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A prospective observational study of a novel 2-phase infusion protocol for the administration of acetylcysteine in paracetamol poisoning

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**ABSTRACT**

**Context:** The current 3-phase acetylcysteine infusion for paracetamol poisoning delivers half the dose over 15–60 min and frequently results in adverse reactions. **Objective:** We aimed to determine adverse reaction frequency with a modified 2-phase infusion protocol with a longer initial infusion. **Materials and methods:** A prospective observational study of a modified 2-phase acetylcysteine protocol was undertaken at two hospitals. Acetylcysteine was commenced on admission and ceased if paracetamol concentrations were low-risk (below the nomogram line). The first infusion was 200 mg/kg over 4–9 h based on ingestion time or 4 h for staggered/chronic ingestions. The second infusion was 100 mg/kg over 16 h. Pre-defined outcomes were frequency of adverse reactions (systemic hypersensitivity reactions or gastrointestinal); proportion with alanine transaminase (ALT) > 1000 U/L or abnormal ALT. **Results:** 654 paracetamol poisonings were treated with the new protocol; median age 29 y (15–98 y); 453 females; 576 acute and 78 staggered/chronic ingestions. In 420 (64%) acetylcysteine was stopped for low-risk paracetamol concentrations. An adverse reaction occurred in 229/654 admissions (35%; 95% CI: 31–39%); 173 (26.5%; 95% CI: 23–30%) only gastrointestinal, 50 (8%; 95% CI: 6–10%) skin only systemic hypersensitivity reactions; and three adverse reaction occurred in 111/231 (48%) receiving full treatment compared to 116/420 (28%) in whom the infusion was stopped early (absolute difference 20%; 95% CI: 13–28%; p < 0.0001). In 200 overdoses < 10 g, one had toxic paracetamol concentrations, but 53 developed reactions. Sixteen patients had an ALT > 1000 U/L and 24 an abnormal ALT attributable to paracetamol; all but one had treatment commenced > 12 h post-ingestion. **Conclusion:** A 2-phase acetylcysteine infusion protocol results in a fewer reactions in patients with toxic paracetamol concentrations, but is not justified in patients with low-risk paracetamol concentrations.

**Introduction**

Paracetamol (acetaminophen) overdose remains one of the most common and important self-poisonings in the world.[1–4] Fortunately, it is one of a few poisonings in which a relatively safe and effective antidote, acetylcysteine (N-acetylcysteine; NAC), is available and this has resulted in a very low morbidity and mortality.[5] The management of paracetamol poisoning has not changed much over the last four decades since the introduction of acetylcysteine. Most changes to the treatment of paracetamol poisoning have been associated with lowering the treatment threshold for the administration of acetylcysteine, rather than the way acetylcysteine is administered.[6,7]

A 3-phase intravenous acetylcysteine infusion is currently used for paracetamol poisoning in most countries if the paracetamol concentration, taken ≥ 4 h post-overdose, is above the nomogram line. The regimen is 150 mg/kg over 15 min, 50 mg/kg over 4 h and then 100 mg/kg over 16 h. This delivers half the total dose over 15 min and adverse reactions occur frequently. In some countries the initial dose is given over 60 min. Adverse reactions are either gastrointestinal or non-immune-mediated systemic hypersensitivity reactions (anaphylactoid type) and generally occur in the first hour or two of administration.[8] The frequency of adverse reactions varies enormously between studies, with higher rates in prospective studies compared to retrospective studies.[9] Prospective studies over the last decade report total adverse effect rates of 29% to 77% and systemic hypersensitivity reactions in 14% to 75% with acetylcysteine administration.[2,8,10–12]

Recently a number of different regimens have been investigated to determine if slowing the first part of the infusion will reduce the reaction rates with acetylcysteine administration. A randomised controlled trial compared the standard 3-phase protocol with a modified 12 h protocol (100 mg/kg over 2 h; 200 mg/kg over 10 h – the SNAP protocol) in which the loading dose is given more slowly. The study demonstrated a reduced frequency of gastrointestinal adverse reactions.
effects and systemic hypersensitivity reactions with the modified regimen.[2]

A recent simulation study investigated the administration of a slower infusion rate for the loading dose, using a published population pharmacokinetic three compartmental model of acetylcysteine.[13] To explore slower infusion rates, the study investigated a scenario in which acetylcysteine was commenced on arrival in patients presenting early, unlike the conventional approach. A lower dosing rate commenced immediately in the patients presenting 2 h after ingestion was simulated and compared to the conventional regimen. A loading dose of 200 mg/kg over 9 h followed by the third infusion of the conventional regimen (100 mg/kg over 16 h) produced an area under the curve of the concentration-time curve (up until the end of the first two infusions of the conventional protocol) that was the same or greater than the conventional regimen on 90% of occasions (Fig. 1). This was identical to combining the first two infusions of the conventional protocol and giving them over 9 h.

Based on this simulation study,[14] we modified our practice to give a novel infusion protocol in which the initial two infusions were combined and given over an extended period. To extend this modified infusion protocol to include patients presenting any time post overdose, we modified the duration of the first infusion to be given over an increasingly shorter time the longer they presented after 2 h, with the shortest duration of the loading dose being reduced to 4 h. Four hours was based on this being approximately the time over which the first two infusions of the conventional regimen are given (i.e., 150 mg/kg over 15 min and then 50 mg/kg over 4 h). Acetylcysteine was commenced on presentation in all cases of paracetamol overdose and then stopped if the paracetamol concentration was low-risk (below the Australian nomogram line). This meant more patients would receive at least some acetylcysteine prior to a paracetamol concentration being done. The aim was that the overall reaction rate would be reduced sufficiently to justify some reactions occurring in patients with low-risk paracetamol concentrations who would not normally receive acetylcysteine. This did not affect patients presenting more than 7 h post-ingestion, who already have acetylcysteine commenced prior to a paracetamol concentration being done.

The aim of this study was to investigate the safety of a novel 2-phase infusion protocol for acetylcysteine in paracetamol overdose and determine if the rate of reactions was reduced by a slower initial infusion rate. In addition, we report the effectiveness of acetylcysteine to make sure that the modified regimen did not result in a markedly higher rate of hepatotoxicity.

**Methods**

**Design and setting**

We performed a prospective observational study as part of quality assurance monitoring of a clinical practice change for acetylcysteine administration in paracetamol poisoning in two hospitals. The primary outcome of the study was the proportion of patients who developed an acute systemic hypersensitivity reaction following the administration of acetylcysteine. The study was approved as a quality assurance review in one hospital by the Hunter New England Human Research Ethics Committee and as a low or negligible risk study by the Metro South Health Research Ethics Committee.

The study was undertaken in two adult metropolitan hospitals. One hospital has a large tertiary toxicology unit admitting all primary presentations and referrals (>15 years age) with an overdose or poisoning from a population of over 500,000 people. Demographic and clinical information is recorded for all patients managed by the toxicology unit with a data collection form that is part of the medical record. Further information is recorded throughout the admission in the medical record. All patient information is then entered into a purpose designed database by the research assistants. Approval to use the database and patient medical record for research has been granted by the Hunter New England Human Research Ethics Committee.

The second hospital is a large tertiary adult (>16 years age) referral hospital with an emergency department that has approximately 60,000 presentations each year. A dedicated toxicology service has been developed and all overdose presentations are discussed with a clinical toxicologist, including all paracetamol overdoses.

**Participants**

The study included all patients with a paracetamol overdose or poisoning in which >4 g of paracetamol was ingested, either as an acute overdose or as a staggered or chronic ingestion. For staggered or chronic ingestions >4 g had to be ingested.

![Diagram comparing the standard 3-phase acetylcysteine regimen with the modified 2-phase regimen for a patient who presents 2 h post-ingestion.](image-url)
over a 24 h period to be included. Patients were excluded if they were less than 16 years of age, were transferred from another hospital (the first hospital received tertiary referrals) or where the emergency department did not follow the paracetamol treatment algorithm or consult with the admitting clinical toxicologist.

Protocols

The clinical toxicologists at both hospitals reviewed a simulation study of acetylcysteine administration[14] and an international controlled trial of a smaller loading dose for acetylcysteine administration,[2] and based on these decided to change their clinical practice. A new protocol for the administration of acetylcysteine in paracetamol poisoning was then introduced into each hospital. The new protocol was a modified 2-phase infusion regimen that was to be commenced on admission in all patients ingesting >4 g paracetamol, and ceased if the paracetamol concentration was low-risk (below a nomogram line commencing at 150 mg/mL or 1000 mmol/mL at 4 h) or the liver function tests (alanine transaminase [ALT]) were normal 24 h after the last dose of paracetamol in staggered/chronic ingestions. The first infusion was to be 200 mg/kg in 500 ml of 5% dextrose given over a variable duration based on the time since overdose: 11 h minus the time since ingestion. If the patients presented 2 h post-overdose they were given the first dose over 9 h similar to the scenario simulated in Shen et al.[14] This was the longest duration so patients presenting <2 h post-ingestion also had it over 9 h. Then for later presentations, the first dose was given over 8 h if they presented at 3 h, 7 h if they presented at 4 h, until it was given over 4 h if the patient presented at 7 h or later. The presentation time was rounded up or down to the nearest hour. The first infusion was to be given over 4 h for staggered, repeated supratherapeutic ingestions or those in which the ingestion time was unknown. The second infusion was to be 100 mg/kg in 1000 ml of 5% dextrose given over 16 h (Figure 1). To monitor and audit the change in practice an acetylcysteine observation chart was developed [Supplementary File 1].

Data Collection

In both hospitals information regarding the modified acetylcysteine infusion protocol was recorded on the acetylcysteine observation chart by the nursing and medical staff (Supplementary File 1). This included: the intended duration of the infusion based on the presentation time post-overdose, whether the infusion was stopped and when it was stopped; reason for stopping (low-risk paracetamol concentration or adverse reaction); the time the infusion was stopped and any adverse reactions (nausea, vomiting, rash, flushing, urticaria, itchiness, dyspnoea, wheeze, hypotension or hypoxia). Observations were recorded at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h after commencing acetylcysteine (see Supplementary File 1).

In the first hospital additional information was extracted from a toxicology database including: patient age and sex, information on the paracetamol ingestion (dose, acute or chronic/staggered ingestion), laboratory results (ALT); and specific complications (death, liver failure). Additional information in patients with abnormal liver function tests was obtained to assess causality. In the second hospital, the same data were extracted from EDIS (Emergency Department Information System) and AUSLAB™, which electronically record all clinical notes and laboratory results. Paracetamol concentrations were measured at the first hospital by an Abbott AxSYM paracetamol assay which may be affected by high concentrations of acetylcysteine (minor under-estimate of ~5%), and at the second hospital by a Beckman Coulter Emit® tox™ paracetamol assay which is not affected.

Outcomes

The primary outcome was the proportion of patients with adverse reactions, including the proportion with only gastrointestinal symptoms and the proportion with systemic hypersensitivity reactions. Systemic hypersensitivity reactions were defined as either skin only hypersensitivity reactions, or non-immune mediated anaphylaxis (also referred to as anaphylactoid reaction), if they met NIAID-AAAN consensus criteria for this diagnosis.[15] They were defined as severe anaphylaxis based on the grading system developed by Brown[16] - hypotension or hypoxia. Secondary outcomes were the proportion with paracetamol hepatotoxicity (ALT > 1000 U/L) in patients administered acetylcysteine within 8 h post-overdose; proportion with an abnormal ALT (above the reference range) attributable to paracetamol toxicity and number of medication errors.

Analysis

Continuous variables are summarised as medians, interquartile range (IQR). For proportions, 95% confidence intervals (CI) were calculated using the Wilson’s procedure with a continuity correction. Statistical analyses and graphical analysis were performed using GraphPad Prism, version 6.05 for Windows. (GraphPad Software, La Jolla, CA; www.graphpad.com).

Results

There were 654 patients with paracetamol poisoning treated with the modified two bag protocol – 200 mg/kg in the first bag over 4–9 h and 100 mg/kg over 16 h. (260 over 4 h, 37 over 5 h, 46 over 6 h, 95 over 7 h, 143 over 8 h and 73 over 9 h). The median patient age was 29 years (15 to 98y) and 453 (69%) were female. There were 576 acute overdoses and 78 staggered/chronic ingestions. The median dose ingested in 593/654 patients in whom the dose was known was 12 g (Range: 1.5–240 g; IQR: 8–20 g). Ninety five patients were not given the modified two bag protocol and almost half of these were transfers from other hospitals where acetylcysteine had been commenced using the standard regimen (Figure 2).

In 420 overdoses (64%), the acetylcysteine infusion was stopped because of a low-risk paracetamol concentration. The infusion was stopped after a median time of 3 h (IQR: 2–5 h). In 231 overdoses the infusion was continued until completion
or until the liver function tests had peaked. In one of the 231 cases, acetylcysteine was stopped for an adverse reaction and then restarted after 50 min and the infusion completed. In two cases with late presentations of supra-therapeutic ingestions, acetylcysteine was stopped early because the liver function tests (LFTs) were normal at 24 h or more after the last dose of paracetamol. In a third case acetylcysteine was stopped in error (Figure 2).

**Adverse reactions**

An adverse reaction occurred in 229/654 cases (35.0%; 95% CI: 31.4–38.8%): 173 cases (26.5%; 95% CI: 23.1–30.0%) were only gastrointestinal, 50 (8%; 95% CI: 6.1–10.4%) included skin only systemic hypersensitivity reactions and three had severe anaphylaxis (0.5%; 95% CI: 0.1–1.5%); all hypotension (Table 1). In all three patients who developed hypotension (systolic BP <90 mmHg; Table 2), this was not recognised by the treating clinicians as a reaction to acetylcysteine. In none of the three was acetylcysteine ceased because of the reaction, but in two it was ceased within 2 h because of low-risk paracetamol concentrations (Table 2).

There were adverse reactions in 111/231 (48%) receiving the full course of acetylcysteine compared to only 116/420 (28%) in whom the infusion was stopped, which was significantly different (absolute difference 20%; 95% CI: 13–28%; p <0.0001). The 231 patients with a toxic paracetamol overdose had 105 gastrointestinal reactions (45%), 25 skin only hypersensitivity reactions (11%), one case of anaphylaxis (skin and respiratory manifestations) and one had severe anaphylaxis with hypotension.

There were similar reaction rates, including gastrointestinal and systemic hypersensitivity reactions, in patients who received the first infusion over 4 h compared to all patients (Table 1). There were similar reaction rates at each hospital site with adverse reactions in 141/393 (36%) patients at the first hospital (9% hypersensitivity reactions), compared to 88/261 (34%) at the second hospital (7% hypersensitivity reactions).

**Paracetamol hepatotoxicity**

In 200 acute and staggered overdoses <10 g, there was only one case (a small female who took 9.31 g (14 × 665 mg) modified-release paracetamol over 2.5 h) with a paracetamol concentration above the nomogram who was treated. No patient ingesting <10 g developed hepatotoxicity. There were adverse reactions in 53 of the 200 patients ingesting <10 g (26%) (Table 1).

Sixteen patients had an ALT >1000 U/L and all had acetylcysteine commenced >12 h post-ingestion except one (at 11 h). Twenty four had an abnormal ALT (<1000 U/L) attributable to paracetamol. There were four medication errors, three of these were the incorrect infusion rate for the first bag, and in one the acetylcysteine was stopped in error.

**Discussion**

We found that a modified 2-phase acetylcysteine regimen, in which the first dose was given over an extended period of time, resulted in a lower frequency of systemic hypersensitivity adverse reactions (8%), compared to previous prospective studies of acetylcysteine reactions (Table 3). The rate of gastrointestinal reactions was similar to previous studies (Table 3). There were no cases of hepatotoxicity in patients given acetylcysteine within 8 h suggesting similar effectiveness of the modified regimen. We also found that ingestions <10 g were rarely associated with a toxic paracetamol concentration and over a quarter of these patients had adverse reactions to acetylcysteine. In a sub-group of patients given the first infusion over 4 h, the adverse reaction rate was similar to the group as a whole. This would justify giving the first infusion over 4 h in all patients, simplifying the loading dose and treatment regimen.

**Table 1. Frequency of adverse reactions in all patients and then in each subgroup of patients.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total reactions</th>
<th>Gastrointestinal reactions</th>
<th>Systemic hypersensitivity reactions</th>
<th>Severe anaphylaxis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>All Patients</td>
<td>654</td>
<td>229 (35%)</td>
<td>212</td>
<td>32.4% (28.9–36.2%)</td>
</tr>
<tr>
<td>Dose &lt;10 g</td>
<td>203</td>
<td>53 (26%)</td>
<td>45</td>
<td>22.2% (17–29%)</td>
</tr>
<tr>
<td>4 h infusion</td>
<td>260</td>
<td>93 (36%)</td>
<td>73</td>
<td>28% (23–34%)</td>
</tr>
<tr>
<td>Infusion stopped (non-toxic)</td>
<td>420</td>
<td>116 (28%)</td>
<td>104</td>
<td>25% (21–29%)</td>
</tr>
<tr>
<td>Full course of NAC (toxic)</td>
<td>231</td>
<td>111 (48%)</td>
<td>105</td>
<td>45% (39–52%)</td>
</tr>
</tbody>
</table>

*Severe anaphylaxis is the presence of hypotension or hypoxia with systemic hypersensitivity reactions as defined by Brown et al. [15].

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Dose ingested</th>
<th>Toxic*</th>
<th>Adverse reaction</th>
<th>Baseline BP</th>
<th>Lowest BP</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>63F</td>
<td>7 g</td>
<td>No</td>
<td>Hypotension</td>
<td>130/60</td>
<td>89/40</td>
<td>1L normal saline over 1 h.</td>
</tr>
<tr>
<td>18F</td>
<td>26.5 g</td>
<td>No</td>
<td>Nausea, vomiting, hypotension, syncope</td>
<td>122/66</td>
<td>89/43</td>
<td>2L normal saline</td>
</tr>
<tr>
<td>56F</td>
<td>25 g</td>
<td>Yes</td>
<td>Nausea, vomiting, hypotension</td>
<td>116/67</td>
<td>72/49</td>
<td>1L normal saline</td>
</tr>
<tr>
<td>37F</td>
<td>Unknown</td>
<td>Yes</td>
<td>Nausea, vomiting, itch, flushing and shortness of breath (no hypoxia)</td>
<td>Nil</td>
<td>Acetylcysteine ceased for 50 min and then re-started. Ondansetron given.</td>
<td></td>
</tr>
</tbody>
</table>

BP – blood pressure.

*Paracetamol concentration above the nomogram.

†In none of the 3 with hypotension was this recognised as a reaction to acetylcysteine by the treating clinicians and acetylcysteine was not stopped;
reducing medication errors. The majority of adverse reactions were not severe and the acetylcysteine infusion was only stopped in one patient because of a reaction.

There are a number of previous studies that report proportions of patients who have adverse reactions to acetylcysteine. However, these studies use different definitions for reactions, record different clinical observations and have differing designs. One important difference in a number of studies from the U.K. is that they report reactions based on them being treated (i.e., the use of antiemetics rather than reporting the symptoms/signs such as nausea or vomiting).[2,7] Retrospective studies are likely to report lower rates of reactions, particularly more minor reactions such as gastrointestinal reactions. Table 3 provides a summary of previous prospective studies on reaction rates and attempts to provide this broken down by reaction types in which it was possible to extract this information from the publication. [2,7,8,10–12,17–19]

Although it is impossible to make a direct comparison, the reported rates of systemic hypersensitivity reactions were higher than in our study in most cases, excepting three studies. One recent study by Graudins et al. which used a similar modified 2-phase regimen where the first infusion was given over 4 h; an early small study by the Bateman which reported very low rates, but provided no methodology of data collection and did not report gastrointestinal adverse effects; and thirdly a recent study from the U.K. which reported similar reaction rates to our study using the conventional regimen. However, the last study based adverse reactions on the use of treatment for reactions (antiemetics, antihistamines and salbutamol), rather than observations of the reactions which is likely to under-report the reaction rate and is difficult to compare. In contrast, studies in which the information was available, similar rates of gastrointestinal reactions were reported (Table 3). It is important to remember that when comparing the reaction rates we found to those in previous studies, it is only the reaction rates in patients with a toxic concentration that can be compared.

The majority of the reactions were gastrointestinal and systemic hypersensitivity reactions only occurred in about 10% of patients administered acetylcysteine. Less than 1% of

### Table 3. Reaction rates from previous prospective studies in the literature.

<table>
<thead>
<tr>
<th>Study</th>
<th>Loading dose (time)</th>
<th>Total reactions</th>
<th>Gastrointestinal reactions</th>
<th>Systemic hypersensitivity reactions</th>
<th>Severe anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Bateman et al. [16]</td>
<td>NR</td>
<td>44</td>
<td>4% (3–23%)</td>
<td>2</td>
<td>5% (1–17%)</td>
</tr>
<tr>
<td>Lynch et al. [17]</td>
<td>150 mg/kg over 15 min</td>
<td>64</td>
<td>NR</td>
<td>14</td>
<td>22% (13–34%)</td>
</tr>
<tr>
<td>Kerr et al. (15 min) [8]</td>
<td>150 mg/kg over 15 min</td>
<td>109</td>
<td>49% (36–55%)</td>
<td>42</td>
<td>39% (30–48%)</td>
</tr>
<tr>
<td>Kerr et al. (60 min) [8]</td>
<td>150 mg/kg over 60 min</td>
<td>71</td>
<td>27% (27–50%)</td>
<td>22</td>
<td>31% (21–43%)</td>
</tr>
<tr>
<td>Waring et al. [10]</td>
<td>150 mg/kg over 15 min</td>
<td>362</td>
<td>41% (36–46%)</td>
<td>90</td>
<td>25% (21–30%)</td>
</tr>
<tr>
<td>Pakravan et al. [11]</td>
<td>150 mg/kg over 15 min</td>
<td>169</td>
<td>77% (70–83%)</td>
<td>121</td>
<td>72% (64–78%)</td>
</tr>
<tr>
<td>Bateman et al. (Standard) [2]</td>
<td>150 mg/kg over 15 min</td>
<td>109</td>
<td>NR</td>
<td>80* (102)</td>
<td>79% (69–86%)</td>
</tr>
<tr>
<td>Bateman et al. (Modified) [2]</td>
<td>150 mg/kg over 1 h</td>
<td>108</td>
<td>NR</td>
<td>60* (101)</td>
<td>59% (49–69%)</td>
</tr>
<tr>
<td>Bateman et al. (Standard) [2]</td>
<td>100 mg/kg over 2 h</td>
<td>100</td>
<td>NR</td>
<td>60* (101)</td>
<td>59% (49–69%)</td>
</tr>
<tr>
<td>Bateman et al. (15 min) [7]</td>
<td>150 mg/kg over 6 h</td>
<td>409</td>
<td>29% (25–33%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bateman et al. (60 min) [7]</td>
<td>150 mg/kg over 4 h</td>
<td>514</td>
<td>28% (24–32%)</td>
<td>107</td>
<td>21% (17–25%)</td>
</tr>
<tr>
<td>Pakravan et al. [11]</td>
<td>200 mg/kg over 4 h</td>
<td>169</td>
<td>NR</td>
<td>60* (101)</td>
<td>59% (49–69%)</td>
</tr>
<tr>
<td>Kerr et al. (15 min) [7]</td>
<td>150 mg/kg over 15 min</td>
<td>323</td>
<td>87% (22–32%)</td>
<td>74</td>
<td>23% (19–28%)</td>
</tr>
<tr>
<td>Kerr et al. (60 min) [7]</td>
<td>150 mg/kg over 60 min</td>
<td>514</td>
<td>145% (24–32%)</td>
<td>107</td>
<td>21% (17–25%)</td>
</tr>
<tr>
<td>Grudins et al. [18]</td>
<td>200 mg/kg over 1 h</td>
<td>362</td>
<td>147% (27–50%)</td>
<td>22</td>
<td>31% (21–43%)</td>
</tr>
</tbody>
</table>

*Systemic hypersensitivity reactions were taken as the sum of immune system disorders and skin/subcutaneous tissue disorders (Table 4; Kerr).

†Used patients with vomiting or retching or nausea, from 0 h to 12 h.

‡Systemic hypersensitivity reactions were deduced from the “absence of anaphylactoid symptoms” and appear to be higher than expected.

Severe anaphylaxis was defined differently in Bateman et al. (i.e. acetylcysteine interrupted or anti-allergy drug administered). NR – not reported OR unable to determine from publication.
patients developed severe reactions and these were all hypotensive in nature. This is consistent with studies of anaphylaxis in which severe reactions to drugs are cardiovascular (hypotensive) type.[20] Only a few previous studies have separately reported the number of severe reactions and have similar very low rates of severe reactions.[8,19]

We found that there were more adverse reactions in patients requiring the full course of acetylcysteine (toxic paracetamol concentration) and fewer in those taking less than 10 g. However, when the types of reactions were considered separately, there was a similar proportion of systemic hypersensitivity reactions for all the groups (Table 3) and the difference in total reactions was accounted for by the difference in gastrointestinal reactions. In the <10 g group, only 22% had gastrointestinal reactions compared to 45% in the patients with toxic paracetamol concentrations (larger doses). The reason for this may be that paracetamol toxicity itself causes nausea and vomiting, so more patients will have gastrointestinal effects which may not be a result of a reaction to acetylcysteine. It is sometimes difficult to determine if gastrointestinal symptoms are due to the paracetamol toxicity or the acetylcysteine when interviewing patients.

Over one quarter of patients developed a reaction if they ingested less than 10 g suggesting that these patients should not be treated unless they have toxic paracetamol concentrations. This finding is consistent with a previous study from the same unit prior to the commencement of this study.[4] In these patients, it would be more appropriate to wait for a 4 h paracetamol concentration prior to commencing acetylcysteine (as per the standard protocol). Another finding of the study was that patients receiving the first infusion of 200 mg/kg over 4 h had a similar reaction rate to the whole study. Taking these two findings together suggests that an appropriate modified acetylcysteine regimen would be waiting for paracetamol concentrations prior to commencing, but giving a 2-phase infusion protocol – 200 mg/kg over 4 h and then 100 mg/kg over 16 h as treatment. Our findings also support the common practice of commencing acetylcysteine in patients presenting late (>8 h post-ingestion) and then stopping if the paracetamol concentration is low-risk (below the local nomogram line).

An unusual finding in our study was that in patients in whom the infusion was stopped i.e., low-risk paracetamol concentrations, there was a similar number of reactions or slightly less compared to those with toxic paracetamol concentrations. This differs from previous studies in which lower paracetamol concentrations have been associated with a greater risk of adverse reactions.[7,10,21] The reasons why this occurred are not clear, but previous studies have all used the conventional loading dose, compared to the modified first dose we used. In addition, our patients received a much shorter duration of therapy because it was stopped, compared to those receiving the full dose of acetylcysteine. Further prospective studies, comparing dose ingested and paracetamol concentrations to adverse reactions rates, are required to determine why this occurs.

There are a number of limitations to the study including the observational design. A better design would be to randomise patients to the different acetylcysteine regimens as in the SNAP study.[2] The nature of the modified regimen meant that this would have been difficult and the treating toxicologists had already decided on a change in clinical practice based on a simulation study[14] and the expectation that reducing the rate of administration was highly likely to reduce the reaction rate. However, this meant that we were unable to compare the reaction rate using the new protocol to a control group. Comparison with previous studies is also fraught with problems, because previous studies have different study designs, define reactions differently and use different data collection methods. However producing a summary of previous studies in Table 3 as a comparison, does provides some perspective on the reaction rates we found; but should not be over-interpreted.

An obvious problem with this new protocol as described is the complexity of having a variable duration for the first infusion. Although there were only a few medication errors in the study, the study was undertaken in two hospitals where all patients are admitted to a dedicated toxicology service. This gives further support to giving the first infusion over 4 h and not a variable time period. Another problem was that at one hospital the paracetamol assay was affected by the presence of acetylcysteine which may have resulted in lower concentrations in some cases. This is another problem with starting acetylcysteine prior to measuring paracetamol.

This study supports other recent studies that suggest that slower initial infusion rates for acetylcysteine reduce systemic hypersensitivity reactions.[2,19] However, we report an unacceptable rate of reactions in patients who ultimately did not need treatment and future regimens should follow a “wait and see” approach similar to the conventional regimen. The study also supports the current practice of commencing acetylcysteine immediately in late presenters. The modified regimen was not associated with a marked increase in hepatotoxicity, with no patients developing hepatotoxicity who were treated within 8 h (although the study was not powered for this purpose). Finally, the study supports giving all patients requiring acetylcysteine an initial dose over 4 h (200 mg/kg in 500 mL) followed by 100 mg/kg (in 1000 mL) over 16 h, but only treating patients with a toxic paracetamol concentration.

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