Novel Regimens in the Treatment of Paracetamol (Acetaminophen) Poisoning

R Dilip Kumar, Umalakshmi Premnath

Introduction

Acetaminophen poisoning is the most common cause of fulminating hepatitis and drug induced liver injury worldwide. Eventhough its not the commonest cause of fulminating hepatitis in India poisoning is still common and confusions prevail regarding the optimum and modern regimens in Indian population. Acetaminophen poisoning may occur either as a result of acute ingestion or following cumulative effects. The important steps in management include hemodynamic stabilization, decontamination, and administration of N-acetylcysteine-the specific antidote. The duration of treatment with N-acetylcyseteine depends on the type of ingestion and the presence of transaminitis.

The novel regimens for the management of acetaminophen poisoning is been discussed here.

Management Protocol

The management of the patient depends widely on the time after consumption at which the patient presents. Most of them who present in the initial 24 hours of presentation will be asymptomatic, while a few may need treatment for the symptoms caused by the co-ingestants.

As symptoms pertaining to acetaminophen poisoning are uncommon in the first few hours of presentation, the severity of the event is assessed by plotting the Rumack-Mathew normogram (Figure 1)

The normogram chart will be useful only if the patient presents within 24 hours of ingestion. It is not useful for those who present after 24 hours of acute ingestion, unknown time of ingestion, or those who have a staggered overdose.

Symptoms and signs of acetaminophen poisoning usually occur between 24 and 72 hours after consumption. Patients may present with nausea, vomiting, jaundice, abdominal pain, renal injury, coagulopathy (eg, gastrointestinal bleeding), hepatic encephalopathy, cerebral edema, or hypotension, the presence of the above necessitates maintaining hemodynamic stability, including airway management, fluid resuscitation, ionotropes, renal replacement therapy as and when required, or management of raised intracranial pressure.

Gastrointestinal Decontamination

This finds role in those patients who present following an acute ingestion of toxic dose of acetaminophen of >7.5 grams. Activated charcoal, 1g/kg (upto a maximum dose of 50 g) can be all patients who presenting within the first 4 hours of consumption as a means of reducing the absorption.

The toxic dose in children <6 years is 200mg/kg or more within an 8 hour period, while in adults it is 200mg/kg or 10 g whichever is less over a single 24 hour period or 6g or 150mg/kg whichever is less within a single 24 hour period. For individuals at risk, like pregnant women, prolonged fasting, chronic alcoholism or chronic isoniazid use, the threshold for referral would be 4 g or 100 mg/kg within a 24 hour period.

It may be withheld in those whose airway is compromised, like in unconscious patients, as they stand a chance of aspiration, unless they are intubated. However, intubation is not warranted with the sole purpose of administering charcoal or when the patient presents later than 4 hours after consumption.

Studies have proved that activated charcoal has reduced the risk of exposure considerably:

- Studies have revealed that those treated with activated charcoal had a higher decrease in serum acetaminophen levels than those who are not. When compared to those treated with gastric lavage and anti-emetics. 2

- Observation studies have also proved that administration of activated charcoal has lowered the toxicity that can result from it. 3

- Further, a retrospective study involving 981 patients following an acute acetaminophen overdose revealed that the requirement of N-acetyl treatment was less for those who were pretreated with
Antidote: n-Acetylcysteine

1) in cases of glutathione depletion; (commencing 660 μmol/L)
All cases above this line (commencing 1300 μmol/L)
Infuse with acetylcysteine as follows:

It has proved to reduce the risk of poisoning worldwide and is N-acetylcysteine has been accepted as activated charcoal. 2,6

overdose, have not proved to be as effective as activated charcoal. 2,6

activated charcoal within the first 2 hours of ingestion.

- A prospective observational study also revealed that even those who were treated with activated charcoal after 4 hours of ingestion had a lower peak of alanine aminotransferase, and these effects were irrespective of time of administration of N Acetyl cysteine, suggesting that activated charcoal may also be given after 4 hours of ingestion. 5

Clinical trials have shown that induced emesis 6,7 and gastric lavage 6,8 though limit the absorption of acetaminophen after overdose, have not proved to be as effective as activated charcoal. 2,6

Antidote: n-Acetylcysteine

Efficacy of acetylcysteine — N-acetylcysteine has been accepted as an antidote for acetaminophen poisoning worldwide and is administered to all patients at significant risk for hepatotoxicity. It has proved to reduce the risk of serious hepatotoxicity and mortality. 10-12

The aim of management is to start N Acetyl Cysteine much earlier than the rise in the alanine aminotransferase, which can be safely achieved within 8 hours of ingestion.

The mechanism by which N Acetyl cysteine has shown to reverse the hepatotoxicity is by restoring the glutathione stores.

So far no randomized placebo controlled trials have been done to evaluate the efficacy of N Acetyl Cysteine due to ethical reasons. Further, it has also been shown that late administration after hepatotoxicity has set in, has reduced the mortality and has helped in improving the hepatic and cerebral function. 17-19

However, some queries remain with respect to mode of administration of N Acetyl Cysteine following an acute ingestion. The two protocols commonly followed are the 20 hour intravenous (IV) protocol 15 and the 72 hour oral protocol 17 which have been reviewed here.

There are also studies showing reports that hepatotoxicity continues following ingestion of massive doses of acetaminophen (ingestion >30 g, or serum concentration >500 mg/L [3300 μmol/L]) despite early administration of N A Cysteine. 20,21 Many of these cases were those in which diphenhydramine was co-ingested and the patients had raised acetaminophen concentrations at the end of the intravenous 20 hour protocol. Pharmacokinetic models suggest that a higher dose of N-acetylcysteine treated for a longer duration may be beneficial in such cases. 22,23 In such occasions, consultation with a toxicologist who is familiar with the management of acetaminophen overdose may be sought.

Indications — Indications for N-acetylcysteine therapy include:
- Serum level of acetaminophen concentration at four hours or more following acute ingestion above the “treatment” line of the nomogram for acetaminophen poisoning (Figure 1)
- In a suspected case of consumption of 150 mg/kg (7.5 g total dose regardless of weight) or more for a patient whose serum acetaminophen levels may not be available for at least the first 8 hours of consumption.
- A patient with serum acetaminophen concentration of more than or equal to 10 microgram/ml (66 μmol/L) following an acute ingestion.
- Patient with a history suggestive of acetaminophen overdose and evidence of hepatotoxicity.
- Those with a delayed presentation of more than 24 hours and having laboratory evidence of liver injury (ranging from mild transaminitis to fulminant hepatic failure) with a history of excessive acetaminophen ingestion. Patients with delayed presentation and hepatic injury should be managed in consultation with a regional poison control center (1-800-222-1222 in the United States) or a medical toxicologist.

20 hour IV protocol — The 20 hour intravenous (IV) protocol for N-acetylcysteine treatment has commonly been used since the 1970s.

The approved 20 hour IV dosing regimen may be complicated and is performed as follows:
- An initial loading dose of 150 mg/kg in 200 ml diluent is given over 15 to 60 minutes (we recommend 60 minutes)
- This is followed by a 4 hour infusion at 12.5 mg/kg per hour IV (ie, total of 50 mg/kg over 4 hours) in 500 ml of diluent.
- Finally, at a rate of 6.25 mg/kg per hour IV (ie, total of 100 mg/kg over 16 hours) in 1000 ml diluent over 16 hours.
In children between 20-40 kgs
- loading dose of 150mg/kg in 100 ml diluents over 1 hour,
- then 50 mg/kg /hour in 250 ml of diluent over 4 hours
- then 100mg/kg in 500 ml diluent over 16 hours.

In children <20 kgs,
- 150mg/kg into 3ml/kg diluents in 1 hour
- Then 50mg/kg into 7 ml/kg diluents over 4 hours
- Finally 100 mg/kg into 14 ml/ kg diluents into 16 hours.

This treatment protocol provides a total of 300 mg/kg over 20 to 21 hours.15

The duration of treatment may be extended if the patient presents following large doses and has evidence of hepatotoxicity.

Simplified 20 hour IV protocol — The results of a large retrospective study and experience at some hospitals suggest that non-allergic anaphylactic reactions during treatment with IV N-acetylcysteine can be reduced by using a two-bag regimen instead of the traditional three-bag regimes. In the study, non allergic anaphylactic reactions occurred in 10 percent of the 389 patients treated with the standard regimen versus 4.3 percent of the 210 patients treated with a modified two-bag regimen (odds ratio [OR] 2.5; 95% CI 1.1-5.8).24

Another randomized trial using a slightly different protocol that also slowed the initial infusion rate reported similar decreases in the rate of adverse events.25 While further trials are needed to confirm the improved safety of the two-bag regimen, it is believed to be a reasonable treatment approach in adults and older adolescents.

The two bag regimen can be given in the following manner:
- First, administer a 4 hour infusion at 50 mg/kg per hour IV (ie, total of 200 mg/kg over 4 hours)

- Next, administer a 16 hour infusion at 6.25 mg/kg per hour IV (ie, total of 100 mg/kg over 16 hours)

72 hour oral protocol — The 72 hour oral (PO) dosing protocol for N-acetylcysteine treatment has been used successfully for more than 30 years, and consists of the following:
- A loading dose of 140 mg/ kg PO, followed by
- A dose of 70 mg/kg PO every four hours for a total of 17 doses.

No dose adjustment is needed if the patient has been treated with activated charcoal.

The incidence of hepatotoxicity for patients treated within eight hours of ingestion is less than 10 percent, but increases to approximately 40 percent if treatment is delayed beyond 16 hours. In the largest study of oral N-acetylcysteine, no deaths occurred among patients treated before the onset of transaminase elevation.31

Other protocols — A 12-hour protocol for N-acetylcysteine treatment of APAP overdose has been described.23 This protocol involves the administration of 100 mg/kg of N-acetylcysteine over two hours as a loading dose, and then administration of 200 mg/kg over 10 hours. In a randomized trial, this protocol resulted in fewer adverse effects than the standard 20-hour protocol. However, the study was not large enough to draw conclusions about efficacy.

For patients with recurrent supratherapeutic ingestion or unknown time of ingestion, serum acetaminophen and transaminases should be measured, and NAC must be started until serum acetaminophen levels are below 10 micrograms /ml or until the transaminases normalize.

IV versus oral — There have been no trials comparing patients who have been treated with the 20 hour IV and the 72 hour oral routes. The best available data suggest that both routes are effective and differences are minimal.26,27 In most patients, either the oral or IV route is acceptable. IV administration preferred in the following:
- Vomiting
- Contraindications to oral administration (ie, pancreatitis, bowel ileus or obstruction, bowel injury)
- Hepatic failure
- Patients who refuse oral administration

Patients showing evidence of hepatic failure require IV therapy.

However, in children dilutional hyponatremia and seizures from free water load associated with infusion have been reported in some cases. Massive doses may also cause raised intracranial hypertension, cerebral edema and status epilepticus.

Effect of patient weight on dosing — In the United States, dosing depends on the weight of the individual. However, the maximum dose is based upon a weight of 100 kg for IV therapy and 110 kg for oral therapy.28,29 The basis for this has not been proved however it has been showed that dosing above this has not resulted in increased efficacy.31 However, in a large observational study, clinicians often based dosing on actual weight with a low rate of adverse events.31

Adverse reactions — Dosing errors may occur during common IV N-acetylcysteine administration,32 however significant adverse events arising from such miscalculations are rare. The most common adverse drug reaction described with intravenous preparation has been non IgE mediated anaphylaxis (anaphylactoid reactions), while that associated with oral administration has been vomiting.

Anaphylaxis (anaphylactoid
reaction) — Prospective studies suggest that between 10 to 20 percent of patients treated with IV N-acetylcysteine develop a hypersensitivity reaction (ie, anaphylaxis that is not IgE-mediated, formerly known as an anaphylactoid reaction).\textsuperscript{33,34} Reactions may not be very severe and most individuals are able to tolerate the infusion when it is resumed. However, patients receiving IV N-acetylcysteine need close monitoring and medications handy so as to counteract the adverse drug reactions including airway management.

These include oxygen, antihistamine medication (eg, diphenhydramine), salbutamol, nor adrenalin e(1:1000 for intramuscular use), steroid (eg, methylprednisolone), a resuscitation cart, and emergency airway management equipment. Even those restarted on N-acetylcysteine infusion after anaphylactoid reaction must be monitored in a critical care setting for the remainder of the infusion.

Limited observational evidence is available regarding the continuation of N-acetylcysteine in patients with anaphylaxis.

Based upon one small case series, the following approach is suggested:\textsuperscript{35}

• Patients who experience flushing without pruritus or urticaria don’t need interruption of the infusion, which can be continued, unless more severe signs develop. There is no convincing evidence that slowing the infusion rate would reduce the risk of hypersensitivity reactions.

• Patients who develop urticaria should have the infusion discontinued temporarily and they must be administered norepinephrine, as well as diphenhydramine and a glucocorticoid. The infusion may be restarted once urticaria resolves.

• The same protocol applies to those who develop angioedema or respiratory symptoms and if wheeze is present, nebulization is needed. The infusion may be resumed after the symptoms abate and an hour after epinephrine is administered.

• Patients who develop hypotension or other signs of systemic anaphylaxis after IV N-acetylcysteine therapy should have the infusion stopped and receive treatment for anaphylaxis in such situations. Restarting IV N-acetylcysteine should not be resorted to as it may be hazardous. Oral N-acetylcysteine therapy should be provided as an alternative, which may be tolerated by most of them.

Vomiting — Approximately 33 percent of subjects treated with oral N-acetylcysteine develop nausea and vomiting.\textsuperscript{37} The palatability of N-acetylcysteine may be improved by converting it into a juice form.

It is reasonable to administer an antiemetic to nauseated patients or those who have vomited prior to receiving oral N-acetylcysteine. 5-HT3 receptor antagonists (eg, ondansetron) are effective antiemetics that are widely used in this setting.\textsuperscript{37}

If a patient vomits within an hour of oral dose of N-acetylcysteine, the dose be may be repeated. Persistent vomiting despite oral anti-emetic is an indication for intravenous administrations.

Duration of treatment — While the efficacy of IV and oral administration is similar, controversy persists about the optimal duration N-acetylcysteine therapy. The current treatment protocols approved by the Food and Drug Administration (FDA) are time-based (20 and 72 hours).

Many authors recommend that therapy be tailored to each patient, using clinical endpoints rather than time to determine duration.\textsuperscript{38-40} We suggest the following approach for three common clinical scenarios based upon the type of ingestion and the clinical status of the patient:

• Following an acute ingestion with treatment started before transaminitis or within eight hours of ingestion - Administer IV or oral N-acetylcysteine for a minimum of 20 hours (which may be extended if oral route is administered).\textsuperscript{41}

The aminotransferase must be checked regularly and particularly as the treatment duration is coming to an end (approximately 18 hours after starting treatment). If transaminitis is present or serum acetaminophen is detected, treatment with N-acetylcysteine at 6.25 mg/kg per hour (for IV protocol) or 70 mg/kg every four hours (for oral protocol) must be continued and ALT and serum acetaminophen concentration must be rechecked every 12 hours. PT INR must also be measured as it is an indicator of acute liver injury.

Treatment may be stopped when the serum acetaminophen is <10 microgram/ml, INR<1.3 and there is no increase in aminotransferases. There is no uniformly accepted definition of “clearly decreasing.” One conservative definition is a decrease of more than 50 percent from the peak measurement or three consecutive decreasing values, all below 1000 international units/L.

Monitoring during treatment — Some authors recommend that once N-acetylcysteine is initiated within 8 hours of ingestion, further evaluation of aminotransferases may not be warranted. However, others say that it is advisable to check the levels as some individuals might develop liver injury during the treatment period also which might necessitate extension of the treatment.\textsuperscript{43}

Serum acetaminophen
**Table 1: King College Criteria for liver transplantation**

<table>
<thead>
<tr>
<th>Acetaminophen-induced ALF</th>
<th>Non-acetaminophen-induced ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.3 (regardless of HE) OR all 3 of the following</td>
<td>OR INR &gt;6.5</td>
</tr>
<tr>
<td>- INR &gt;6.5</td>
<td>- INR &gt;3.5</td>
</tr>
<tr>
<td>- Creatinine &gt;300 μmol/L</td>
<td>- Bilirubin &gt;300 μmol/L</td>
</tr>
<tr>
<td>- HE grade 3-4</td>
<td>- Etiology: indeterminate, drug-induced</td>
</tr>
<tr>
<td>- Time interval icterus to encephalopathy &gt;7 days</td>
<td>- Age &lt;10 or &gt;40 years</td>
</tr>
<tr>
<td>- INR &gt;3.5</td>
<td>- Creatinine &gt;300 μmol/L</td>
</tr>
</tbody>
</table>

Measurement is also recommended during the end of treatment in order to guide if treatment duration needs to be extended.20,38,39

Some guidelines recommend measuring serum acetaminophen, INR, serum bicarbonate, and serum creatinine at the end of treatment and continuing treatment if any value is abnormal.44 The ALT is used to monitor the degree of hepatic injury and the other tests are used to determine the need for liver transplant.45

Measuring the ALT and INR every 12 hours for any patient who develops ALT elevation is beneficial. If the patient has an ALT greater than 1000 international unit/L, coagulopathy (ie, INR >1.5), or encephalopathy, then the serum bicarbonate, glucose, and creatinine should also be measured every 12 hours. Intense monitoring is required as a need for transplantation may arise.

**Antidote Treatment in Special Circumstances**

**Treatment in hepatic failure** — In the face of hepatic failure, N-acetyl Cysteine must be given as it improves the hepatic microcirculatory functions.

There is no role of oral N-acetylcysteine in hepatic failure. The dosing protocol is the same as the 20 hour regimen used for the prevention of hepatic injury, except the final infusion rate (6.25 mg/kg per hour) is continued until the patient receives a transplant OR the hepatic encephalopathy resolves and the international normalized ratio (INR) is less than two.44,47

Additional supportive therapies for the management of acute hepatic failure and its complications (including encephalopathy, coagulopathy, and acute renal injury) are started as indicated.

The following is King’s college criteria that is used as a guide to know the indication for liver transplantation in paracetamol poisoning.

**Treatment in pregnancy** — Management of acetaminophen poisoning in pregnancy doesn’t differ significantly from the general population. However, intravenous administration is preferred to ensure rapid delivery to the fetus and to prevent vomiting.

As acetaminophen crosses the placenta, maternal overdose may also cause fetal compromise and there are case reports of fetal and neonatal death from hepatic necrosis following maternal overdose.48,49 However, most cases of pregnant women with an acetaminophen overdose are uneventful.49,50

The risk of hepatotoxicity also doesn’t change in pregnancy hence Rumack-Mathew normogram may also be used in pregnant population.14

In pregnant patients with repeat or chronic ingestions, serum acetaminophen and transaminase concentrations should be measured. Treatment with N-acetylcysteine is indicated if the serum acetaminophen concentration is greater than 20 mcg/mL or a serum transaminase concentration is elevated (>50 international unit/L).42 Dosing and the duration of treatment do not differ in the pregnant patient.

Though there are several reports of good outcomes among mothers with hepatic injury following acetaminophen overdose,51,52,53 it is likely that maternal toxicity increases the risk for adverse pregnancy outcomes. The incidence of fetal malformations have not shown to be to be increased following acetaminophen overdose if treatment is started on time, but data are limited.50,54

The most important intervention to avoid toxic effects of acetaminophen poisoning is timely treatment with N-acetylcysteine. In a prospective observational study of 60 pregnant women with acetaminophen overdose, increasing time to N-acetylcysteine administration was associated with an increased risk of miscarriage and fetal death.48 Multiple case reports describe similar findings.55-57

As against what many claim both IV and oral routes have been used successfully to treat pregnant patients with acetaminophen overdose, and oral formulations may be used when IV N-acetylcysteine is not available. Oral administration produces therapeutic N-acetylcysteine concentrations in cord blood.55

Standard laboratory studies and monitoring should be performed in pregnant patients with acetaminophen overdose.

**Other Treatments**

Cimetidine and other medications — Several other treatments have been suggested as possible adjuncts for the prevention
of acetaminophen-induced liver injury. The most commonly cited is cimetidine, an inhibitor of acetaminophen metabolism. 59-63 While this treatment was useful in animal models, it had no effect in a clinical trial where patients were treated with N-acetylcysteine. 64 Other substances have also been evaluated in animal models, but none is considered standard care in humans.65-68

Older studies evaluated therapies such as methionine, mand dimercaprol, but these therapies such as methionine, acetaminophen metabolism. 59-63

injury. The most commonly cited of acetaminophen-induced liver injury. The most commonly cited of acetaminophen-induced liver injury. The most commonly cited

be considered a standard therapy for these cases.

some toxicologists recommend doubling the standard dose during hemodialysis.74,75 However, it is not clear that the amount of N-acetylcysteine removed affects clinical outcomes, so increasing the rate is not universally recommended and should not be considered.

Prognosis

The outcome of acetaminophen intoxication is almost always good as long with timely administration of N Acetyl cysteine, particularly when given with the first 10 hours.10,11,76 A study of around 333 cases of acetaminophen overdose found that hepatotoxicity was reported in only 4 percent of patients and mortality rate was less than 1 percent when NAC was rapidly administered.77 Hence, fulminant hepatic failure and death from acetaminophen poisoning result from inability to recognize poisoning, or delayed initiation of management.

Studies are ongoing in order to find out some biomarkers that can predict the risk of hepatotoxicity early at the time of presentation following acetaminophen overdose.78,79

References

20. Schwartz EA, Hayes BD, Sarmiento KF. Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and


55. Al-Mustafa ZH, Al-Ali AK, Qaw FS, Abdul-Cader Z. Cimetidine enhances
the hepatoprotective action of N-acetylcysteine in mice treated with toxic doses of paracetamol. Toxicology 1997; 121:223.


66. Reisman SA, Aleksunes LM, Klaassen CD. Oleanolic acid activates Nrf2 and protects from acetaminophen hepatotoxicity via Nrf2-dependent and Nrf2-independent processes. Biochem Pharmacol 2009; 77:1273.


