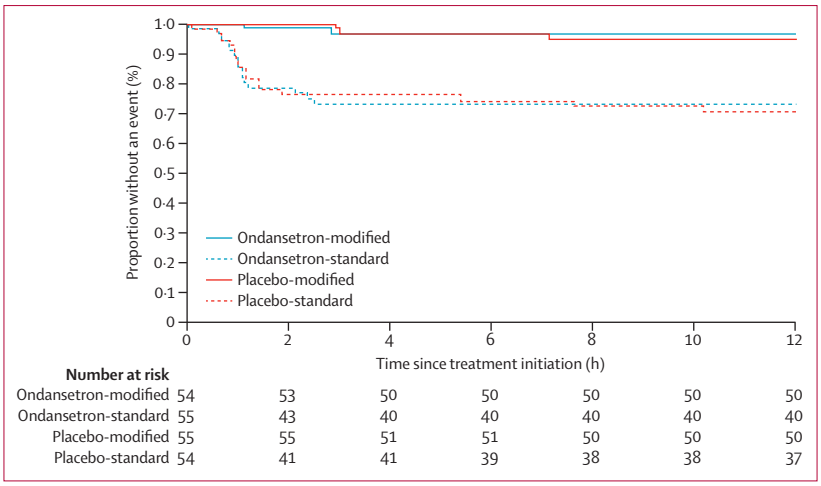

Figure 3: **Kaplan-Meier plot of patients who did not need treatment for anaphylactoid reactions for 0–12 h, by treatment regimen**

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, nine who were allocated to the standard acetylcysteine regimen and 13 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 ΔΔCt 0·5 [IQR 0·2–3·4] *vs* modified, ΔΔCt 1·1 [0·4–2·4]; p=0·79). However, miR-122 was higher in patients pretreated with ondansetron than those who received placebo (ΔΔCt 1·3 [0·4–3·4] *vs* ΔΔCt 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[23] and traditional[25] 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.[1] 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.[8,12,29,30]

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.[26] 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,[27] 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.[28] 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).

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