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REVIEW

What is the most appropriate dose of *N*-acetylcysteine after massive acetaminophen overdose?

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ABSTRACT

While the traditional intravenous *N*-acetylcysteine (NAC) dosing regimen works well for the vast majority of acetaminophen overdoses, there may be cases of massive overdose where additional NAC may be necessary. Recent evidence suggests that patients with acetaminophen concentrations above the "300-line" develop hepatotoxicity at a higher rate than those below the 300-line, suggesting that an increase of dose may be beneficial at this cut-off. Additional clinical data suggest a further increase in doses at the 450-line and 600-lines. I propose a strategy for step-wise increases in NAC dosing in response to high acetaminophen concentrations at the 300-, 450-, and 600-lines after acute massive acetaminophen overdoses.

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Introduction

Acetaminophen (APAP) toxicity results from oxidation by CYP2E1 to *N*-acetyl *p*-benzoquinoneimine (NAPQI), which is hepatotoxic and nephrotoxic. NAPQI depletes hepatic glutathione, then binds to cellular proteins causing a cascade of events that lead to hepatic and renal cell death. Treatment of acetaminophen toxicity is aimed at replenishing glutathione supply by providing the precursor molecule cysteine, in the form of *N*-acetylcysteine (NAC). NAC is used in either intravenous (IV) or oral (PO) forms and with variable dosing regimens. However, all current dosing regimens are single dose, with no variation in dose for a larger ingestion or higher serum concentration. Recent evidence suggests that an alternative treatment protocol may be necessary when the amount of acetaminophen ingested is massive or if the acetaminophen kinetics are severely altered [1–4]. The purpose of this narrative review is to discuss the current data on massive acetaminophen ingestions and create a rationale for a treatment protocol with NAC for future prospective study.

What is a massive acetaminophen overdose?

There is no accepted or standard definition of a "massive" acetaminophen overdose. Various authors have defined a "massive" acetaminophen overdose based upon the ingested dose with definitions of >50g [1,2], >40g [3], >30g [4], or >30g with co-administered opioid or antimuscarinic agent [1]. Alternatively, some have defined it by highly elevated acetaminophen serum concentration, such as >250 mcg/mL or >500 mcg/mL [4] at 4 h. Whether defined by dose or serum concentration, massive ingestions represent a minority of acetaminophen overdoses, and standard care adequately treats most overdoses. Exactly how many cases of acetaminophen overdose are "massive" is not clear, though <8% of overdoses have a serum acetaminophen over the "500-line" [4–7] and <10% have a reported ingestion of greater than 24g [8]. This narrative review will define a massive ingestion as greater than 32g or an acetaminophen concentration that is greater than the 300-line and indicative of a change in NAC dosing. The logic for this consideration follows.

Why should we treat massive acetaminophen overdoses differently than standard overdoses?

For several decades in the United States, acute acetaminophen overdoses were treated with an oral formulation of NAC. In 2002, the US FDA approved an IV NAC formulation (Acetadote®, Cumberland Pharmaceuticals, Nashville TN), and IV NAC has subsequently eclipsed oral NAC in the United States. The IV formulation and dosing have been used throughout Europe, UK, Canada, Japan, and Australia for decades. Although published dosing protocols for the IV and oral formulations have a similar loading dose (140–150mg/kg) of NAC, the recommended dosing after the load is different, with the oral NAC protocol delivering 17.5mg/kg/h(70mg/kg every 4 h) and the IV NAC protocol delivering 12.5mg/kg/h over 4 h, then 6.25mg/kg/h. Table 1 depicts the dosing protocols and total NAC dosing.

Between the 1970s and 2004, when the oral formulation and dosing predominated in the United States, there were

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Table 1. Comparison of NAC infusion rate and total dose per day for traditional IV NAC, PO NAC and potential altered IV NAC protocols.

Protocol	Initial infusion	"Second bag"	Total NAC in first 5h	NAC continuous infusion rate	Total NAC in first 24h	Total NAC per day all additional days
FDA IV NAC (Prescott protocol)	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	6.25 mg/kg IV	300 mg/kg (319 mg/kg if continued at 6.25 mg/kg/h)	150 mg/kg
Oral NAC	140 mg/kg PO	70 mg/kg every 4 h	210 mg/kg	17.5 mg/kg PO*	560 mg/kg	420 mg/kg
SNAP protocol	100 mg/kg IV over 2 h	20 mg/kg/h IV over 10 h	160 mg/kg	20 mg/kg/h (×10h)	300 mg/kg (540 mg/kg if continued at 20 mg/kg/h rate)	N/A
IV NAC with "double dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	12.5 mg/kg IV	438 mg/kg	300 mg/kg
IV NAC with "triple dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	18.75 mg/kg IV	556 mg/kg	450 mg/kg
IV NAC with "quadruple dose" continuous infusion	150 mg/kg IV	12.5 mg/kg/h IV over 4 h	200 mg/kg	25 mg/kg IV	675 mg/kg	600 mg/kg

*PO NAC is dosed at 70 mg/kg every 4 h. The reference to 17.5 mg/kg/h "continuous infusion" is not meant to suggest that PO NAC be given as a continual infusion, but as a way to compare the dose per hour of IV and PO NAC. Additional differences in bioavailability, etc, exist between PO and IV NAC and should not be considered an exact comparison.

no cases reported in which a patient was treated with NAC within 8 h of an acute ingestion and developed liver failure or died. This contributed to the predominant theory that the single dose of NAC was adequate for all acetaminophen overdoses regardless of dose. Since the advent of IV NAC in the United States, there have been several cases of massive acetaminophen ingestion treated with the standard course of IV NAC within 8 h of ingestion who progressed to liver failure [1,3,9–12]. In addition, there is an incremental increase in the risk of elevation of aminotransferases (hepatic injury) or aminotransferase elevation over 1000 IU/L(hepatotoxicity) with higher acetaminophen concentrations [13,14] even when treated with IV NAC early after ingestion (Table 2) [4,6], suggesting that a threshold exists where NAC dosing is inadequate.

Which patients should be treated with an alternative increased NAC dosing protocol?

Is there a way to identify patients who may require additional NAC? Several recent manuscripts shed light on an acetaminophen concentration at which to treat with an alternative dose of NAC. Cairney et al. [6] evaluated patients treated within the first 8 h after overdose with IV NAC and found that, even with appropriate and early NAC therapy, the risk of hepatic injury(ALT > 150IU/L) and hepatotoxicity(ALT >1000IU/L) increased incrementally at the 300-line and 500-line, suggesting that current IV NAC dosing may not be adequate above the 300-line and that dosing may need to be increased above both the 300-line and 500-lines. Marks et al. [4] evaluated massive acetaminophen overdoses and also found an incremental increase in acute hepatic injury at the 300 line, increased hepatotoxicity at the 300 and 600 lines, and incrementally increased incidence of coagulopathy at the 300, and 500 lines. Chiew et al. [3] noted an increase in the rate of hepatotoxicity over the 300- and 450-lines.

These data suggest that both hepatotoxicity and liver failure (coagulopathy) increase with acetaminophen concentrations above the 300-line and 450-lines and suggest the need for higher doses of NAC at these thresholds.

Unfortunately, at this time, evidence for improved efficacy of higher NAC dosing is limited. Chiew et al. [3] found a significant decrease in hepatotoxicity in patients treated with a 12.5 mg/kg/h final infusion ("double NAC dose") with an acetaminophen concentration over the 300-line after controlling for time to NAC therapy and initial acetaminophen concentration. No patients with APAP concentrations between the 300- and 450-lines developed hepatotoxicity when receiving

Table 2. The risk of hepatotoxicity by initial acetaminophen concentration in patients treated with an IV NAC 6.25 mg/kg/h final infusion and with NAC started within 8 h of their ingestion [4,6].

Acetaminophen concentration range	Risk of hepatotoxicity (ALT > 1000 IU/L)
<150-line	<1%
150–300 line	1–4%
301–500 line	7–13%
>500 line	31–33%

the 12.5 mg/kg/h "double NAC dose". All four patients who developed hepatotoxicity while receiving NAC infusions at 12.5 mg/kg/h had APAP concentrations above the 450-line and were treated >7 h after ingestion. This suggests the need for an even higher NAC infusion rate above the 450-line.

These publications suggest a need to increase dosing to 12.5 mg/kg/h of NAC above the 300 line, that there is a need to increase dosing above 12.5 mg/kg/h when acetaminophen concentrations are above the 450-line, and that additional risk of liver failure occurs above the 600-line.

While the prevention of liver failure and death is the ultimate goal of therapy, it seems reasonable to aim to prevent hepatotoxicity since the intervention (increased NAC dose) is relatively low risk and since hepatotoxicity increases resource utilization. The goal of this narrative review will be to explore the 300-, 450-, and 600-lines as thresholds to minimize morbidity by intensifying treatment. An increase in the dose of NAC may only be necessary at a higher cutoff to prevent liver failure rather than hepatotoxicity, such as the 450-, 500-, or 600-line. However, the risk of coagulopathy, and therefore liver failure, is incrementally higher at the 300-line [4], so it seems the most reasonable and conservative initial cut-off.

There are few clinical data to guide dosing other than that described above. Several authors have suggested alternative dosing strategies, including doubling the dose of the final infusion (i.e., "16-hour bag") of NAC to 12.5mg/kg/h [3,4,6] for some patients, but specific doses and triggers have not been determined. I will explore if there are theoretical scaffolds on which to build a NAC dosing regimen by looking at the initial derivation of the NAC protocol and by exploring whether we can determine NAC dosing by using stoichiometric and kinetic parameters.

Initial derivation of the IV NAC protocol (Prescott or "traditional" protocol)

Rumack and Bateman [15] described the derivation of the Prescott IV NAC dosing protocol and noted that the final infusion rate of 6.25mg/kg/h was calculated to treat an ingestion of 15.9g of acetaminophen. Since an approximately 16g dose of acetaminophen is the basis for the 6.25mg/kg/h NAC dose, it is logical, as Rumack and Bateman [15] suggest, that a 32g dose of acetaminophen may require 12.5mg/kg/h of NAC, a 48g dose may require 17.5mg/kg/h, and a 64g dose may require 25mg/kg/h. How do these correlate with the 150, 300, 450, etc. lines? Using the pharmacokinetic model of Edwards et al. [16] and in a 60kg person, ingestion doses should correlate with the 4-hour acetaminophen concentrations depicted in Table 3.

These data suggest that an alternative dosing regimen should include increases in dosing at approximately the 300, 450, and 600 lines and that the final NAC infusion rate should be 12.5, 18.75, and 25 mg/kg/h, respectively.

Pharmacokinetic/stoichiometric evaluation

In principle, NAC should be supplied in a 1:1 molar ratio with the NAPQI that is produced at that time. This stoichiometric relationship is based on the concept that the main role of NAC early after overdose is to supply cysteine for the production of glutathione which directly binds to NAPQI and produces a non-toxic metabolite. Calculating the exact amount of NAC required for a given concentration of acetaminophen in massive overdoses would require accurate information about toxicokinetics and metabolism, which do not exist. However, a model of required NAC for a given acetaminophen concentration may be used to check the logic in the preceding paragraphs.

The model includes many assumptions and is used here to simply determine if these cutoffs are reasonable. First, the initial bolus of NAC (i.e., 150 mg/kg IV over 15–60 min) is adequate for the vast majority of doses of acetaminophen. Second, the model assumes that the amount of glutathione initially present in the liver is nil and that NAC is necessary to neutralize all of the NAPQI produced (i.e., 1 mole of NAPQI requires 1 mole of NAC). [17] Third, the assumed half-life of acetaminophen after massive overdose is 4 h [3,18–20]. Fourth, 25–50% of APAP present after massive overdose will become NAPQI [17,19]. Fifth, the dose of NAC required for any acetaminophen concentration will be delivered over 4 h. Sixth, the volume of distribution of acetaminophen is 0.9 L/kg [20]. Seventh, the NAPQI: NAC molecular weight ratio is approximately 0.9 (MW for NAPQI = 149 Da, MW for NAC = 163 Da). Eighth, the MW ratio of 0.9 and the Vd of 0.9 L/kg will cancel out except for the units. Ninth, there is no further absorption of acetaminophen after the initial overdose.

Given these assumptions, the range of hourly infusion rates of NAC required is simply (0.25–0.5) × 0.5 × [acetaminophen] which is equal to [acetaminophen]/32 to [acetaminophen]/16 in mg/kg/h, converted into moles of NAPQI and

Table 3. Correlation of ingested dose of acetaminophen with the predicted 4-hour [APAP] [16], the approximate "Treatment line", and predicted dose of NAC [15].

Ingested dose	Predicted $[APAP]_{4h}$	Approximate APAP "line"	Predicted dose of NAC
16g	157 mcg/mL	~150-line	6.25 mg/kg/h
32g	314 mcg/mL	~300-line	12.5 mg/kg/h
48g	472 mcg/mL	~450-line	18.75 mg/kg/h
64g	629 mcg/mL	~600-line	25 mg/kg/h

Column 2 (Predicted $[APAP]_{4h}$) is the predicted 4 h acetaminophen concentration that is produced from the ingested dose in column 1. Column 3 (APAP "line") is the treatment line that correlates most closely with the value in column 2 – note that these are not exact matches, simply approximations. Column 4 is the predicted dose of NAC needed with an acetaminophen concentration above the treatment line in column 3 – details of this approximation are in the text.

NAC. Using this formula, a patient with a 4 h [acetaminophen] of 300 mcg/mL which correlates roughly to a 32g ingestion, would need approximately 9–18 mg/kg/h of NAC.

This confirms that the 300-line may be an appropriate trigger to increase NAC to 12.5mg/kg/h and corroborates a 17.5 mg/kg/h infusion for the 450-line (14–28mg/kg/h), and a 25 mg/kg/h infusion over the 600-line (19–37mg/kg/h). However, there are many limitations to this simple model including the number of assumptions, the lack of reliable data on kinetics and metabolism, and the known variability of elimination half-life, absorption, and rates of sulfation, glucuronidation, and CYP2E1 activity.

One additional remaining question is whether there should be dosing necessary above the 18.75 mg/kg/h dose ("triple dose NAC infusion"). The 18.75 mg/kg/h NAC dose suggested here is similar to the dose administered with the oral NAC protocol (17.5 mg/kg/h) (Table 1). There are no cases of liver failure in patients treated with oral NAC within 8 h. However, there is a risk of hepatotoxicity in patients treated within 10 h with the 17.5mg/kg/h oral dosing [7,21–23], and that risk increases with higher acetaminophen concentrations; 3.45% between the 150 and 200 lines to 7.73% above the 200-line [7,15]. This suggests that there is a group of patients who may benefit from a NAC dose that is larger than 17.5 mg/kg/h. Detailed data are not published for this subgroup of patients, but a tiered increase in hepatotoxicity is evident at all time periods even with 17.5 mg/kg/h NAC [15]. For this reason, patients with acetaminophen concentrations above the 600-line should receive NAC infusions at a final rate of 25mg/kg/h. This can be attained by increasing the dose of IV NAC by four times, but may also be attained by treating the patient with both IV NAC(6.25 mg/kg/h) plus PO NAC(17.5 mg/kg/h) for a total of 23.75 mg/kg/h. This may be advantageous in situations where treating practitioners are not willing to alter the dosing recommended in the package insert. Of course, contraindications to both PO and IV NAC apply and this strategy may not be appropriate for patients with intractable vomiting or those with scenarios where IV NAC is potentially advantageous, such as pregnant women and those with acute liver failure.

Figure 1 is a visual depiction of the cutoffs and NAC dosing described. Given that massive overdoses may produce altered kinetics, it seems reasonable to change the NAC infusion dose if serial serum concentrations cross a dosing line.

How is an increased NAC dosing regimen delivered?

Patients with massive ingestion and highly elevated acetaminophen concentrations should be treated with the traditional first and second bags over 4–5 h. The APAP concentration and Figure 1 should determine the final NAC infusion rate. For APAP concentrations above the 450-line, the NAC infusion rate exceeds the 12.5mg/kg/h rate for the second bag in the Prescott protocol.

Options for increasing the NAC dose include increasing the rate or the concentration of the second or third bag. First, the infusion concentration can remain the same as the traditional "3rd bag" (100mg/kg in 1000mL D5W) and the rate of infusion increased. For example, if 12.5mg/kg/h NAC is needed, infusing the traditional "3rd bag" over 8 h instead of 16 h may be appropriate. This method is straight-forward with 12.5mg/kg/h dosing, but may become difficult when higher NAC dosing strategies are desired as it delivers a large volume of fluid. The second option is to increase the concentration of the infusion. For example, a 12.5mg/kg/h dose may be delivered by mixing 200mg/kg NAC into 1000mL of D5W and infused over 16 h (Table 4). This is a simple method which reduces total fluid volume delivered and, even with

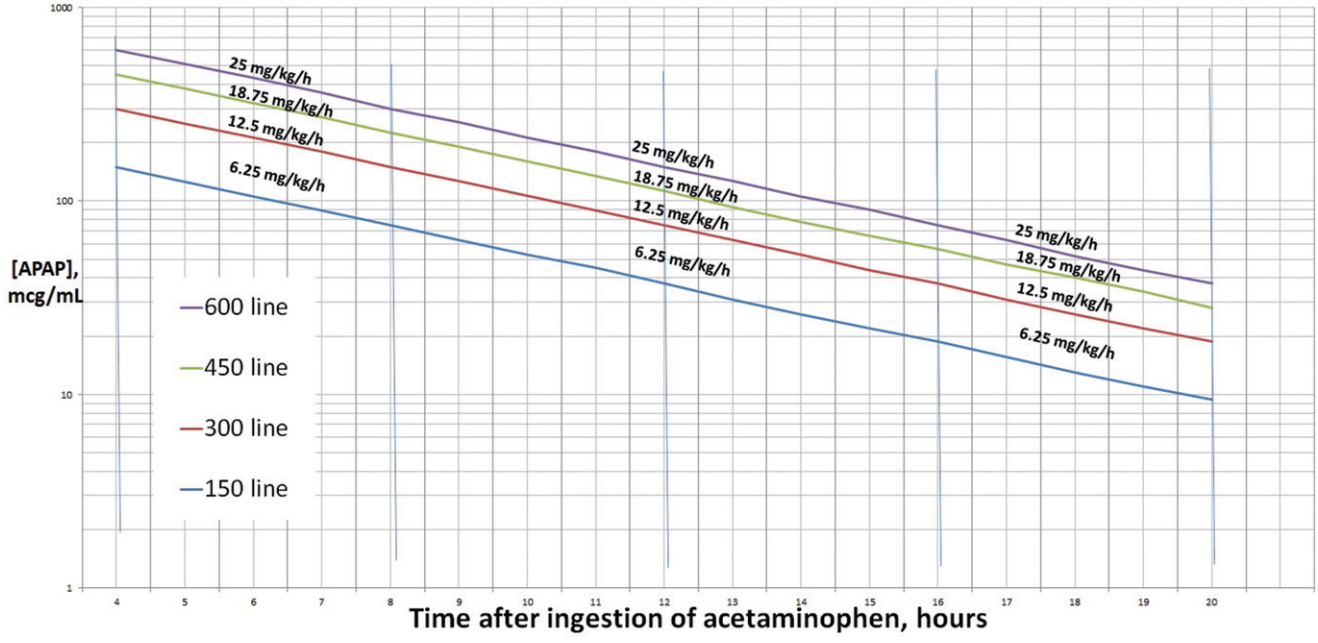

Figure 1. NAC dose adjustment for massive acetaminophen overdoses. Plot the time and concentration of acetaminophen after massive overdose to determine the continuous NAC infusion rate.

Table 4. NAC concentration and osmolarity of alternative dosing strategies for NAC in massive overdoses.

Dosing formulation	Dose of NAC	Min-Max dose of NAC	Diluent/solution	Max concentration	Max osmolarity
"1st bag"	150 mg/kg	6–15 g	200 mL D5W	75 mg/mL	603–890 mOsm/L
"2nd bag"	50 mg/kg	2–5 g	500 mL D5W	10 mg/mL	297–368 mOsm/L
"3rd bag"	100 mg/kg	4–10 g	1000 mL D5W	10 mg/mL	297–368 mOsm/L
Double 3rd bag	200 mg/kg	8–20 g	1000 mL D5W	20 mg/mL	344–485 mOsm/L
Triple 3rd bag	300 mg/kg	12–30 g	1000 mL D5W or sterile H_20	30 mg/mL	156–390 mOsm/L (sterile H_20) 391–603 mOsm/L (D5W)
Quadruple 3rd bag	400 mg/kg	16–40 g	1000 mL D5W or sterile H_20	40 mg/mL	208–520 mOsm/L (sterile H_20) 438–720 mOsm/L (D5W)

All formulations are for patients between 40 and 100 kg.
Calculations assume the following: 20% NAC = 2.6 mOsm/mL, D5W = 0.25 mOsm/mL, 1/2NS = 0.154 mOsm/mL. Solutions are reduced by the amount of NAC volume added. For example, if 150 mL of NAC is in 1000 mL D5W, calculations are based on 150 mL of NAC and 850 mL of D5W, since 150 mL of D5W would be removed prior to mixing. All calculations are for patients 40–100 kg.

25mg/kg/h dosing, the maximum concentration of NAC remains below that of the initial 1 h bolus dosing (Table 4). However, in individual situations with a large patient (e.g., >100kg), concentrated solutions mixed in D5W may be hyperosmolar and NAC may be put into solution with sterile water or half-normal saline. Table 4 lists the dosing, NAC concentration, and osmolarity of the various solutions.

Existing alternative NAC dosing strategies

Several 1-bag and 2-bag NAC dosing strategies have been developed and shown to decrease errors associated with NAC administration [24–26]. The regimen proposed here can be used with any of the 1- or 2-bag protocols by using the final dose proposed after the initial bolus. In this way, a "2 bag" solution may be attained that remains consistent with the traditional IV NAC protocol as well as other "2-bag" solutions, including the SNAP protocol [25].

Safety

Safety is a primary consideration when altering a well-established dosing protocol. The primary concerns when increasing NAC dose are the rate of anaphylactoid reactions, fluid overload, and osmolarity of the solution.

Anaphylactoid reactions to NAC are associated with both the rate of the infusion and concentration of the solution. They have primarily been reported during or just after the initial bolus of NAC with the traditional dosing protocol [27] where a higher concentration NAC solution is used and is infused at a faster rate than the subsequent infusions (150mg/kg NAC in 200mL D5W over 15–60 min; maximum 75mg/mL) (Tables 1 and 4). For this reason, increasing the dose of NAC in the final infusion may lead to greater rates of anaphylactoid reactions. However, there are two factors that imply that dosing NAC as suggested here may not significantly increase adverse reactions. First, few anaphylactoid reactions occur late in the second infusion (50mg/kg NAC in 500mL D5W; maximum 10mg/mL) or during the third infusion (100mg/kg NAC in 1000mL D5W; maximum 10mg/mL) because of the slower rate of infusion and lower NAC concentration [5,27]. Increasing the concentration of this third infusion 2, 3, or 4 fold will result in solutions with NAC concentrations of 20, 30, or 40 mg/mL, which remain lower than the first bag (maximum 75mg/mL) over 16 h versus 1 h (Table 4). Second, anaphylactoid reaction rates decrease at higher acetaminophen concentrations because acetaminophen decreases histamine release [28,29]. The rate of anaphylactoid reactions in patients with acetaminophen concentrations above 300 mcg/mL is 5% compared to >20% for patients with acetaminophen concentrations below 150 mcg/mL [27,28]. Since patients with massive ingestions have highly elevated acetaminophen concentrations, anaphylactoid reaction rates should remain low. However, this remains a crucial question and major safety concern with altered NAC dosing and requires prospective study.

An additional concern is that higher NAC dosing may expose the patient to a large fluid volume which may be detrimental in patients with renal insufficiency, heart failure, liver failure, or cerebral edema. Concentrated NAC solutions may decrease this risk in vulnerable populations.

Additional considerations in massive acetaminophen overdoses

Cases of massive acetaminophen overdose may require additional therapies beyond increasing the NAC dose.

First and foremost, with both the traditional (6.25mg/kg/h) dosing and increased dosing strategies, patients require NAC until the acetaminophen concentration is undetectable and hepatic dysfunction has resolved [30]. The concept of a set number of hours (e.g., 20 h, 72 h) of treatment is no longer valid.

Hemodialysis efficiently clears acetaminophen and may be used in massive overdoses to both normalize acid/base status and remove acetaminophen from the serum. The EXTRIP group recommends hemodialysis for removal of acetaminophen if the acetaminophen is above the 900-line, if there are signs of mitochondrial dysfunction(e.g., hyperlactatemia, acidemia) after "excessively large overdoses", or for patients with "severe acetaminophen poisoning" [31]. Patients with acetaminophen concentrations above the 600-line have high rates of hepatotoxicity [6] and coagulopathy [4] despite therapy with NAC. If they meet the definition of "severe acetaminophen poisoning", they should receive hemodialysis to enhance acetaminophen clearance.

Hernandez et al. [32] suggest doubling the NAC infusion rate during hemodialysis to account for NAC removal. However, this may create problems with fluid volumes. In the absence of further data, the NAC infusion rate during hemodialysis should not exceed 25 mg/kg/h. Continuous

renal replacement therapy (CRRT) results in much lower NAC clearance [32], so no change in the NAC infusion rate is necessary during CRRT.

Conclusion

Given the recent interest in massive acetaminophen overdoses and toxicokinetics, consideration of an altered dosing protocol for IV NAC is necessary. Although toxicologists and poison centers generally agree that massive acetaminophen overdoses warrant increased or intensified dosing of IV NAC, there is little consensus on how to do this. Extrapolation from prior data suggests that the final NAC infusion rate should be 12.5 mg/kg/h for patients with APAP concentrations above the 300 mg/L line or with ingestions of 32 grams. Similarly, the 450 mg/L line (or 48 g ingestion) and the 600 mg/L line (or 64 g ingestion) may require final infusion rates of 18.75 mg/kg/h and 25 mg/kg/h, respectively. Future prospective research should evaluate this approach and should further refine the thresholds and dosing rates.

Disclosure statement

No potential conflict of interest was reported by the author.

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