NAC regimens for paracetamol overdose – time for a change?

Short title: NAC for paracetamol OD

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Words 1482

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1742-6723.12610

NAC regimens for paracetamol overdose – time for a change?

Abstract

Paracetamol overdose is one of the commonest pharmaceutical poisonings in the world. For nearly four decades intravenous acetylcysteine regimens have been used to treat most patients successfully and prevent or mitigate hepatotoxicity. However, the rate of occurrence of adverse reactions to acetylcysteine is quite high and there is a potential for these to be reduced. Recent studies show that distributing the loading-dose of acetylcysteine over the first few hours of treatment may decrease the incidence of adverse reactions. In addition, varying the duration of acetylcysteine administration may potentially benefit certain cohorts of poisoned patients, depending upon their risk of developing hepatotoxicity.

Paracetamol poisoning is one of the most common causes of acute liver failure in the developed and developing world. Some case series quote an incidence for liver failure of over 40% [1]. After paracetamol overdose, hepatic glutathione stores are depleted and liver injury results from the accumulation of the toxic metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Acetylcysteine (N-acetylcysteine or NAC) is administered to replenish hepatic glutathione and facilitate metabolism of NAPQI to non-toxic glutathione conjugates. The intravenous (IV) acetylcysteine regimen first described by Prescott[2] in 1977 has largely remained unchanged over time and is used in many countries. It is given over 21-hours, in three steps, with a loading-dose of 150mg/kg over 15 minutes or 1 hour, 50mg/kg over 4 hours and 100mg/kg over 16 hours[3]. This regimen has been used as a "one dose fits all" treatment for paracetamol overdose. However, some patients may not develop hepatotoxicity with a shortened duration of treatment, while others may require extended treatment or larger doses of acetylcysteine. This review describes the rationale behind current acetylcysteine dosing, and highlights recent studies that have modified this, with the primary intent to decrease adverse reactions as well as tailor treatment to specific poisoning scenarios.

Rationale for acetylcysteine dosing

No formal studies have been undertaken to determine the appropriate dosing of IV acetylcysteine. In addition, there are no randomised controlled trials (RCTs) evaluating its effectiveness compared with placebo. The rationale for the dosing regimen of IV acetylcysteine has not been published. It delivers a two-part loading-dose, which is larger than the oral regimen used previously in the US. The dosing rationale for IV acetylcysteine can be inferred from the theoretical assumptions used to determine the oral dosing regimen.

In the early 1980s, the US FDA required a detailed rationale for the oral dosing regimen prior to its adoption in 1985. When determining the amount of acetylcysteine required to prevent hepatotoxicity, stoichiometric calculations of acetylcysteine and paracetamol were performed. It was determined that one mole of glutathione depletion would be matched by one mole of acetylcysteine replacement. This made the assumption that the ratio was sufficient to cover endogenous glutathione loss from

paracetamol metabolism. It was also assumed that the average adult liver contains 4 mmol/L of glutathione[4] and that 4% (635 mg) of a 15 gram paracetamol overdose would be metabolised by cytochrome enzymes, to the toxic metabolite NAPQI.

In animal studies, hepatic necrosis was observed when endogenous glutathione stores were depleted to 70% of baseline. Hence, in a 1.5 L liver that contains 6 mmol of glutathione), 4.2 mmol would be required to metabolise a 15 gram ingested dose of paracetamol. The decision was made to replace glutathione at 25% per hour assuming a paracetamol elimination half-life of 4 hours. Therefore replacing glutathione at 1mmol/hour.

These calculations assumed that glutathione is produced at a constant rate and liver glutathione stores were the same for each individual. This mmol per hour calculation translates into a 6mg/kg/hr acetylcysteine dose for the US oral regimen plus a 12mg/kg/hr loading-dose. To further increase the safety factor the FDA recommended a 72-hour regimen of 140mg/kg loading-dose followed by 70mg/kg every four hours (1400mg/kg total dose). This prolonged treatment duration assumed that paracetamol half-life was 12 hours after overdose. In comparison, the IV regimen assumed a paracetamol half-life of four hours after overdose, with infusion duration of five half-lives, which equates to a total time of 20-21 hours. Notably, calculations were performed at a time when serial paracetamol concentrations were difficult to obtain. By performing serial paracetamol concentrations, these treatment regimens may potentially have been shortened.

Another limitation of these calculations was that they assumed a single dose of paracetamol ingestion. Given the accommodation of a safety factor this increased the generalizability of a single approach. The oral regimen was primary treatment regimen used in the U.S. until 2004. After this time, the three-step 20-hour intravenous regimen was also approved. In the UK and Australia, the IV acetylcysteine regimen has been used for nearly four decades.

Adverse Reactions to Acetylcysteine

Adverse reactions to IV acetylcysteine are common and include gastrointestinal effects such as nausea and vomiting and non-allergic anaphylactic reactions (NAARs) or non-IgE mediated reactions. The latter have been reported in 14% to 75% of patients receiving intravenous acetylcysteine [5, 6]. NAARs range from more common, mild cutaneous reactions (rashes, flushing/erythema, urticaria) to less common, and more severe, reactions (angioedema, bronchospasm, hypotension). Previous studies suggest that the incidence and severity of non-allergic anaphylactic reactions may be influenced by the rate of acetylcysteine infusion[3, 6]. Reactions are more common during or immediately following the loading-dose. Transient cessation of the infusion, treating symptoms and restarting at an initial slower rate is the current management. Kerr et al.[3], describe an unblinded RCT of 180 patients receiving acetylcysteine after acute paracetamol poisoning. A non-significant reduction in NAARs was seen when the duration of the acetylcysteine loading-dose was increased from 15 to 60 minutes (18% to 14%). Subsequent to this trial, a number of centres in Australia, the U.S. and the U.K. recommend a one-hour duration for the 150mg/kg loading-dose of acetylcysteine.

Recent studies on alternative acetylcysteine regimens

Three recent studies have reported on reducing the infusion rate of the loading-dose of acetylcysteine to 50mg/kg/hr[6-8]. Bateman et al. undertook an RCT comparing a two-bag 12-hour acetylcysteine regimen (100mg/kg over 2 hours, followed by 200mg/kg over 10 hours) to the three-bag 21-hour Prescott regimen (150mg/kg over 15-minutes, 50mg/kg over 4-hours, 100mg/kg over 16-hours). They observed a reduction in the incidence of gastrointestinal side effects and need for anti-emetic rescue treatment at 2-hours post initiation of acetylcysteine (36% vs 65%, OR 0.26, $p<0.0001$) with the two-bag regimen compared to the three-bag regimen. In addition, the incidence of severe anaphylactoid reactions was also decreased (5% vs 28%). Eleven percent of all patients had a 50% rise in alanine aminotransferase (ALT) which did not differ significantly between the two groups, All of these patients received prolonged acetylcysteine treatment. However, the outcome of hepatotoxicity (defined as an ALT>1000) was low overall (2% with two-bag vs 3% with 3-bag regimen).

Wong and Graudins[7] reported on 210 patients treated with a two-bag acetylcysteine

regimen (200mg/kg over 4 hours, followed by 100mg/kg over 16 hours) and compared this to a historical cohort of 389 patients receiving the three-bag regimen. The two-bag regimen combined the first two treatment bags of the three-bag regimen and was administered over four hours. They found that the two-bag regimen was associated with significantly less NAARs (4.3% vs 10%, p=0.02) when compared to the three-bag regimen. In addition, no patients required treatment with adrenaline in the management of NAARs when given the two-bag regimen. The incidence of hepatotoxicity was similar between groups.

Isbister et al[8] performed a prospective observational study also using a two-bag acetylcysteine treatment regimen in 654 patients. The first bag (200mg/kg) was administered to all patients reporting an acute overdose of paracetamol over a variable time period (4 to 9 hours), depending upon the time to presentation. The second bag (100mg/kg) was infused over 16 hours. Acetylcysteine was stopped if the serum paracetamol concentration was subsequently found to be under the nomogram treatment line. The authors found that those taking a toxic dose of paracetamol had fewer adverse reactions to acetylcysteine compared to those taking a non-toxic dose of paracetamol. Gastrointestinal reactions were seen in 26.5% of patients, skin reactions in 8% and severe anaphylaxis in 0.5%. This regimen was more complex than those with a fixed loading-dose infusion rate. Interestingly, 64% of those treated were subsequently found to not-require acetylcysteine treatment as defined by a non-toxic serum paracetamol concentration. None of the three abovementioned studies was large enough to assess the effect of the infusion regimens on the incidence of hepatotoxicity.

Future directions and trials

The three studies cited above suggest that a reduction in the rate of administration of the acetylcysteine loading-dose to 50mg/kg/hr is safe and appears to result in a reduced rate of NAARs compared to the standard dosing regimen. In addition, a reduction in the number of changes to infusion rates and preparation of acetylcysteine bags may have added benefits by reducing the risk of dispensing errors and reducing nursing time on infusion preparation. A larger trial is required to assess these outcomes as well as any difference in the incidence of hepatotoxicity compared to the

three-bag regimen. Currently in Australia, a number of hospitals with clinical toxicology units have adopted the two-bag acetylcysteine regimen (200mg/kg over 4 hours, 100mg/kg over 16 hours).

Finally, there is a cohort of patients with paracetamol poisoning who can be defined as having a low risk for developing hepatotoxicity with acetylcysteine treatment. [9, 10]. This group may respond favourably to an abbreviated course of acetylcysteine. Benefits of this approach may include reduced hospital treatment times and earlier referral for mental health assessment and admission. Future trials should aim to study whether abbreviated acetylcysteine regimens are practical and safe in low risk-patients.

Competing Interests:

AG is a toxicology section editor for EMA.

Funding:

AW has received a NHMRC Postgraduate Scholarship.

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