MIL

Oxford University Hospitals NHS
NHS Foundation Trust

Volume 11, No.8 **March 2024**

This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Guideline for the Management of Paracetamol Overdose in Adults and Children

Modified 12-hour Acetylcysteine Regimen: Scottish and Newcastle Acetylcysteine Protocol (SNAP)

Paracetamol overdose is a medical emergency and management should be started immediately once diagnosis is confirmed and treatment criteria are met. Toxic doses of paracetamol may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis[1]. This MIL should be used in conjunction with TOXBASE guidance. In all cases of intravenous paracetamol poisoning, clinicians are encouraged to contact the National Poisons Information Service (NPIS) for advice on risk assessment and management[1].

To contact UK NPIS, phone 0344 892 011

Use of the SNAP regimen for infusion of acetylcysteine is endorsed by the NPIS and Royal College of Emergency Medicine (RCEM).

Clinical presentation

- Nausea and vomiting (usually settle within 24 hours)[1,2].
- Recurrence of nausea and vomiting after 2-3 days, often associated with right subcostal pain (suggestive of hepatic necrosis – this may lead to encephalopathy, cerebral oedema, hypoglycaemia, haemorrhage and death)[2].

However, please also note that patients are frequently asymptomatic[2]. Paracetamol is a 'delayed-action poison', so patients may appear well on first presentation but later deteriorate[1]. Liver damage is maximal 3–4 days after paracetamol overdose and may lead to liver failure, encephalopathy, coma, and death[1]. Always consider co-ingestion of other toxins.

Treatment criteria

Patients at risk of liver damage from paracetamol overdose can be identified from a single measurement of the plasma-paracetamol concentration related to the time from ingestion, provided this time interval is not less than 4 hours[1].

Acetylcysteine treatment should commence in the following patients[1]:

Note: Use actual body weight for calculations unless the patient weighs more than 110kg (refer to 'Management in Obesity' section below).

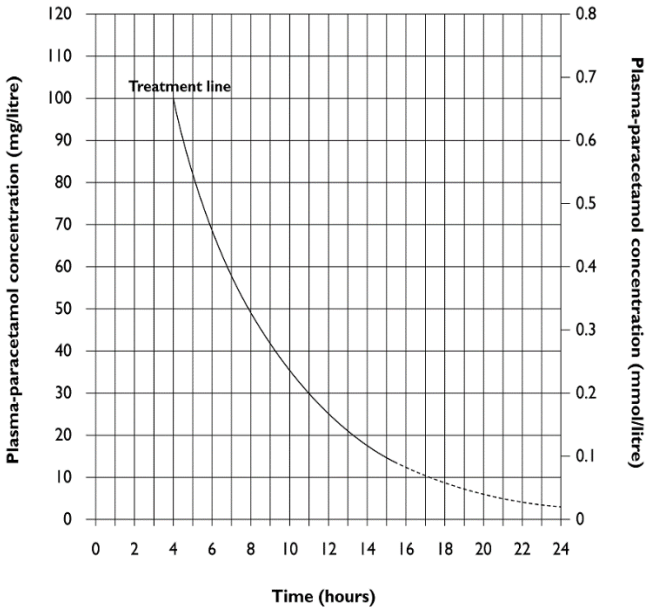
- Those with a plasma-paracetamol concentration falling on or above the treatment line on the paracetamol treatment graph (shown below).
- Those who present within 8 hours of ingestion of more than 150mg/kg of paracetamol, if there is going to be a delay of 8 hours or more in obtaining the paracetamol concentration after the overdose.
- Those who present 8-24 hours after ingestion of an acute overdose of more than 150mg/kg of paracetamol, even if the plasma-paracetamol concentration is not yet available.
- Those who present more than 24 hours after ingestion of an overdose, if they are clearly jaundiced or have hepatic tenderness, their

Alanine Aminotransferase (ALT) is above the upper limit of normal (patients with chronically elevated ALT should be discussed with the NPIS), their INR is greater than 1.3 (in the absence of another cause), or the paracetamol concentration is detectable.

Additional Treatment Considerations

- Acetylcysteine treatment can also be considered in patients who present within 24 hours of an overdose if biochemical tests suggest acute liver injury, even if the plasma concentration is below the treatment line on the paracetamol treatment graph (shown below).
- Where the time of ingestion is unknown, patients should be managed as a staggered overdose (refer to 'Management of Staggered Overdose' section below).
- For an unintentional therapeutic excess refer to 'Management of Paracetamol Therapeutic Excess' section below.
- Haemodialysis may be indicated in addition to acetylcysteine if a patient has very high paracetamol concentrations associated with coma and elevated blood lactate concentrations – this should be discussed with NPIS.

Paracetamol Treatment Graph[3]



The prognostic accuracy after 15 hours is uncertain, but a plasma-paracetamol concentration on or above the treatment line should be regarded as carrying a serious risk of liver damage[1].

Patients who have ingested more than 150 mg/kg of paracetamol in any 24-hour period are at risk of serious toxicity[1]. Toxicity rarely occurs with paracetamol doses between 75–150 mg/kg in any 24-hour period[1]. Doses consistently less than 75 mg/kg in any 24-hour period are very unlikely to be toxic; however risk may be increased if this dose is repeatedly ingested over 2 or more days[1].

Management

Acetylcysteine is recommended for all patients who meet treatment criteria[4]. It prevents or reduces the severity of liver damage if given up to, and possibly beyond, 24 hours of ingesting paracetamol[1]. It is most effective if given within 8 hours of paracetamol ingestion, after which effectiveness declines[1].

Current practice at OUH is to administer the unlicensed, modified 12-hour acetylcysteine intravenous infusion regimen, known as the Scottish and Newcastle Acetylcysteine Protocol (SNAP) (please refer to the Procedure for the use of unlicensed and 'off-label' medicines[5]). The total dose of intravenous acetylcysteine is the same as the standard 21-hour regimen (i.e. 300 mg/kg) but the rate and duration of treatment are different[6]. SNAP consists of two separate infusions, the first one lasting for 2 hours and the second one lasting for 10 hours[4]. For the dosing table and the method of administration, please refer to the local injectable monograph for acetylcysteine, which can be found on the OUH intranet[7], or in the tables in appendix 2. Use of the SNAP regimen is endorsed by the NPIS and the Royal College of Emergency Medicine (RCEM). Please see monographs on Medusa[12] or Toxbase[4] for further information.

When prescribing on ePMA, use one of the following PowerPlans:

- **Acetylcysteine Paediatric Paracetamol Poisoning PowerPlan**
- **Acetylcysteine Adult Paracetamol Poisoning PowerPlan**

Cautions with acetylcysteine use

- Anaphylactoid hypersensitivity reactions to acetylcysteine – more common in women, patients with a family history of allergies and people with asthma or atopy[6].
- Coagulation – may affect prothrombin time or slightly increase INR (consider contacting Hepatology and/or Haematology for advise if INR is greater than 1.3)[6,8].
- Patients requiring fluid restriction or weigh less than 40kg – risk of fluid overload[9].

Note: There are NO contraindications for the treatment of paracetamol overdose with acetylcysteine[3,8,9] and no known drug interactions[9].

Adverse effects of acetylcysteine[9]

- Common: nausea, vomiting, flushing, skin rash.
- Less common: angioedema, bronchospasm/ respiratory distress, hypotension, tachycardia, hypertension.

Adverse reactions usually occur between 15 to 60 minutes after the start of the acetylcysteine infusion (refer to 'Management of Anaphylactoid Reactions' section below).

Recommended Monitoring

In all patients re-check the plasma-paracetamol concentration, INR, creatinine, venous pH or plasma bicarbonate and ALT at, or just before, the end of the second treatment bag. The patient may be considered for discharge if all blood results are normal:

1. INR is 1.3 or less **and**
2. ALT is within the normal range **and**
3. Paracetamol concentration is less than 10 mg/L **and**
4. Patient has no symptoms suggesting liver damage.

See Appendix 1 at the end of this MIL for further guidance on actions to take for abnormal blood results or refer to TOXBASE.

Monitor for anaphylactoid reactions – these are dose-related and usually occur during or shortly after the first infusion. Common features include: nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia and bronchospasm[6].

Hypokalaemia and ECG changes have been noted in patients with paracetamol poisoning irrespective of the treatment given. Monitoring of plasma potassium concentration is recommended[9].

Management of Anaphylactoid Reactions[6]

1. Temporarily stop the acetylcysteine.
2. H_1 antihistamine (e.g. chlorphenamine 10mg IV) and nebulised salbutamol if bronchospasm is present.
3. Re-start acetylcysteine as soon as the reaction has settled, to ensure the total dose is administered. Consider slowing the infusion rate initially (e.g. administer the first bag over twice as long as usual. The normal infusion rate can be used for subsequent bag).

Prophylactic Management of Patients with previous Anaphylactoid Reactions to Acetylcysteine[6]

1. Before starting an acetylcysteine infusion consider prophylactic treatment with H_1 and H_2 antihistamines.
2. Pre-treatment with nebulised salbutamol may be considered in those patients with a history of bronchospasm following acetylcysteine.

Note: A history of anaphylactoid reactions is NOT a contra-indication to intravenous acetylcysteine.

Management of Staggered Overdose

A staggered overdose involves ingestion of a potentially toxic dose of paracetamol over more than 1 hour, with the possible intention of causing self-harm. All patients who have ingested a staggered overdose should be treated with acetylcysteine without delay[1].

Management in Pregnancy

The dose for intravenous acetylcysteine should be calculated using the patient's actual pregnancy weight (up to a maximum of 110kg)[4,10]. However, when calculating the ingested, toxic dose for

paracetamol the patient's pre-pregnancy weight should be used instead[4].

Management in Obesity

For any patient weighing more than 110kg, the ingested, toxic dose for paracetamol and the treatment dose for intravenous acetylcysteine should be calculated using a weight of 110kg rather than their actual weight[1].

Management of Paracetamol Therapeutic Excess[11]

A therapeutic excess is defined as paracetamol ingested at a dose greater than the licensed daily dose and more than or equal to 75 mg/kg/24 hours, with intent to treat pain or fever and without self-harm intent. This can involve the use of excessive doses of the same paracetamol product or inadvertent use of more than one paracetamol-containing product at the same time. The underlying clinical reason for the chronic excess dosage should be considered and rectified if possible (e.g. counsel patient on maximum daily dose of paracetamol).

Patients with clinical features of hepatic injury, such as jaundice or hepatic tenderness, should be treated urgently with acetylcysteine.

In other patients, management is determined by the maximum dose of paracetamol ingested in any 24-hour period (see below). Clinicians should be aware that reported doses may be unreliable and should take this into account when making judgements about the need for further assessment.

Maximum dose more than 75 mg/kg within any 24-hour period

Check paracetamol concentration, liver function tests (LFTs), INR, urea and electrolytes (U&Es), creatinine, bicarbonate and full blood count (FBC) at least 4 hours after the last paracetamol ingestion. Plasma paracetamol concentrations before this time cannot be interpreted. Acetylcysteine should be commenced if the patient is symptomatic or blood tests indicate a risk of hepatotoxicity:

- Paracetamol is more than 10mg/L **and**
- ALT is increased above the upper limit of the normal range **and**
- INR is more than 1.3 **and**
- Patient has clinical features suggesting liver damage

Maximum dose more than the licensed 24-hour dose, but less than 75mg/kg/24hours over the preceding 2 or more days:

Risk of clinically important hepatotoxicity is extremely small, but blood tests may be considered, especially if there is doubt about the doses used or other factors are present that may increase the risk of hepatotoxicity. These include:

- Long-term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Regular consumption of ethanol in excess of recommended amounts.
- Likely glutathione depletion (e.g. HIV, eating disorders, cystic fibrosis, starvation, cachexia).

Acetylcysteine should be commenced if the patient is symptomatic or blood tests indicated a risk of hepatotoxicity (see above for blood test indicators).

Maximum dose consistently less than the licensed 24-hour dose AND consistently less than 75 mg/kg for that patient over the preceding 24-hour period:

Further assessment is not needed, provided a reliable history has been obtained and the patient is well.

Information for discharge[12]

All patients should be asked to return to hospital if they develop new nausea, vomiting, abdominal pain or jaundice. All patients treated with acetylcysteine should be advised to avoid paracetamol and paracetamol-containing products for 2 weeks.

For patients who did not meet the criteria for treatment with acetylcysteine but who had an initial plasma paracetamol concentration above 20mg/mL, they should be advised to avoid paracetamol and paracetamol-containing products for the 12 hours.

Acetylcysteine in Acute Liver Failure

A different regimen of acetylcysteine is also used for management of acute liver failure at OUH. This is an unlicensed indication and should only be prescribed by a hepatology consultant[7].

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Review date: *March 2027*

Appendix 1:

Dosing tables for acetylcysteine[4]

Acetylcysteine prescription for children (and adults) weighing 39 kg or less				
12-hour Regimen	**First Infusion**		**Second Infusion**	
Drug	**Acetylcysteine 200 mg/mL for infusion, 10 mL ampoule**			
Infusion fluid	**5% glucose or 0.9% sodium chloride**			
Duration of infusion	**2 hours**		**10 hours**	
Drug dose	**100 mg/kg acetylcysteine**		**200 mg/kg acetylcysteine**	
Concentration of infusion	**50 mg/mL**		**10 mg/mL**	
Patient Weight [1]	**Total infusion volume[2]** (NB. NOT AMPOULE VOLUME)	**Infusion Rate**	**Total infusion volume[2]** (NB. NOT AMPOULE VOLUME)	**Infusion Rate**
kg	**mL**	**mL/h**	**mL**	**mL/h**
1	2	1	20	2
2	4	2	40	4
3	6	3	60	6
4	8	4	80	8
5	10	5	100	10
6	12	6	120	12
7	14	7	140	14
8	16	8	160	16
9	18	9	180	18
10 – 14	24	12	240	24
15 - 19	34	17	340	34
20 - 24	44	22	440	44
25 - 29	54	27	540	54
30 - 34	64	32	640	64
35 - 39	74	37	740	74

Acetylcysteine prescription for adults and children weighing 40 kg or more (each ampoule = 200 mg/mL acetylcysteine)				
12-hour Regimen	**First Infusion**		**Second Infusion**	
Infusion fluid	**200 mL 5% glucose or 0.9% sodium chloride**		**1000 mL 5% glucose or 0.9% sodium chloride**	
Duration of infusion	**2 hours**		**10 hours**	
Drug dose	**100 mg/kg acetylcysteine**		**200 mg/kg acetylcysteine**	
Patient Weight[1]	**Ampoule volume[2]**	**Infusion Rate**	**Ampoule volume[2]**	**Infusion Rate**
kg	**mL**	**mL/h**	**mL**	**mL/h**
40-49	23	112	45	105
50-59	28	114	55	106
60-69	33	117	65	107
70-79	38	119	75	108
80-89	43	122	85	109
90-99	48	124	95	110
100-109	53	127	105	111
≥110	55	128	110	111

Appendix 2:

Guidance on when to take bloods and interpretation of these results at the end of the modified 12-hour acetylcysteine infusion regimen (SNAP)[11]

In all patients re-check the plasma paracetamol concentration, INR, creatinine, venous pH or plasma bicarbonate and ALT at, or just before, the end of the 2nd treatment bag (12-hour infusion).

If all blood results are normal:

- INR is 1.3 or less **AND**
- ALT is within the normal range **AND**
- Paracetamol concentration is less than 10 mg/L **AND**
- Patient has no symptoms suggesting liver damage.

The patient can be considered for discharge; see also management advice below.
Note: These criteria differ from those used for discontinuation of the standard (21-hour) acetylcysteine regimen.

Or

If blood results are abnormal:

- The ALT is increased above the upper limit of the normal range, **OR**
- the INR is greater than 1.3 (in the absence of another cause, e.g. warfarin), **OR**
- the paracetamol concentration is greater than 10 mg/L

continue acetylcysteine at the dose and infusion rate used in the 2nd treatment bag. It is not necessary to give a further loading dose unless a second overdose has been taken. Repeat all blood tests in a further 10-hours (i.e. 22-hours after start of NAC) and follow guidance below.

Guidance to follow at the end of third treatment bag of acetylcysteine i.e. the end of the second 10-hour treatment bag (22-hours after starting NAC):

Re-check the INR, plasma creatinine and ALT at, or just before, the end of the 3rd bag of acetylcysteine.

In patients with severe liver toxicity, also check lactate, venous pH or plasma bicarbonate.

Acetylcysteine treatment may be stopped if the blood results meet the following criteria:

- INR is 1.3 or less, **AND**
- ALT is within the normal range

If the ALT is above the normal range (with an INR of 1.3 or less), acetylcysteine may still be stopped if:

- ALT is less than two times the upper limit of normal **AND**
- The increase in ALT value is not more than a doubling of the admission value

Acetylcysteine should be continued if blood results are abnormal and meet ANY of the following criteria:

- the ALT is more than two times the upper limit of normal **OR**
- the ALT has doubled or more since the admission measurement AND is above the upper limit of normal **OR**
- the INR is greater than 1.3 (in the absence of another cause e.g. warfarin) AND the ALT is above the upper limit of normal **OR**
- the INR has risen by 0.5 or more from the admission measurement*

Continue acetylcysteine at the dose and infusion rate used in the 3rd treatment bag. It is not necessary to give a further loading dose unless a second overdose has been taken. Repeat all blood tests in a further 8 hours. Follow management below for patients with liver toxicity, liver failure or acute kidney injury.

***Patients with an isolated rise in INR of less than 0.5**
Both paracetamol and NAC treatment may cause an increase in INR in the absence of liver injury. For patients who have an isolated rise in INR of less than 0.5, stop acetylcysteine treatment and recheck INR and ALT after 4-6 hours.

After this 4-6 hour period without acetylcysteine, the patient can be considered for discharge if the blood tests meet the following criteria:

- INR is unchanged or falling AND
- ALT is less than two times the upper limit of normal

otherwise restart acetylcysteine at the dose and infusion rate used in the 3rd treatment bag.

Patients with a chronically elevated ALT (e.g. chronic liver disease) may not require ongoing acetylcysteine treatment if the ALT value has not changed significantly from admission. These cases should be discussed with the NPIS.

Management of patients with liver toxicity receiving extended treatment with acetylcysteine (i.e. receiving fourth treatment bag or more)

Further bags of acetylcysteine should be given at the dose and infusion rate used in the last treatment bag until:

- the INR is 1.3 or less, **OR**
- the INR is falling towards normal on two consecutive blood tests, and less than 3.0.

Recheck U&Es, creatinine, ALT and INR every 10-16 hours to assess the course of liver injury: this allows early assessment of liver toxicity progression.

There is no clinical advantage to treating ALT rises with acetylcysteine after normalisation in INR (indicating restoration of hepatic synthetic function).

The patient can be considered for discharge; see below for advice to be given to patients at discharge.