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RESEARCH ARTICLE

Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions

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ABSTRACT

Context: Adverse reactions to intravenous (IV) acetylcysteine treatment in paracetamol overdose, are common. Previous studies suggest the incidence and severity of non-allergic anaphylactic reactions (NAARs) are influenced by the rate of acetylcysteine infusion. **Objective:** We compared the incidence of adverse drug events of a two-bag IV acetylcysteine regimen with that of the traditional three-bag regimen. **Materials and methods:** This was a retrospective analysis of patients presenting with paracetamol overdose requiring treatment with acetylcysteine to three emergency departments. We prospectively identified all presentations where IV acetylcysteine was administered using a 20 h, two-bag regimen (200 mg/kg over 4 h followed by 100 mg/kg over 16 h) from February 2014 to June 2015. We compared this to an historical cohort treated with the 21 h three-bag IV regimen (150 mg/kg over 1 h, 50 mg/kg over 4 h and 100 mg/kg over 16 h) from October 2009 to October 2013. Medical and nursing notes were searched retrospectively for entries suggesting the presence of an adverse reaction. The primary outcome was incidence of NAARs and gastrointestinal reactions in each group. **Results:** 389 presentations were treated with the three-bag regimen and 210 presentations received the two-bag regimen. NAARs were recorded more commonly with the three-bag acetylcysteine regimen than the two-bag regimen (10% vs 4.3%, $p = 0.02$, OR 2.5, 95% CI 1.1–5.8). There was no difference in reports of gastrointestinal reactions between cohorts (three-bag 39% vs two-bag 41%, $p = 0.38$, OR 1.17 95% CI (0.83–1.65)). **Discussion:** The incidence of NAARs was significantly reduced by combining the first two bags of the traditional three-bag regimen and infusing these over 4 h at 50 mg/kg/hr. Simplifying the administration of acetylcysteine may have other benefits such as better utilisation of nursing time and reduced infusion administration errors. **Conclusions:** A two-bag 20 h acetylcysteine regimen was well tolerated and resulted in significantly fewer and milder NAARs than the standard three-bag regimen.

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Introduction

Paracetamol overdose is the most common pharmaceutical poisoning in developed countries and its incidence is increasing in the developing world.[1,2] Untreated, overdose can lead to liver failure, and in the worst circumstances, death.[3] In overdose, the increased production of N-acetyl para-benzoquinoneimine (NAPQI) depletes hepatic glutathione stores and eventually causes hepatocyte injury.[4] Timely administration of acetylcysteine prevents the development of hepatotoxicity following a paracetamol overdose and can mitigate toxicity in late presenting patients. The currently recommended IV acetylcysteine regimen, used in many countries, utilises a 21 h, three-step administration, with a loading dose of 150 mg/kg over 15 min or 1 h, 50 mg/kg over 4 h and 100 mg/kg over 16 h.[5]

Adverse reactions to acetylcysteine infusions are common and include gastrointestinal effects such as nausea and

vomiting and non-allergic anaphylactic reactions (NAARs) which are reported with 14% to 75% of administrations.[6,7] NAARs range from more common mild cutaneous reactions (rashes, flushing/erythema, urticaria) to less common and more severe reactions (angioedema, bronchospasm, hypotension).[6,7] Previous studies suggest that the incidence and severity of NAARs may be influenced by the rate of acetylcysteine infusion.[5,7]

Our institution recently implemented a two-bag acetylcysteine regimen in which the first two bags of the standard regimen were combined to administer a 200 mg/kg loading-dose over 4 h. The 16 h infusion (100 mg/kg) was left unchanged. The aim was to simplify the administration regimen. Based upon the previous reports, we also theorised that the slower loading-dose infusion may be associated with a lower rate of histamine-type reactions.[5,7] We compared the rate of adverse drug events after the first two-years of implementation

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of the two-bag regimen with that of an historical control cohort from our hospital network treated with the standard three-bag regimen prior to the change.[8]

Methods

Study design and settings

This was an analysis of patients presenting with the paracetamol overdose requiring treatment with acetylcysteine to any of the three Emergency Departments (ED) of the Monash Health Emergency Medicine Program in Victoria, Australia. Monash Health comprises Monash Medical Centre Clayton (tertiary and paediatric), Monash Dandenong and Monash Casey Hospital, Berwick (both with mixed adult and paediatric patients). The Monash Emergency network patient census comprises approximately 200 000 presentations per year, with around 2500 poisoning presentations. The study was approved by the Monash Health Human Research and Ethics Committee as a low-risk clinical audit.

The new acetylcysteine regimen was commenced across the network in February 2014. From this date, patients with paracetamol poisoning requiring treatment with acetylcysteine were prospectively identified after referral to the toxicology service. At Monash Dandenong Hospital, all paracetamol overdoses requiring admission were managed directly by the toxicology team in a dedicated toxicology unit. At Monash Clayton and Monash Casey Hospitals, patients were admitted under the relevant general medical units with toxicology consultation. Medical records were reviewed post-discharge.

Data for the traditional three-bag regimen control group was obtained for the period October 2009 to October 2013, when the toxicology service was purely a consult service across the network. Admissions with paracetamol poisoning were identified from a search of the ED electronic medical record database (EMR) (Symphony, Version 2.29, Ascribe, Bolton, UK) by ED discharge diagnosis "Poisoning/overdose, Paracetamol" or "Poisoning/overdose Paracetamol with liver damage", or looking for free text in the triage information "paracetamol", "panadol" or "overdose" to identify any patients who were a missed referral to the toxicology service and treated with acetylcysteine. The ED EMR was also searched regularly during the new treatment regimen period to identify any admissions with acetylcysteine-treated paracetamol poisoning that may not have had a toxicology consultation.

A spreadsheet was created to collate relevant demographic and clinical data including: type of paracetamol product and formulation; patient age and sex; dose of paracetamol ingested; total acetylcysteine dose; duration of infusion; adverse reactions to acetylcysteine; time from overdose to acetylcysteine; length of stay; type of paracetamol overdose (deliberate self-poisoning, supra-therapeutic ingestions, accidental); prescribing errors; median paracetamol concentration; time to paracetamol concentration; initial and subsequent alanine transaminase (ALT).

We identified all admissions where IV acetylcysteine was administered using the two-bag regimen (200 mg/kg in 500 ml of 0.9% saline over 4 h followed by 100 mg/kg in 1 l of 0.9% saline over 16 h) from February 2014 to June 2015. We

compared this group to a historical cohort of patients with paracetamol overdose treated with the standard three-bag IV acetylcysteine regimen (150 mg/kg in 200 ml 0.9% saline over 1 h, 50 mg/kg in 500 ml 0.9% saline over 4 h and 100 mg/kg in 1 l 0.9% saline over 16 h) from October 2009 to October 2013, and described previously.[8] Patients presenting with the paracetamol overdose and not receiving acetylcysteine were excluded from analysis.

Outcome measures

Our primary outcome was the incidence of NAARs and gastrointestinal reactions in each group. NAARs were classified into cutaneous symptoms (flushing, rash, urticaria, wheals, itch); and more severe reactions including respiratory symptoms (bronchospasm, wheeze, dyspnea, shortness of breath) and angioedema or cardiovascular instability (i.e., hypotension). Gastrointestinal symptoms included nausea, vomiting or both. Patient medical records were examined retrospectively for both patient groups. The medical and nursing notes were searched for key words suggesting an adverse reaction (e.g., hot, flushing, rash, urticaria, wheals, short of breath, wheezing, bronchospasm, hypotension). Medication charts were reviewed for the presence of any possible adverse reaction treatments (antiemetics, adrenaline, salbutamol, antihistamines). Fluid order charts (acetylcysteine doses) and the hospital pathology database (paracetamol concentration, serum aminotransferases, INR) were also used to source the study data. Secondary outcomes included length of hospital stay and prescribing errors.

Descriptive data are reported as mean with 95%CI or medians and interquartile range (IQR). Categorical variables were analysed using the Fisher exact test. Comparative continuous variables were compared using unpaired *t*-test for normally distributed data and the Kolmogorov–Smirnov test for non-normally distributed data. Statistical analysis was performed using GraphPad InStat V 3.1 and GraphPad Prism V6 (GraphPad software, La Jolla, CA)

Results

There were 470 presentations with a diagnosis of paracetamol overdose with or without liver toxicity identified during the two-bag treatment period. Of these, 210 (44.7%) received the acetylcysteine two-bag regimen (Table 1). In the historical cohort, there were 920 presentations identified during the study period, with 389 (42.3%) receiving the acetylcysteine three-bag regimen. The majority of presentations were female and up to one-quarter were adolescents. In-patient medical ward median length of stay was similar between both cohorts. With the implementation of an admitting toxicology unit at Dandenong Hospital, where patients are treated in the ED short stay unit, the median length of stay for patients was significantly less than for patients admitted to a medical unit (1 day vs 2 days respectively, $p < 0.001$). There was a larger proportion of supratherapeutic paracetamol ingestions treated with acetylcysteine in the two-bag regimen group and deliberate self-poisoning was the commonest reason for the paracetamol overdose in both groups (Table 1).

Table 1. Demographic data of patients presenting with paracetamol overdose who received acetylcysteine.

	2 bag regimen Total= 210	3 bag regimen Total= 389
Gender % female (n)	80 (168)	78 (305)
Median weight kg (IQR*)	64 (55–80)	64 (55–80)
Median Age years (IQR)	27 (18–42)	22 (17–35)
Age <18 years old % (n)	23.8 (50)	28.2 (107)
12–18 years old % (n)	21 (44)	27.5 (106)
Intent – deliberate % (n)	84 (177)	95 (370)
- supratherapeutic % (n)	15 (32)	4.3 (17)
Reported to ingest only paracetamol % (n)	35 (74)	50 (195)
Presentation deliberate self poisonings for acute ingestions (<8 h) % (n)	42 (88)	71 (276)
Treated in ED Short Stay % (n)	38 (80)	8.4 (33)
Median (IQR) length of stay/hours	24 (24–48)	11 (11–20)
Ward admission median length of stay -days (IQR)	2 (2–3.25)	3 (2–4)

*IQR: Interquartile range

Patients receiving the two-bag acetylcysteine regimen had a smaller median total reported dose of paracetamol ingested in acute and supratherapeutic ingestions. However, this group had a higher mean dose of ingestion by weight compared to the three-bag regimen (Table 2) for supratherapeutic ingestions. There was no significant difference in mean paracetamol concentration on presentation between cohorts. There was a similar number of late presenters (>8 h post overdose) with acute overdose, in each group, who failed to have acetylcysteine started on presentation (8.5% vs 8.9% in the two-bag and three-bag regimens, respectively).

There was no difference in the reports of gastrointestinal reactions between cohorts (two-bag 41% vs three-bag 39%, $p=0.38$, OR 1.17 95%CI (0.83–1.65)) (Table 3). Nausea and vomiting together were recorded more frequently than nausea alone in both groups. NAARs were recorded less commonly with the two-bag acetylcysteine regimen than the three-bag regimen (4.3% vs 10%, $p=0.02$, OR 2.5, 95%CI 1.1–5.8). There were also more severe NAARs recorded when the three-bag regimen was used. One episode of hypotension (86/55 mmHg) occurred during the two-bag regimen and responded to 1 l of crystalloid alone and temporary acetylcysteine cessation. The seven severe NAARs that occurred using the three-bag regimen required the temporary cessation of acetylcysteine in all and use of subcutaneous adrenaline ($n=2$), intravenous steroids ($n=3$), bronchodilators ($n=2$), antihistamines ($n=3$) and intravenous crystalloid fluids ($n=2$). The median paracetamol concentration was significantly lower in patients who had NAARs versus those that did not receiving the two-bag acetylcysteine regimen (153 (69–952) mmol/l vs 894 (325–1360) mmol/l, $p=0.04$) and three-bag regimen (644 (111–950) mmol/l vs 1048 (671–1385) mmol/l, $p=0.0002$).

There were no deaths or transfers to the liver transplant unit in either cohort during the study periods. There was no significant difference between the rates of hepatotoxicity (ALT >1000 IU/L) between patients using the two-bag regimen compared to the three-bag regimen (5.2% vs 4.3%, $p=0.68$, OR 1.2 95%CI 0.55–2.63).

Discussion

The treatment of paracetamol overdose with a three-bag IV acetylcysteine regimen has remained largely unchanged in

Table 2. Comparison of overdose and treatment data between patients who received acetylcysteine following paracetamol overdose.

	2 bag regimen Total= 210	3 bag regimen Total= 389	p
Median reported paracetamol dose single ingestion grams (IQR)	15 (10–22)	18 (12–25)	0.05
Total number ingestions	155	370	
Median reported paracetamol dose supratherapeutic ingestion grams (IQR)	12.5 (9.6–20)	17.8 (11.6–23)	0.54
Total number of ingestions	32	17	
Mean reported paracetamol dose for single ingestions by weight mg/kg (95%CI)	275 (253–299)	320 (297–343)	0.29
Mean reported paracetamol dose for supratherapeutic ingestions by weight mg/kg (95%CI)	293 (150–436)	239 (192–436)	0.04
Mean serum paracetamol concentration micromol/L in acute overdose (<24 h post-ingestion) (95%CI)	917 (822–1014)	1100 (1040–1160)	0.7
Median time to concentration – hours (IQR)	6 (4–11)	5 (4–8)	
Median acetylcysteine dose grams all patients (IQR)	19.5 (16.5–27)	19.5 (16–24.6)	0.40
Median acetylcysteine duration hours (Range)	20 (1–100)	21 (1–133)	-
Prolonged acetylcysteine infusion % (n)	12 (25)	11.5 (45)	0.89*

*Denotes Fisher's exact test, otherwise the Kolmogorov–Smirnov test.

Table 3. Comparison of the incidence of adverse reactions between the TWO-bag and THREE-bag acetylcysteine regimens.

	2 bag regimen (n= 210)	3 bag regimen (n= 389)	p
NAARs** total % (n)	4.3 (9)	10 (40)	0.01
rash/urticaria/itch % (n)	3.8 (8)	8.4 (33)	0.04
Severe reaction % (n)	0.5 (1) hypotension	2.5 (7) Wheeze, angioedema or hypotension	0.0001
Median paracetamol concentration mmol/l (IQR) for NAARs	153 (69–952)	644 (111–950)	0.27*
Median paracetamol concentrations mmol/l (IQR) in patients without NAARs	894 (325–1360)	1048 (671–1385)	0.001*
GI reactions total % (n)	41 (87)	39 (150)	0.38
Nausea only % (n)	15(32)	7 (28)	0.003
Nausea and vomiting % (n)	26 (55)	32 (122)	0.11
Prescribing errors % (n) (all ten-fold acetylcysteine under-dosing)	1.4 (3)	0.5(2)	0.35

*Denotes Kolmogorov–Smirnov's test, otherwise Fisher's exact test used.

**NAARs non-allergic anaphylactic reaction

Australia for the last 35 years.[9] The duration of the loading-dose was increased from 15 min to 1 h in Australia following the study by Kerr et al.[5] that showed a non-significant drop in observed histamine-release reactions from 18% to 14% with this intervention. Unfortunately, this study did not reach its predetermined sample size. A similar loading-dose rate is currently used in the US and UK.[5] The current study found that the incidence of NAARs was reduced significantly by combining the first two bags of the traditional three-bag regimen and infusing these over 4 h at 50 mg/kg/hr. Bateman et al.[7] have reported a prospective study with a lower incidence of gastrointestinal reactions and histamine reactions with a loading-dose of acetylcysteine of 100 mg/kg over 2 h followed by 200 mg/kg acetylcysteine infused over 10 h as part

of a 12 h regimen.[7] They observed around a 20% reduction in NAARs compared to their three-bag regimen control group. However, the incidence of significant anaphylactic-type reactions was higher. NAARs have also been reported more commonly in patients with lower serum paracetamol concentrations.[10,11] We also found that the median paracetamol concentration was lower in patients with NAARs, with both regimens compared to patients who did not exhibit this adverse event.

There was a higher percentage of patients receiving the two-bag regimen reporting supratherapeutic ingestions than with the three bag regimen. Reasons for this may include the prospective identification of this group with the two-bag regimen and a lack of correct diagnosis coding in the historical cohort or lack of referral to the toxicology unit during the control period.

We noted a shorter median length of stay in patients receiving the two-bag acetylcysteine regimen. This was most likely the influence of a change in admission disposition of paracetamol poisoned patients to the toxicology unit co-located in the ED short-stay unit, rather than as a medical admission to the hospital ward setting (the historical cohort). Emergency medicine observation units have been shown to decrease the length of stay of selected patient populations.[12] In particular, the 24 h model of care in such units allows self-poisoning patients to receive timely mental health assessment once medically cleared. Earlier formulation of a mental health plan means disposition decisions and need for mental health admission can be made more efficiently than in the general ward setting.

Prescribing errors were similar in both groups. All of these were ten-fold acetylcysteine under-dosing errors. Although not assessed in this study, use of a fewer infusion bags has the potential to decrease the incidence of prescribing and administration errors in the long term. Numbers were too small to assess this as an outcome in our study. Electronic prescribing or preformatted acetylcysteine prescribing forms may also help decrease these errors.[13,14]

There are a number of limitations that should be considered with regard to a retrospective study of paracetamol poisoning. Patients presenting with the other drug ingestions who have taken paracetamol requiring acetylcysteine treatment may not have been identified in the search. Patients with incorrect discharge diagnoses entered onto the hospital database may not have been identified as having a paracetamol overdose. While this may have affected the numbers collected in the control group, during the period where the new regimen was implemented most patients receiving acetylcysteine were referred to the toxicology service or identified by the team on regular checks of the ED SMR of poisoning admissions. In both groups, the search for adverse reactions was retrospective, from ED and ward medical and nursing notes. It is possible that very mild reactions may not have been recorded in both cohorts and the incidence may have been greater than reported in the notes. This is consistent with previous retrospective studies in which the incidence of NAARs has been up to 23%[15,16] compared to prospectively collected observational data where reports have been in the range of 40–65%.[5,7] However, the absolute incidence between our two cohorts

should be internally valid, given that the data were collected in a similar way for both time periods. Also, we searched for evidence of treatment of more severe reactions and the use of agents to treat these (e.g., antihistamines, adrenaline, bronchodilators) and found no recorded use of such agents with the two-bag regimen.

A larger study would be required to detect any difference in incidence of hepatotoxicity developing in patients between the two regimens. During the two periods, no patients were transferred to the state liver transplant service or died with either regimen. Notably, most patients presented within 8 h of ingestion in both groups when the risk of hepatotoxicity with timely treatment is very low. The total dose of acetylcysteine delivered in each regimen was the same over a similar time period. The number of patients with established hepatotoxicity on presentation was small in both the groups. Given the lower risk of NAARs with the two-bag regimen, it may be advantageous to have a slower loading-dose rate in the late presenter group, where serum paracetamol concentration is usually much lower than in early presenters. The late presenter subgroup may be sicker and the risk of a significant NAARs reaction may be greater, particularly with the three-bag regimen.

Conclusions

A two-bag acetylcysteine regimen was well tolerated and resulted in significantly a fewer and milder NAARs compared with the standard three-bag regimen. There was no change in the incidence of gastrointestinal reactions between regimens. The optimal infusion regimen for acetylcysteine has not been elucidated. Further tailoring of acetylcysteine dosing based upon clinical risk, paracetamol concentration, time post-ingestion and liver function may, in the future, result in variations in infusion duration based upon these variables.

Declarations of interest

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