Bateman DN, Dear JW, Thomas SHL.

New regimens for intravenous acetylcysteine, where are we now?

***Clinical Toxicology* 2016, 54(2), 75-78.**

New regimens for intravenous acetylcysteine, where are we now?

D Nicholas Bateman, [1] James W. Dear[1] and Simon HL Thomas[2]

[1]Pharmacology and Toxicology, University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, EH16 4TJ, United Kingdom

[2]Medical Toxicology Centre, Institute of Cellular Medicine, Newcastle University, Newcastle NE2 7HH

Address for correspondence
Professor D. Nicholas Bateman,
Honorary Professor of Clinical Toxicology,
Pharmacology and Toxicology,
University/BHF Centre for Cardiovascular Science
University of Edinburgh,
Edinburgh,
EH16 4TJ,
UK.
E-mail: drnickbateman@gmail.com

Abstract

Acetylcysteine has been used as a treatment for paracetamol overdose as a 20.25 or 21 h infusion for nearly 40 years. These regimens give 50% of the dose in the first 15 min or 1 h, and are associated with high rates of adverse reactions.
A randomised controlled trial has demonstrated that a shorter (12 h) and simpler (2 infusions) acetylcysteine regimen using a slower initial infusion rate produces lower rates of adverse events than the original 20.25h regimen. However this study was not sufficiently large to show therapeutic equivalence as a hepatoprotective therapy in paracetamol overdose. Two further studies are now reported, which also suggest lower rates of adverse reactions with lower initial rates of acetylcysteine administration. These modified regimens can now be accepted as better tolerated, but it is unlikely that a randomised study of sufficient size to demonstrate non-inferiority of any novel regimen this would ever be funded. Against this background we suggest what can be done to establish the efficacy of these less toxic and potentially shorter alternative acetylcysteine regimens and to establish them into routine clinical use.

Background

Intravenous acetylcysteine has been used widely to treat paracetamol (acetaminophen) poisoning for almost 40 years. (1, 2) An oral regimen is also effective and was previously the antidote of choice in the United States (3), but an appropriate intravenous preparation became available in 2004 and use of this is now much more common than oral therapy.(4)

The original dosing regimen for intravenous acetylcysteine, developed by Prescott and colleagues in Edinburgh (referred to here as the Prescott regimen), was empirically based and intended to deliver a large dose of antidote rapidly. It involved half the total dose of acetylcysteine (150 mg/kg) being given over 15 minutes with the remainder delivered over a further 20 hours (50 mg/kg over 4 h then 100 mg/kg over 16 h). While this regimen is undoubtedly effective and has saved countless lives, it has four major disadvantages: the high rate of

adverse reactions, the complexity of the infusion regimen, the risk or medication error and the prolonged duration of treatment.

Adverse reactions are common, especially nausea and vomiting and so-called anaphylactoid reactions. Risks of these were initially considered reasonable compared to those of untreated paracetamol poisoning. These anaphylactoid reactions, sometimes termed non allergic anaphylactic reactions (NAAR) are not allergic in nature, but arise from dose related stimulation of histamine release. They occur most commonly during, or soon after, the initial infusion, when acetylcysteine concentrations are at their highest. Importantly, they are more common in patients with lower paracetamol concentrations who have lower risk of paracetamol-induced hepatotoxicity (5-7).

In Canada, USA and subsequently in Australia, a one-hour initial infusion was adopted with the aim of reducing peak acetylcysteine concentrations and causing fewer adverse reactions. A randomised clinical trial in Australia, however, did not demonstrate a statistical difference in ADRs between a one-hour and a 15-minute initial infusion, although this trial was underpowered to demonstrate small clinically relevant differences. (8) Nevertheless, an initial 1 hour infusion was incorporated into the license for acetylcysteine in the UK in 2012 by the Medicines and Healthcare Products Regulatory Agency.(9) However comparing data collected before and after the change we found no reduction in the rates of medication use for treating adverse reactions. The only difference was that ADRs were delayed in those receiving the slower infusion.(7)

The complexity of the intravenous regimen, requiring 3 separate infusions, is a problem because this requires staff time to manage each infusion. Importantly dose calculation errors are common, in part arising from the complexity of the regimen. These may result in substantial overdose, and most deaths associated with acetylcysteine have occurred under these circumstances. (10) The duration of infusion (20.25 or 21 hours) is an important disadvantage because it leads to significant hospital bed occupancy that may not be necessary in all patients, especially those at lower risk. Given the pressures on hospital emergency

departments, enhancing tools to safely discharge patients earlier than is currently possible should be a clear research priority across all poisonings.

Modified intravenous acetylcysteine regimens

There has recently been increasing interest in making modifications to the intravenous acetylcysteine protocol. This is primarily to reduce adverse reactions, but also to simplify and shorten the regimen. However there are challenges in demonstrating that changes made are of clinical benefit. Ideally, new and current regimens would be compared using an adequately powered and well-designed randomised controlled trial. Such studies are difficult to organise and perform: even those adequately powered to demonstrate differences in adverse reaction rates require hundreds of participants. Ensuring that efficacy is maintained is especially difficult because adverse hepatic outcomes are rare with the currently used acetylcysteine regimens and thus clinical trials need to involve thousands of patients to demonstrate non-inferiority. Without evidence of comparative efficacy, however, regulatory authorities are unlikely to license novel acetylcysteine regimens.,

Although challenging, we have demonstrated that randomised controlled trials can be done successfully. We compared a novel 12 h regimen employing 2 sequential acetylcysteine infusions (100 mg/kg over 2 h, 200 mg/kg over 10h), the 'SNAP' regimen, with the standard Prescott approach.(11) This new method was designed to provide lower initial paracetamol concentrations with the aim of reducing adverse reactions and also to be shorter, potentially allowing earlier discharge from hospital for lower risk patients.(12)

This study was designed as a 4 arm factorial study, with the effects of ondansetron on rates of vomiting also studied. Predefined endpoints were used, based on a formal statistical calculation of the likely impact of additional antiemetic therapy, with data collected at predefined time points. Using this design, we showed a marked reduction in the frequency of both vomiting (adjusted odds ratio 0·26, 97·5% CI 0·13–0·52; p<0·0001) and anaphylactoid

reactions which required either treatment interruption or specific therapy (adjusted common odds ratio 0·23, 97·5% CI 0·12–0·43; p<0·0001) with the new regimen.(11)

It had been our original intention to obtain funding for a non-inferiority efficacy study, but funding bodies were unwilling to underwrite the size of trial we calculated was necessary to achieve this objective. Thus, the study we published was underpowered to assess comparative efficacy using standard criteria. In an attempt to address this we used an approach to hepatic toxicity not generally applied by others working in the area of paracetamol poisoning. This was to consider much smaller rises in ALT than the 1000 IU/L traditionally applied. Even doing this and using a novel microRNA biomarker miR-122 we could not separate the conventional and modified 12 h acetylcysteine regimens with respect to prevention of liver injury.

Although randomised controlled trials remain the gold standard, valuable information may be obtained from non-randomised studies, for example comparing data collected with a new regimen with historical data collected in the same unit or published in the literature. It is challenging, however, to ensure that comparisons made are valid and without confounding or bias. This is especially true for assessing adverse reactions, where symptoms may be subjective and different methodologies provide substantially different estimates of incidence. Several studies have used chart review, but because adverse reactions are often not recorded in medical records, these often detect only the more severe reactions. For example, when evaluated prospectively in a clinical trial setting, anaphylactoid reactions occurred in about 30% of patients treated with the original acetylcysteine regimen. If minor symptoms self-reported by patients are included the rate of these reactions rises to 70%.(11) In contrast, while using a chart review approach in the same unit anaphylactoid reactions were recorded in only about 10%.(7)

In this context we were interested to review the two non-randomised studies published in this issue of the journal. (13, 14) As in our study, both of the

regimens studied used a reduced initial infusion rate of acetylcysteine. Both combined the total acetylcysteine dose in the first two bags of the Prescott regimen (200 mg per kilogram) into a single infusion and administered it over at least four hours, but unlike with our regimen, the total duration of acetylcysteine was not substantially reduced.

Wong and Graudins studied 210 patients using a 20 hour regimen consisting of 200 mg/kg acetylcysteine over four hours followed by 100 mg/kg over 16 hours.(13) They used chart review to assess adverse events, compared to 389 historical controls. While this may underestimate true adverse reaction rates, the comparison is valid if identical methodology is used. There was a significant reduction in anaphylactoid responses [10 v 4.3% OR 2.5 (95%CI 1.1-5.8) p=0.02]. Interestingly, in contrast to us, their longer, larger initial infusion showed no difference in GI adverse effects [vomiting 39% conventional; 41% 4 h initial infusion]. No difference in efficacy was detected, but the study, like ours, was not adequately powered for this.

Isbister and colleagues (14) used a variable infusion rate, starting acetylcysteine as soon as possible after presentation and tailoring the duration of the initial infusion from 4 to 9h so that the loading dose would be completed within 11 hours of the overdose. This has the advantage of reducing the infusion rate, and thus incidence of adverse reactions, for many patients. It also ensures that the initial acetylcysteine infusion is completed within a time frame thought to be associated with optimum efficacy. However this regimen suffers from 2 major disadvantages. Firstly, treatment is started before results of paracetamol concentrations are known, meaning that many patients receive treatment that subsequent blood results demonstrate is not needed. Indeed, acetylcysteine was subsequently stopped in 420 of the 654 patients studied as they were deemed to be below the nomogram treatment line. Secondly, the variable duration of the initial infusion is complex and likely to be difficult to deliver consistently in non-specialist units. The results demonstrated a lower rate of adverse reactions compared to other published series, but the validity of this comparison is questionable as methodology may vary between studies.

The results of both of these studies confirm those of our randomised controlled study, demonstrating that reduction in the initial acetylcysteine infusion dose rate to 50mg/kg/hr reduces the incidence of adverse reactions. However, we believe that new acetylcysteine regimens should also be shorter than currently used, to allow safe early discharge of low risk patients. In our trial population 96% had paracetamol concentrations below 20 mg/L at the end of the 12 h acetylcysteine regimen and no patient who had a normal ALT at this point went on to develop significant liver injury. It is therefore likely that patients with a normal ALT at that time could be discharged safely, freeing up many acute hospital beds. However, data collection is needed from a much larger number of patients to confirm this, and this needs to involve patients excluded from our clinical trial such as those ingesting staggered overdoses and those presenting more than 24 hours after overdose.

Acetylcysteine concentrations with different regimens

Giving a fixed dose of a drug in different ways will inevitably result in different plasma concentration profiles. Chiew and colleagues have recently published a detailed analysis of a variety of regimens using a 3-compartment pharmacokinetic model. They clearly show that the modified 2 stage regimens, using either our 12h (2h 100mg/kg + 10h 200mg/kg), or the 20 h (4 h 200mg/kg + 16 h 100mg/kg), result in different acetylcysteine concentrations. Thus modelling indicates that, inevitably, all slower regimens result in lower concentrations over the first hour than the conventional regimen. Our regimen, where acetylcysteine is discontinued after 12 h, results in lower acetylcysteine concentrations at 20 h post infusion commencement than the 20 h infusions used by Wong and Graudins or Isbister et al.(13, 14) For this reason, when our regimen is used a further 10h acetylcysteine infusion is recommended for high risk patients, such as those with persisting paracetamol concentrations or evolving liver function abnormalities at 12h. Few patients, however, require additional therapy after the initial 12 h protocol. In our study only 8 of 110 patients on the modified regimen had a 50% increase in ALT at 12 h, and 96%

had a paracetamol concentration <20mg/L. Only 2 of these had an ALT of >1000 at 20.25 h, and no patient developed severe hepatotoxicity who was not identified as abnormal at 12 h using our criteria.(11) These rates were similar to the standard 20.25 h regimen. We believe this finding is reassuring, but recognise the limitations of our study in terms of size and patient group.

The way forward

There is now strong and consistent evidence that reducing the initial infusion rate of acetylcysteine reduces the rate of adverse reactions, and we probably don't need further evidence of that. The challenge going forwards is to demonstrate that newer regimens are as effective as the original in preventing serious hepatotoxicity. Since serious hepatotoxicity is uncommon in those treated with currently licensed regimens, very large patient numbers are needed, and perhaps no funding agency can underwrite a formal controlled trial of an appropriate size. In this situation a pragmatic approach is needed: it is reasonable for clinical units to take individual decisions on which evidence-based treatment regimen to adopt, but they should collect robust data prospectively using consistent methods that are comparable across units and can be pooled centrally in an anonymised format. This approach is being adopted by several specialist Clinical Toxicology Units in the UK, which are switching to the 'SNAP' 12h acetylcysteine protocol but with careful audit of liver injury outcomes. While there are difficulties comparing rates of adverse reaction between different centres and patient cohorts, such data are now less important as lower adverse reaction rates are now established. To demonstrate that efficacy is maintained, objective data less subject to possible bias is needed, such as results of liver function tests. It might require several thousand patients in each arm to be confident of non-inferiority compared to historic data using an ALT 1000 IU/L cut off, so it might be prudent to also collect all ALT data in order to study increases of lower magnitude, as we reported, since this is not readily available in historic data. In addition, samples for novel biomarkers may also assist in helping to clarify efficacy and facilitate early discharge at the end of 12h treatment (15).

There now seems to be an opportunity for the academic organizations that sponsor this journal to take a clear lead on this issue internationally to provide independent peer review and support for proposed new regimens. This would facilitate their wider adoption in appropriate patient groups, and support the rapid collection of consistent clinical outcome data for patients treated for paracetamol overdose. Collection of such data from large numbers of patients is now essential for the widespread adoption of improved acetylcysteine infusion regimens.

References

1. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet. 1977;2(8035):432-4.
2. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. British medical journal. 1979;2(6198):1097-100.
3. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). The New England journal of medicine. 1988;319(24):1557-62.
4. Mowry JB, Spyker DA, Cantilena LR, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers ' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol. 2014;52:1032-283.
5. Waring WS, Pettie JM, Dow MA, Bateman DN. Paracetamol appears to protect against N-acetylcysteine-induced anaphylactoid reactions. . Clinical toxicology. 2006;44:441-2.
6. Schmidt L. Identification of patients at risk of anaphylactoid reactions to N-acetylcysteine in the treatment of paracetamol overdos. Clinical toxicology. 2013;51:467-72.
7. Bateman DN, Carroll R, Pettie J, Yamamoto T, Elamin ME, Peart L, Dow M, Coyle J, Cranfield KR, Hook C, Sandilands EA, Veiraiah A, Webb D, Gray A, Dargan PI, Wood DM, Thomas SHL, Dear JW & Eddleston M.. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. British journal of clinical pharmacology. 2014;78(3):610-8.
8. Kerr F, Dawson A, Whyte IM, Buckley N, Murray L, Graudins A, Chan B & Trudinger B. The Australasian Clinical Toxicology Investigators Collaboration

randomized trial of different loading infusion rates of N-acetylcysteine. Ann Emerg Med. 2005;45:402-8.
9. Benefit risk profile of acetylcysteine in the management of paracetamol overdose. [Internet]. 2012 [cited 13 May 2013]. Available from: http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con184709.pdf Accessed 13th May 2013
10. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clinical toxicology. 2009;47(2):81-8.
11. Bateman DN, Dear JW, Thanacoody HK, Thomas SH, Eddleston M, Sandilands EA, Coyle J, Cooper JG, Rodriguez A, Butcher I, Lewis SC, Vliegenthart AD, Veiraiah A, Webb DJ, & Gray A. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet. 2014;383(9918):697-704.
12. Thanacoody HK, Gray A, Dear JW, Coyle J, Sandilands EA, Webb DJ, Lewis S, Eddleston M, Thomas SH & Bateman DN. Scottish and Newcastle antiemetic pre-treatment for paracetamol poisoning study (SNAP). BMC Pharmacol Toxicol. 2013;14(20):1-12.
13. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol. 2015.
14. Isbister GK, Downes M, McNamara K, Berling I, Whyte I, Page CA. A prospective observational study of a novel 2-phase infusion protocol for the administration of acetylcysteine in paracetamol poisoning. Clin Toxicol. 2015.
15. Antoine DJ, Dear JW, Lewis PS, Platt V, Coyle J, Masson M, Thanacoody RH, Gray AJ, Webb DJ, Moggs JG, Bateman DN, Goldring CE & Park BK. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology. 2013;58:777-87.