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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetic modelling of modified acetylcysteine infusion regimens used in the treatment of paracetamol poisoning

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Abstract
Purpose Paracetamol overdose is common and is treated with acetylcysteine to prevent the development of hepatotoxicity. N-acetyl-p-benzoquinone imine (NAPQI) is the toxic metabolite of paracetamol overdose. We aimed to assess the expected acetylcysteine concentration time profiles following delivery of modified acetylcysteine regimens proposed for those at high and low risk of hepatotoxicity. In addition, we will determine acetylcysteine concentrations post-cessation of abbreviated infusions.
Method We performed pharmacokinetic simulations using Berkeley Madonna (version 8.3.23.0) comparing the time course of acetylcysteine concentration during and after the cessation of an abbreviated 12-h regimen (250 mg/kg) using a two-bag infusion and compared this to the standard 21-h three-bag (300 mg/kg) regimen. We also simulated extended duration acetylcysteine regimens and other increased dosing strategies that have been recommended in specific paracetamol poisoning scenarios.
Results A more sustained serum concentration is achieved when the acetylcysteine loading dose is delivered over 4 h using the two-bag compared to the 1-h loading dose of the three-bag regimen. When administering an abbreviated 12-h acetylcysteine regimen, circulating acetylcysteine is detectable for 8 h after cessation of the infusion. This may provide a continued hepatoprotective effect if NAPQI is still being generated after the infusion is ceased.
Conclusion This pharmacokinetic simulation study is an important step in determining plasma acetylcysteine concentrations that are likely to be achieved using various modified treatment regimens. Importantly, for patients at low risk of liver injury after acute overdose, acetylcysteine is likely to be detectable many hours post-cessation of a 12-h regimen. This should provide a safety factor against development of hepatotoxicity for any ongoing paracetamol metabolism after cessation of the acetylcysteine infusion.

Keywords Acetaminophen · Hepatotoxicity · Abbreviated · NAC

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Introduction

Paracetamol is one of the most common medications taken in overdose around the world [1]. It is readily available and does not require a prescription to purchase. N-acetyl-p-benzoquinone-imine (NAPQI) is the toxic intermediary metabolite of paracetamol that accumulates in the liver after overdose when glutathione stores are depleted. Acetylcysteine (*N*-acetylcysteine or NAC) is the antidote used to replenish glutathione stores and treat patients at risk of developing hepatotoxicity following paracetamol overdose [2].

The decision to treat acute paracetamol overdose with acetylcysteine is based on a timed paracetamol concentration plotted on a treatment nomogram, as described in the current Australasian management guideline [3]. The standard

acetylcysteine treatment regimen, used for several decades, lasts 20.25 to 21 h (150 mg/kg of acetylcysteine intravenously (IV) over 15–60 min, followed by 50 mg/kg acetylcysteine over 4 h and 100 mg/kg acetylcysteine over 16 h [4]) and requires admission to hospital.

To simplify acetylcysteine dosing, we instituted a two-bag acetylcysteine regimen in our institution, consisting of 200 mg/kg infused over 4 h followed by a further 100 mg/kg infused over 16 h. Previously, we have reported our experience with this in a cohort of patients treated in our centre [5]. The total acetylcysteine dose and duration of administration was similar to the standard acetylcysteine regimen [4]. However, the incidence of non-allergic anaphylactic reactions was substantially reduced.

When the original intravenous acetylcysteine regimen was first proposed in the 1970s, serum paracetamol assays were not widely available in hospitals. The 20-h infusion duration was empirically selected assuming five paracetamol elimination half-lives of 4 h would result in low or undetectable serum concentration at the end of the infusion [6]. Serial paracetamol serum assays are now routine. These can provide reassurance that hepatic function is preserved when the serum paracetamol concentration falls by at least 90% over 12 h (i.e., greater than three half-lives) [7]. An additional factor that confers safety is that acetylcysteine has an elimination half-life longer than paracetamol in patients at low risk of hepatotoxicity.

A recent randomized trial of 300 mg/kg acetylcysteine administered over 12 h demonstrated the feasibility of a shortened duration treatment regimen. It also noted a decrease in adverse reactions when compared to the original three-bag regimen [8]. Such trials are important to help determine which patients will benefit from shorter acetylcysteine regimens, as well as those likely to need extended treatment.

In a previous study, various acetylcysteine regimens have been simulated using a computer-based pharmacokinetic model [9]. However, to date, no studies report the pharmacokinetics of acetylcysteine when stopping our institutional two-bag infusion regimen at 12 h, in patients at low risk of hepatotoxicity. Low risk is defined as a paracetamol serum concentration less than 20 mg/L and normal hepatic aminotransferases after 12 h of acetylcysteine infusion. Similarly, there have been no simulations undertaken of an abbreviated regimen for treatment of repeated supratherapeutic paracetamol ingestion (RSTI) [10]. In addition, for patients at high risk of hepatotoxicity, the pharmacokinetics of higher dose, or more commonly used extended duration acetylcysteine regimens for those with ongoing paracetamol metabolism or evidence of liver injury have not been modelled.

We aimed to model acetylcysteine concentration after early cessation of the infusion using the abovementioned two-bag acetylcysteine regimen and determine how long acetylcysteine is present and the concentrations associated. This infusion is stopped at 12-h (250 mg/kg) rather than the 20-h complete infusion (300 mg/kg). We compare this to predicted plasma concentration after administration of the widely used 21-h three-bag regimen [5]. This pharmacokinetic model is being used to inform an ongoing clinical trial assessing the safety of the abbreviated acetylcysteine regimen. In addition, we aimed to model a modified acetylcysteine regimen for RSTI and prolonged and higher dose acetylcysteine regimens.

Method

Computer simulations were performed comparing the expected acetylcysteine concentration during and after cessation of the abbreviated two-bag 12-h regimen (200 mg/kg over 4 h and 50 mg/kg over 8 h, total = 250 mg/kg over 12 h) and compared this to the 20-h three-bag (200 mg/kg over 4 h and 100 mg/kg over 16 h, total = 300 mg/kg over 20 h) regimen. (Table 1).

Expected change in serum acetylcysteine concentration was simulated over the time for the two-bag regimen in the following scenarios:

1. Comparison of the three-, two- and abbreviated two-bag infusion regimens over one treatment cycle.
2. Extension of the traditional three- and two-bag infusion regimens with another 100 mg/kg acetylcysteine infusion over 16 h (extended treatment, i.e. 36 h).
3. Acetylcysteine delivered with three- and two-bag infusion regimens when only 8 h of treatment are given (Australian guideline for RSTI) [10].
4. Acetylcysteine delivered with an abbreviated two-bag infusion when the second bag concentration is doubled (200 mg/kg over 4 h, 100 mg/kg over 8 h) or quadrupled (200 mg/kg over 4 h, 200 mg/kg over 8 h).
5. Acetylcysteine delivered as a two-bag infusion: loading dose and doubled concentration second bag (200 mg/kg over 4 h, 200 mg/kg over 16 h). Doubling of the second acetylcysteine bag is suggested in the Australia and New Zealand paracetamol overdose management guideline for patients with massive paracetamol ingestions (more than 30 g or serum APAP more than two times above the nomogram line) [3].

The simulations were based on a previously published population pharmacokinetic three-compartment model [11] with the following population PK parameter estimates (± inter-individual variability as % coefficient of variation). The central volume of distribution (V1) was 2.59 L/70 kg (± 31.2%) and the shallow and deep peripheral volumes of distribution (V2 and V3) were 14.7 L/70 kg (±10.3%) and 2.45 L/70 kg (±21.8%). Total body clearance was 11.48 L/h/70 kg (±10.7%). The intercompartmental clearance between the central and the shallow peripheral compartment (Q1) and between

Table 1 Standard, two-bag, extended treatment, abbreviated two-bag, and intensified acetylcysteine regimens

	1st infusion	2nd infusion	3rd infusion	4th infusion	Total acetylcysteine delivered
Standard 3-bag regimen	150 mg/kg over 1 h	50 mg/kg over 4 h (12.5 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)		300 mg/kg over 21 h
2-bag regimen	200 mg/kg over 4 h (50 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)			300 mg/kg over 20 h
Abbreviated 2-bag regimen	200 mg/kg over 4 h (50 mg/kg/h)	50 mg/kg over 8 h (6.25 mg/kg/h)			250 mg/kg over 12 h
Extended 3-bag regimen	150 mg/kg over 1 h	50 mg/kg over 4 h (12.5 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)	400 mg/kg over 37 h
Extended 2-bag regimen	200 mg/kg over 4 h (50 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)	100 mg/kg over 16 h (6.25 mg/kg/h)		400 mg/kg over 36 h
ST regimen 3-bag*	150 mg/kg over 1 h	50 mg/kg over 4 h (12.5 mg/kg/h)	18.75 mg/kg over 3 h (6.25 mg/kg/h)		218.75 mg/kg over 8 h
ST regimen 2-bag*	200 mg/kg over 4 h (50 mg/kg/h)	25 mg/kg over 4 h (6.25 mg/kg/h)			225 mg/kg over 8 h
Abbreviated 2-bag regimen, double-dose second infusion	200 mg/kg over 4 h (50 mg/kg/h)	100 mg/kg over 8 h (12.5 mg/kg/h)			300 mg/kg over 12 h
Abbreviated 2-bag regimen, quadrupled dose second infusion	200 mg/kg over 4 h (50 mg/kg/h)	200 mg/kg over 8 h (25 mg/kg/h)			400 mg/kg over 12 h
2-bag regimen, double-dose second infusion	200 mg/kg over 4 h (50 mg/kg/h)	200 mg/kg over 16 h (25 mg/kg/h)			400 mg/kg over 20 h

*Australian guideline protocol for supratherapeutic (ST) paracetamol ingestion

the central and the deep peripheral compartment (Q2) were 8.61 and 30.1 L/h/70 kg, respectively. Five hundred patients were simulated from the model [12]. Berkeley Madonna (version 8.3.23.0) was utilized for the simulations.

Results

Simulated acetylcysteine concentration-time profiles using an abbreviated two-bag acetylcysteine regimen are summarized in Fig. 1 and compared to the 20-h infusion regimen. The 20-h two-bag acetylcysteine infusion regimen resulted in a lower peak concentration but a more sustained drug concentration following the loading dose when compared to the standard three-bag regimen. Plasma acetylcysteine concentrations at 1, 3 and 4 h post-initiation were 540, 121, and 109 mg/L in the standard three-bag vs. 189, 245 and 261 mg/L in the two-bag regimen, respectively. Importantly, when discontinuing the two-bag infusion at 12 h, acetylcysteine is still detectable up to 8 h following treatment discontinuation. However, acetylcysteine concentration was lower than when the infusion continues for the total 20 h.

Using the two-bag (20 h) and abbreviated two-bag (12 h) regimens, acetylcysteine maximal concentration (Cmax) was 261 mg/L, 4 h post-initiation of infusion. Cmax for the three-bag regimen was 567 mg/L, 1 h post-initiation of the infusion. After 12 h of acetylcysteine infusion, concentrations were 43, 45.5 and 45.3 mg/L with the three-, two- (20 h) and abbreviated two-bag (12-h) regimens, respectively. After 20 h of acetylcysteine infusion, concentrations were 38.5, 38.3 and 2.2 mg/L in the three- (20 h), two- (20 h) and abbreviated two-bag (12 h) regimens, respectively.

The area under the curve from the time period of 14 to 15 h post ingestion, where maintenance acetylcysteine is given and the curve is flat, was calculated. A three- and two-bag acetylcysteine regimen delivers 39.76 and 41.22 mg/L acetylcysteine, respectively, during this time period. This is approximately 0.244 mmol/L/h, using a molecular weight of acetylcysteine of 163.2 g per mole. For example, a 70-kg person with plasma volume of 3 L would have a plasma acetylcysteine delivery of 0.732 mmol/h.

The expected concentration time profiles of acetylcysteine when dosing is continued for an additional 100 mg/kg over 16 h, following the initial 20-h treatment course are seen in Fig. 2. With extended treatment duration, acetylcysteine concentration was similar with both two- and three-bag regimens.

The expected concentration of acetylcysteine when infused for a total of 8 h is summarized in Fig. 3. This follows the recommendation in the Australian paracetamol treatment guideline for RSTI. For the three-bag regimen, Cmax was 570 mg/L, 1 h post-initiation of acetylcysteine. For the two-bag regimen, Cmax was 260 mg/L, 4 h post-initiation. Acetylcysteine is still detectable 20 h after starting treatment with both infusion regimens.

A much higher peak serum acetylcysteine concentration can be expected when doubling or quadrupling the second infusion bag of an abbreviated 12-h two-bag regimen (Fig. 4). This also occurs when doubling the second infusion

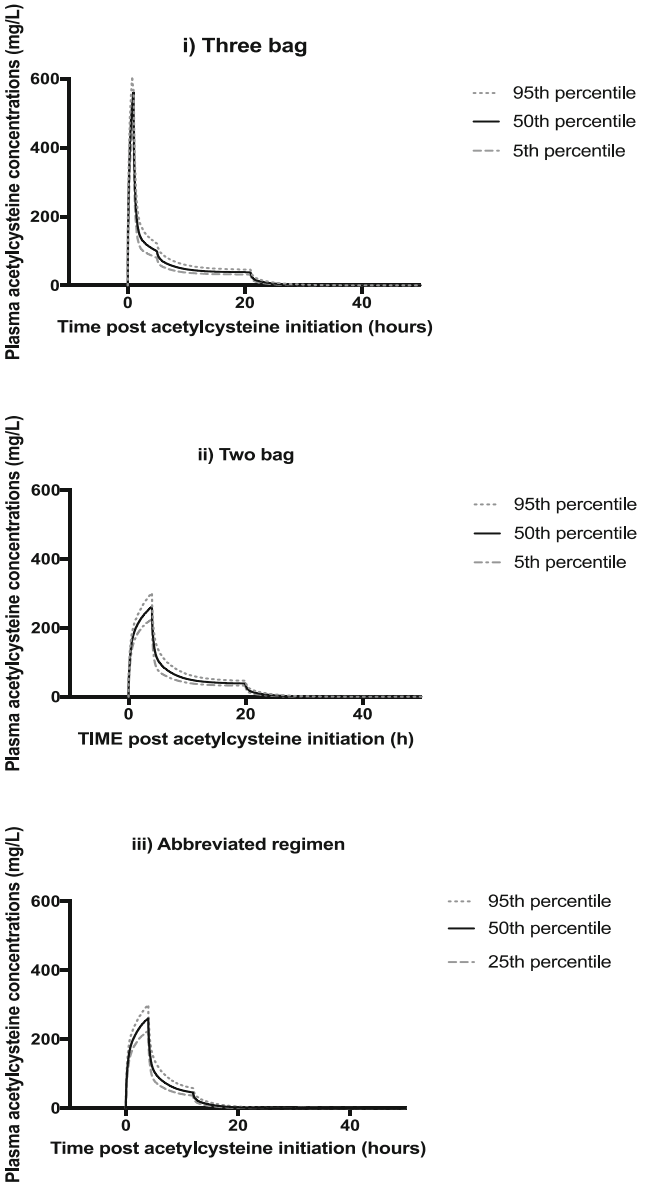

Fig. 1 Pharmacokinetic simulations comparing acetylcysteine concentrations vs. time for (i) three-bag (300 mg/kg/21 h); (ii) two-bag (300 mg/kg/20 h) and (iii) abbreviated two-bag infusion (250 mg/kg/12 h) regimens

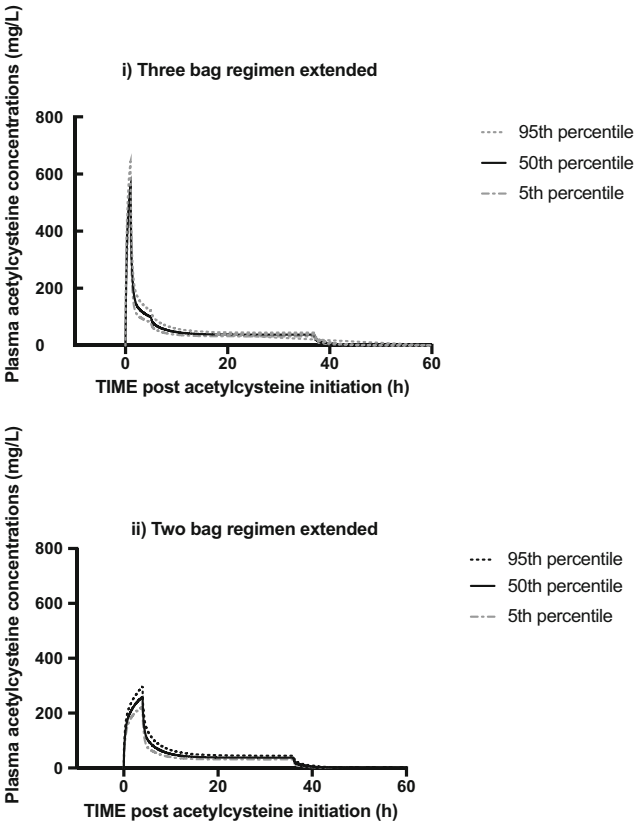

Fig. 2 Pharmacokinetic simulations comparing acetylcysteine concentrations vs. time for (i) three- (21 h) and (ii) two-bag (20 h) infusion regimens for initial treatment extended with the addition of a second 100 mg/kg/16-h infusion bag. Total infusion time 36 h

bag of the 20-h two- and three-bag acetylcysteine regimens (Fig. 5).

Discussion

Currently, treatment of paracetamol poisoning with acetylcysteine takes a "one size fits all" approach. It is clear that paracetamol poisoning may result in a spectrum of risk for hepatic injury, which depends upon multiple factors. A large percentage of patients present early post-overdose and ingest moderately toxic amounts of paracetamol [13]. In addition, the administration of acetylcysteine within 8 h of an acute single paracetamol overdose will prevent the development of hepatotoxicity in almost all patients [4, 14–16]. More recent work has shown that patients with normal liver function tests at presentation are unlikely to develop hepatotoxicity when treated with acetylcysteine [17–20].

Combination of the first two infusions of the traditional three-bag acetylcysteine regimen into a single-bag delivering 200 mg/kg over 4 h results in a lower peak but more sustained and higher concentration of acetylcysteine at 3 and 4 h post-initiation. This has resulted in the decreased incidence of non-allergic anaphylactic reactions [5, 21]. In one study by Wong et al. [5], there was a decreased rate of serious reactions (10 vs. 4%) when comparing the three-bag to the two-bag acetylcysteine regimen. Similar findings were later confirmed in another study using the same regimen [22]. Theoretically, the two-bag regimen provides a more constant delivery of glutathione substrate during the initial stage of poisoning, when paracetamol concentration is at its highest. Given that paracetamol metabolism is continuous, a lower peak but sustained acetylcysteine concentration within the first few hours of treatment may be as effective in preventing liver injury as an initial transient peak in concentration. In addition,

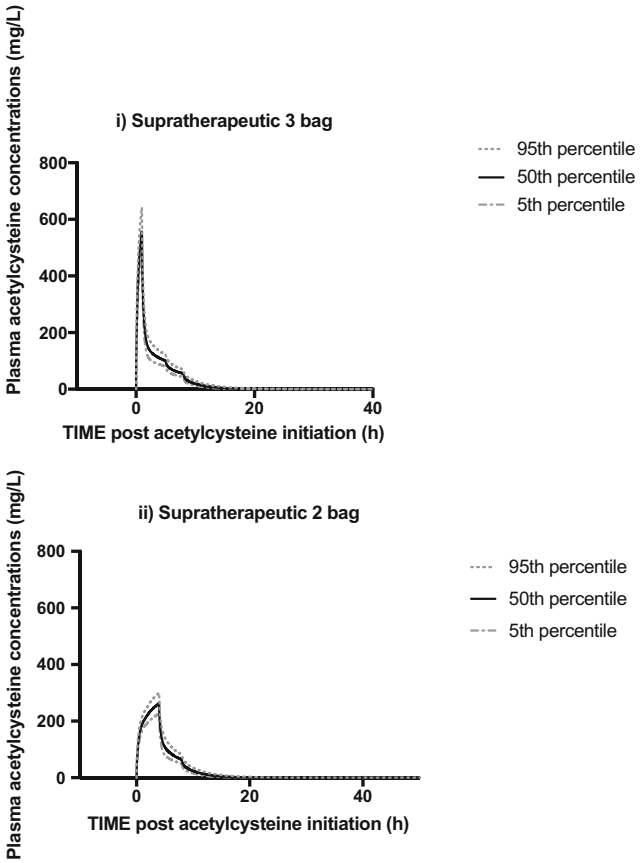

Fig. 3 Pharmacokinetic simulations comparing acetylcysteine concentrations vs. time for (i) three- (8 h) and (ii) two-bag (8 h) infusion regimens for treatment of supratherapeutic ingestions using the Australian paracetamol guideline, where the infusion is stopped after 8 h

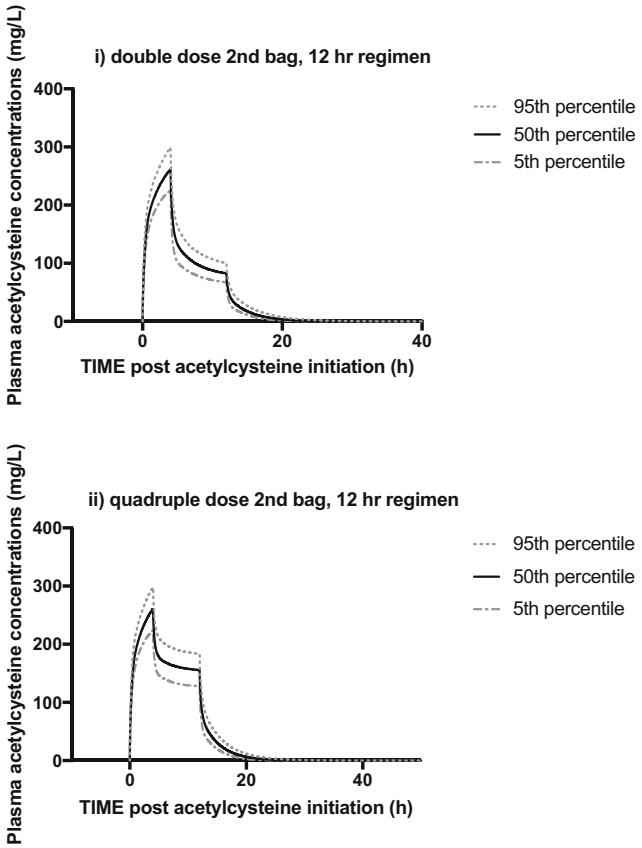

Fig. 4 Pharmacokinetic simulations comparing acetylcysteine concentrations vs. time for (i) double (200 mg/kg over 4 h, 100 mg/kg over 8 h) and (ii) quadruple dose (200 mg/kg over 4 h, 200 mg/kg over 8 h) acetylcysteine administration in second infusion of abbreviated two-bag regimen

the dose of acetylcysteine delivered over the first 4 h using both regimens is similar.

There is a theoretical risk that unconjugated NAPQI, the toxic metabolite of paracetamol metabolism, may still be present if paracetamol is still present in the blood when acetylcysteine is prematurely ceased and hepatic glutathione stores have not been fully replenished. It is currently unclear what the half-life of NAPQI is in humans. This is primarily due its volatile nature resulting in difficulty of quantification. However, NAPQI half-life is likely to vary depending upon paracetamol concentration and glutathione availability in the liver. Data from our simulations suggest that, with the 12-h infusion regimen, there will still be circulating acetylcysteine detectable for up to 8 h after the infusion is ceased. If the serum paracetamol concentration is at or below the therapeutic limit and liver function tests are normal when acetylcysteine if stopped at 12 h, the risk of developing hepatotoxicity is inherently low. However, the presence of a continued low concentration of acetylcysteine over the next 8 h may confer added protection to prevent the accumulation of free NAPQI in the liver and provide ongoing hepatic protection from liver injury.

Future use of an abbreviated two-bag acetylcysteine regimen requires validation in the clinical setting. Patients must be at low risk of developing liver injury prior to commencement of treatment. Multiple safety factors have been added to the

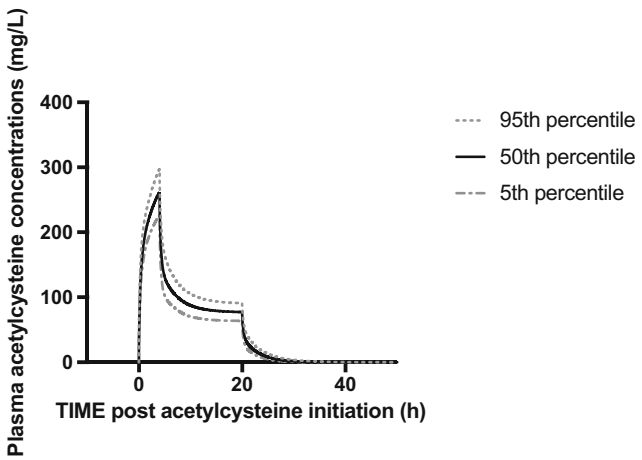

Fig. 5 Pharmacokinetic simulations of acetylcysteine concentrations vs. time for double-dose acetylcysteine administration in second infusion (200 mg/kg over 4 h then 200 mg/kg over 16 h) using a two-bag regimen

paracetamol treatment nomogram over time. In particular, the treatment thresholds for initiation of acetylcysteine have decreased over the years [23, 24]. The Rumack-Matthews nomogram recommends a 25% lower paracetamol concentration threshold for instituting treatment (150 mg/L at 4 h) when compared to the original paracetamol treatment nomogram used in the UK (200 mg/L at 4 h) [6]. In addition, in 2012, the UK Medicines and Healthcare products Regulatory Agency lowered the treatment threshold further to 100 mg/L at 4 h [24]. As a result, it is likely that there is a significant cohort of patients who may be safely be treated with an abbreviated regimen of acetylcysteine. Importantly, many of these patients would not have been treated if their serum paracetamol concentration had been plotted on earlier versions of the nomogram. This group makes up a significant proportion of paracetamol overdoses presenting to emergency departments [7, 25]. Patients with low paracetamol concentration and normal liver function after treatment with an abbreviated acetylcysteine regimen (e.g. 12 h) are extremely unlikely to develop significant hepatotoxicity. Furthermore, risk prediction scores, such as the paracetamol-aminotransferase multiplication product, could be used to identify patients who are candidates for an abbreviated acetylcysteine regimen [17]. Potential benefits of a shorter acetylcysteine regimen include decreased hospital length of stay and earlier disposition to mental health facilities as required.

Nonetheless, there are still patients at higher risk of developing acute liver injury who will require at least 20 h of acetylcysteine. Risk factors include an ongoing high serum paracetamol concentration or presence of rising biomarkers (e.g. AST or ALT) [20]. This group may require extension of the 20-h course of acetylcysteine until clinical and biochemical improvement is seen. It is common to extend treatment with further 16 h (100 mg/kg) acetylcysteine infusion bags when hepatic aminotransferase enzymes are increasing and have not yet peaked. Our data provides the first pharmacokinetic modelling of acetylcysteine concentration after prolongation of both traditional three- and two-bag 20-h regimens. Acetylcysteine concentrations were similar with extended treatment with both regimens. Hence, the degree of protection from hepatotoxicity provided in the latter part of the extended infusion is likely to be the same.

The recommendations for acetylcysteine treatment duration after repeated supratherapeutic paracetamol ingestion vary between countries. In Australia, acetylcysteine is administered for 8 h after which a reassessment of biochemical function is performed [10]. This approach based upon a previous study [26], which suggested that patients with RSTI of paracetamol and abnormal liver function tests on presentation are more likely to progress to hepatotoxicity. In the UK, the recommended strategy is to administer a full course of acetylcysteine to all patients [27]. Our simulations indicate that, if acetylcysteine is stopped after 8 h of treatment, the antidote is still detectable in the blood several hours later. The ongoing presence of acetylcysteine may provide a further buffer against the development of hepatotoxicity.

Toxicologists have debated whether higher doses and longer infusion duration of acetylcysteine are beneficial in preventing or mitigating hepatotoxicity in patients ingesting larger doses of paracetamol [23]. We simulated three additional increased acetylcysteine doses with the abbreviated 12- and 20-h two-bag regimens (Figs. 4 and 5). Not surprisingly, predicted plasma acetylcysteine concentrations were higher than those seen with recommended doses. Also, circulating acetylcysteine was detectable for a similar period (10 h) in all three models post-cessation of infusion. It is currently unknown whether administering larger doses of acetylcysteine during the early or late phases of treatment will prevent or reduce the degree of hepatotoxicity when the ingested dose is large (e.g. more than 0.5 g/kg) or the serum paracetamol concentration is very high (e.g. more than three times the current nomogram line) [28]. Our modelling showed that the maintenance dose of the three- and two-bag acetylcysteine regimens provided less than the original 2.5 mmol/h glutathione required estimated four decades ago [23]. This also assumes 1 mol of acetylcysteine is sufficient to provide 1 mol of glutathione. Other assumptions in the original calculations include that they were based on a 15.9 g ingestion of paracetamol, all of the glutathione is delivered to the liver and that NAPQI production is constant. Despite this, most patients do not develop hepatotoxicity or liver failure. This might be a result of the loading dose of acetylcysteine being adequate to provide enough glutathione for smaller ingestions of paracetamol earlier in the treatment course when paracetamol concentrations are higher. This raises questions of whether current acetylcysteine dosing and bioavailability to the liver is adequate, especially in massive overdoses of paracetamol where high concentrations of paracetamol are detectable throughout the presentation. In addition, hepatotoxicity may develop despite early acetylcysteine treatment [17, 29] in large paracetamol ingestions.

In a previous study by Heard et al., the incidence of hepatotoxicity was not reduced when the dose and duration of acetylcysteine infusion were increased (150 mg/kg over 1 h, followed by 70 mg/kg every 4 h for 12 doses, total 980 mg/kg) when compared with studies using a conventional three-bag 300 mg/kg, 20.25–21-h regimen [30]. The current inability to measure NAPQI in humans and the uncommon outcome of hepatotoxicity in those receiving acetylcysteine post-overdose means that any benefit from increasing the dose or duration acetylcysteine infusion will be difficult to ascertain. Potentially more sensitive biomarkers for liver injury such as microRNA [31] or other risk predictive tools like the paracetamol-aminotransferase product [17, 29] may be useful in determining acetylcysteine regimen efficacy.

Conclusion

This pharmacokinetic simulation study is an important step in confirming plasma acetylcysteine concentrations that may be achieved using various modified treatment regimens. The clinical outcomes of modified acetylcysteine regimens on risk of acute liver injury are less clear and require more study. Importantly, for patients at low risk of liver injury after acute overdose, acetylcysteine is likely to be detectable many hours post-cessation of an abbreviated 12-h regimen. This should provide a safety factor against development of hepatotoxicity for any ongoing paracetamol metabolism after cessation of the acetylcysteine infusion.

Compliance with ethical standards

Competing interests The authors declare no competing interests.

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