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Delays during the administration of acetylcysteine for the treatment of paracetamol overdose

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Structured Summary

Background:

The licensed intravenous acetylcysteine regimen for treating paracetamol overdose in most countries uses three separate infusions over 21 hours. This complex regimen, requiring different infusion concentrations and rates, has been associated with administration errors. The aim was to assess the extent of administration delays occurring during this acetylcysteine regimen.

Method:

A 6-month retrospective observational study was conducted at three English teaching hospitals with clinical toxicology services from October 2014. Patients aged 16-years and over treated with intravenous acetylcysteine for paracetamol overdose were included. The start times for infusions were recorded and the delays compared to the prescribed infusion times were calculated. Anaphylactoid reactions, intravenous cannula problems, overdose intent and smoking status were recorded to assess their contribution to delays.

Results:

From 263 cases identified, 198 met study inclusion criteria. The median time between the start of infusions 1 and 3 was delayed from the intended 5 hours by a median (IQR) of 90 (50-163) minutes, with 135 (68%) cases delayed by more than one hour. Significantly longer delays were observed in patients with anaphylactoid reactions (median delay 267 (217-413) minutes, n=8) and accidental / supra-therapeutic overdose (median delay 170 (95-260) minutes, n=29). There were no significant differences between smokers and non-smokers and for patients with intravenous cannula problems.

Conclusion:
Long delays were identified during the three-infusion acetylcysteine regimen for the treatment of paracetamol overdose. Delays were of clinical significance and could lead to periods of sub-therapeutic plasma acetylcysteine concentrations and potentially avoidable hepatotoxicity, as well as delaying hospital discharge.

What is already known about this subject:
- The licensed intravenous acetylcysteine regimen for treating paracetamol overdose in most countries uses three separate infusions administered over 21 hours.
- This complex regimen, requiring different infusion concentrations and rates, has been associated with administration errors.

What this study adds:
- Long delays were identified during the three-infusion acetylcysteine regimen for the treatment of paracetamol overdose.
- Delays could increase the length of hospital stay and were of clinical significance and could lead to sub-therapeutic plasma acetylcysteine concentrations and potentially avoidable hepatotoxicity.
**Introduction**

In most countries, the licensed intravenous acetylcysteine regimen for treating paracetamol (acetaminophen) overdose involves three separate infusions given over a total of 21 hours. The first infusion is administered over 1 hour, the second over 4 hours and the third (and any subsequent) infusions over 16 hours. [1] Each infusion is prepared by adding the required volume of acetylcysteine solution to three different volume infusion bags of 5% dextrose or 0.9% sodium chloride. There should ideally be no delay in between the infusions to minimise treatment duration and length of stay, whilst providing maximal hepatic protection from the toxic metabolite of paracetamol, N-acetyl-p-benzoquinone imine (NAPQI). Treatment is usually started in the Emergency Department and continued on an admission/medical/observation ward.

The complexity of the regimen, with the requirement for three different infusion concentrations and rates has been associated with administration errors. [2,3,4] In a US retrospective chart review, Hayes and colleagues found medication errors in the treatment of 33% of 221 patients treated with intravenous acetylcysteine for paracetamol overdose. The most frequent error, in 18.6% cases, was the interruption of treatment by more than one hour; in addition, incorrect infusion rates were seen in 5% of cases (the authors did not record whether administration was too fast or slow). [3] In a Malaysian audit of 236 patients treated with acetylcysteine for paracetamol poisoning, interruptions in treatment of more than one hour were seen in fewer cases (5.5%) than in the US study but infusion rate errors were recorded in more (37.3%). [4] In the US study the same three-infusion regimen was in place as currently used in the UK.
In the Malaysian study the three-infusion regimen was the same apart from the initial infusion being administered over 15 minutes, rather than 1 hour, as was routine in the UK until 2012.

Consistent with these US and Malaysian studies, our own experience is that the time taken for acetylcysteine infusions to be completed is often longer than expected. The aim of this study was to assess the extent of delays during the administration of the three-infusion intravenous acetylcysteine regimen in three English hospitals, and to understand when these delays occurred during treatment.

Methods

A retrospective observational study was conducted at three English teaching hospitals with clinical toxicology services. Patients aged 16-years and over, treated with intravenous acetylcysteine for paracetamol overdose between 1st October 2014 and 31st March 2015 were identified from the clinical toxicology databases used at the three hospitals. Patients were excluded if any of the start times for the three infusions were not recorded or if treatment was stopped prior to the start of the third infusion.

In addition to basic demographic data (age/sex), the start/stop times for all infusions were recorded and delays to treatment (in minutes) were calculated comparing times recorded for administration to the predicted times based on the prescribed infusion times. This was recorded for: i) the start of the first and second infusions; ii) the start of the second and third infusions; and iii) the start
of the first and third infusions. The primary outcome measure was the delay between the start of the first and the start of the third infusion. When documented, infusion stop times were also recorded and the total delays to complete all three infusions were calculated. In addition, smoking status, overdose intent (intentional or accidental/ supra-therapeutic overdose), anaphylactoid reactions (defined as documented anaphylactoid reaction, bronchospasm, rash, swelling, or reaction requiring treatment with antihistamines and/or steroids) and intravenous cannula related problems (documentation that an intravenous cannula was misplaced or stopped working) were recorded to assess if these contributed to any delays that occurred.

The data were collated in an Excel spreadsheet and analysed using Excel and SPSS Statistics (version 21, IBM). The impact of the additional factors was assessed using Mann-Whitney U tests. Results from the three hospitals were compared using Kruskal-Wallis tests.

Data for audit of the management of paracetamol overdose are routinely and prospectively collected on databases held within the clinical toxicology units at the study centres and these are approved by the local data protection officers/Caldicott Guardians.

Results

There were 263 cases identified during the 6-month study period at the three hospitals: 86 in London (15 excluded), 108 in Newcastle (31 excluded) and 69 in York (19 excluded). Sixty-five cases were excluded because treatment was
discontinued before the start of the third infusion (19 cases), the start times for all three infusions were not documented (25 cases), or the prescription charts or notes were missing (21 cases). Thus 198 cases were included in the analysis with a mean ± SD age of 33.6 ± 15.9 years and 114 (57.5%) were female. Those excluded had a mean ± SD age of 32.8 ± 13 years and 54.0% were female.

The median (IQR) delay compared to the 5 hour interval intended between the start of infusions 1 and 3 was 90 (50-163) minutes. The median delay compared to the 1 hour interval intended between the start of infusions 1 and 2 was 25 (10-60) minutes and compared to the 4 hour interval intended between the start of infusion 2 and 3 was 50 (15-104) minutes. There was a delay of more than one hour compared to the prescribed times between the start of infusions 1 and 3 in 135 (68.2%) cases, of more than 2 hours in 78 (39.4%) cases and of more than 3 hours in 41 (20.7%) cases. In four cases (2.0%) there were delays of more than 10 hours compared to prescribed times between the start of infusions 1 and 3.

Smoking status, anaphylactoid reactions and cannula problems were recorded at the hospitals in London and Newcastle but not York. Comparisons between smokers and non-smokers, intentional and accidental/supra-therapeutic overdoses and those with/without cannula problems or anaphylactoid reactions are shown in table 1. Smoking status had no significant effect on the delays but patients with accidental / supra-therapeutic overdoses, anaphylactoid reactions experienced significantly longer delays.
Adverse effects were recorded in London and Newcastle. Eight (5.4%) patients had anaphylactoid reactions and 28 (18.9%) experienced nausea and/or vomiting. The median (IQR) delay between the start of infusions 1 and 3 compared to prescribed times for patients with anaphylactoid reactions was 267 (217–413) minutes compared to 90 (53-155) minutes for patients without anaphylactoid reactions (n=147). Delays for patients with anaphylactoid reactions were 188 (140-230) minutes between the start of infusions 1 and 2 and 60 (26-93) minutes between the start of infusions 2 and 3. At the two centres where adverse reactions were recorded, 34 (23.0%) patients experienced delays of more than 3 hours and 6 (17.6%) of these had anaphylactoid reactions. For patients without anaphylactoid reactions, the median (IQR) delay from the start of infusion 1 to infusion 3 remained significantly longer for those with accidental / supra-therapeutic overdose; 155 (90-255) minutes compared to 85 (50-142) minutes for intentional overdoses (p=0.0008).

The stop time for the third infusion was recorded in only 36 (18.2%) cases. For these patients the median (IQR) delay between the start of infusion 1 and the end of infusion 3 was 175 (103-300) minutes. The median (IQR) delay compared to the 16 hour interval intended from the start of infusion 3 to the end of infusion 3 for this group was 60 (20-139) minutes. The median (IQR) delay between the start of infusions 1 and 3 for this group was 75 (45-152) minutes, which was not significantly different to the 90 minute delay observed in the whole cohort.
The delays compared to prescribed times in each of the three hospitals are demonstrated in Figure 1. Comparing the three hospitals, there was a median (IQR) delay between the start of infusions 1 and 3 of 140 (67-197) minutes in London, 75 (40-130) minutes in Newcastle and 90 (45-145) minutes in York. Delays in Newcastle were significantly shorter than in London (p=0.0015). Differences between delays comparing Newcastle and York and London and York were not significant.

Discussion

A delay of more than one hour compared to prescribed infusion times between the start of infusions 1 and 3 occurred for over two-thirds of patients in this study. For the group with total infusion times recorded, further delays occurred both between each infusion and during the infusions. This suggests the delays result from both time preparing and instigating infusions, and during infusions.

The impact of delays in administration on plasma concentrations of acetylcysteine and outcomes has not previously been reported, but Hayes and colleagues [3] suggested that delays of more than one hour should be considered potentially significant based on the elimination half-life for acetylcysteine of 5.7 hours found by Prescott et al. [5] in a pharmacokinetic study of the three infusion regimen. The extent of the delays identified could lead to potentially avoidable hepatotoxicity. However, it is not clear at what point the duration of the delay might lead to an increased risk of liver injury.
Infusion delays prolong the time that patients are admitted to hospital, increase costs and increase acute medical inpatient bed occupancy. Most patients (85% of this cohort) are treated following intentional paracetamol overdoses and prolonging their stay as a medical inpatient delays psychiatric / psychosocial assessment.

Anaphylactoid reactions and intravenous cannula related problems contributed to delays in treatment but there were important delays for patients with no documented evidence of either of these complications. The incidence of anaphylactoid reactions in this study was 5.2%, which is lower than previously reported. [6,7,8,9] The incidence of intravenous cannula related problems was also lower than expected; these included removal, difficulty re-inserting and blockages in tubing. The retrospective data collection and reliance on documentation of anaphylactoid reactions and cannula problems in the medical notes may have resulted in under-reporting of these events.

It was expected that patients leaving the ward to smoke might delay infusions more in smokers compared to non-smokers. However, smoking status had no effect on the delays. This may be because of the use of nicotine replacement in hospital inpatients.

Delays were surprisingly significantly longer for patients presenting following accidental overdose compared to those with intentional overdoses. Patients with lower serum paracetamol concentrations are at greater risk of anaphylactoid reactions. [9] Patients with accidental / supra-therapeutic overdose often
present with lower serum paracetamol concentrations and are therefore potentially, a higher rate of occurrence of adverse reactions in this group could have contributed to their delays. However, delays remained longer in those that did not suffer anaphylactoid reactions, suggesting that other factors were important. It is possible that less severe reactions occurred for some patients and delayed infusions but this was not documented. Patients presenting following intentional overdoses frequently require close observation by staff and occasionally 1:1 observation by a mental health nurse. It is possible that the need for increased observation results in earlier recognition of acetylcysteine infusions finishing or problems with the infusions. Delays could potentially have been caused by waiting for repeat blood test results in deciding on the treatment courses for patients with staggered overdoses. However, local practice is to continue infusions until results are available (up until the end of the third infusion).

Patients are usually transferred between departments at least once during their treatment course with acetylcysteine (most often between the emergency department and admission / medical / observation wards). The prolonged nature of the infusion involves handover of care between medical and nursing staff working in shifts. There may have been delays starting the next infusion while care is handed over between teams.

Electronic infusion pumps are used to set infusion times. Therefore, theoretically, administration during infusions should not be delayed. However, infusion rate errors were noted in previous US and Malaysian studies on
acetylcysteine errors, although the exact nature of these errors was not clear.

Infusion pump calibrations were not assessed as part of this study.

Discrepancies in the volumes in infusion could also contribute to delays. From personal communication with the manufacturer for the infusion bags used in London, the range of volumes in infusion bags were: 265–277mL (250mL bag), 520-540mL (500mL bag) and 1025-1069mL (1000mL bag). Infusion times would be longer than expected if the infusion pumps were not set to account for these volumes and the volume of acetylcysteine added. However, there is a small volume of infusion fluid left in tubing and the infusion bag on completion of the infusion. These factors could contribute to short delays but would not result in the magnitude of delays found in this study.

With stop times inadequately recorded in this study it is difficult to ascertain whether the delays are mostly occurring between infusions or during infusions. Our study demonstrated longer delays between the start of infusions 2 and 3 compared to between the start of infusions 1 and 2, (in view of the longer duration of infusion 2) this suggests that delays are likely also occurring during the infusions rather than simply delays in starting the next infusion. Delays for patients with anaphylactoid reactions were longer between the start of infusions 1 and 2 compared to between the start of infusions 2 and 3. This suggests that reactions may have been more frequent or severe during the first infusion compared to the second infusion. However, there were few patients with documented anaphylactoid reactions limiting the interpretation of this finding.
Acetylcysteine dosing tables produced by the MHRA, as part of the 2012 changes to UK guidelines on the treatment of paracetamol overdose, were used in all three centres. [1] These were produced with the aim of simplifying drug calculations and preparation; and providing the volume of acetylcysteine to be added for each infusion.

Delay to initiation of acetylcysteine is another aspect of the treatment of paracetamol overdose where delays occur. This was not assessed in this study. The RCEM Paracetamol Overdose Clinical Audit 2013-2014 found that for patients presenting less than 8 hours from ingestion 50% received treatment with acetylcysteine within the recommended 8 hours of ingestions. [10] For patients presenting more than 8 hours after ingestion 80% of Emergency Departments did not administer acetylcysteine to any patients within the recommended 1 hour. [10] In a single centre audit, Pettie and colleagues found that for patients presenting either 8-24 hours post-ingestion or with staggered overdose and considered at risk of hepatotoxicity, 12% had acetylcysteine started within 90 minutes of arrival and this improved to 61% following the introduction of an integrated care pathway. [11] Improvements were also made to blood sampling and treatment decisions and prescription errors were reduced.

To improve administration times the problem should be highlighted to those treating patients with intravenous acetylcysteine. During nursing and medical handovers the prescribed planned start and finish times for each infusion could be reviewed and infusion times monitored. All three centres in this study
Currently use paper prescription charts of acetylcysteine - electronic prescribing systems could aid this process, including medication administration timing reminders or alerts to notify staff that there has been a delay in the infusion time. Electronic prescribing should also improve documentation of infusion times and times will be standardised / co-ordinated rather than relating to individual watches / clocks.

Preparation of the second and third infusions immediately after the first has started, so they can be changed more quickly, could reduce delays in between infusions. Improved documentation of infusion stop times would help to identify which steps are associated with the longest delays and determine the extent of the delays for the full three infusions. If a delay is recognised, the infusion rate could be increased to target the planned infusion stop time. This is unlikely to increase adverse effects because these occurred at similar rates when the first infusion was previously administered over 15 minutes in the UK. [12]

Recently, a number of alternative two infusion acetylcysteine regimes have been trialled, and these are associated with a lower incidence of adverse effects. [13,14,15,16,17] By reducing the number of infusions required, these are also likely to reduce delays in infusions. The SNAP regimen used by Bateman and colleagues [13] is shorter (over 12 hours) and therefore would significantly reduce total infusion times irrespective of the delays. However, despite promising initial results, further evidence is required to demonstrate the efficacy of this shorter regimen.
Limitations

The study relied on retrospective data collection for identifying infusion start times; it is possible these may not reflect the actual start time of the infusions. Data collection was from handwritten medical notes, with times recorded from non-standardised clocks. Due to inadequate recording of stop times the delays reported are in most cases between the start of the first and third infusions and therefore will under represent the extent of total delays. Markers of hepatotoxicity, paracetamol concentrations and patient outcomes were not recorded in this study.

Conclusion

Long delays were identified during the three-infusion acetylcysteine regimen for the treatment of paracetamol overdose. Delays will increase the length of hospital stay and were of clinical significance and could lead to sub-therapeutic plasma acetylcysteine concentrations and potentially avoidable hepatotoxicity. Early preparation of infusions, adjusting infusion times to compensate for delays and novel regimens with two infusions are options that may reduce delays.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: SHLT and PID are members of the Commission on Human Medicines Paracetamol Expert Group. No other competing interests.
Table & Figure Legends

Table 1: Comparisons between different groups for median delays between the start of infusions 1 to 3. Groups were compared with the Mann-Whitney U test. Note: smoking status, anaphylactoid reactions and cannula problems were not recorded for all patients.

Figure 1: The delays in minutes compared to prescribed times from the start of infusion 1 to the start of infusion 3 for the three hospitals.

References


