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Paracetamol Overdose Management

CATEGORY:	Clinical Guidelines
CLASSIFICATION:	Clinical
Controlled Document Number:	CG163
Version Number:	**1**
Controlled Document Sponsor:	Clinical Guidelines Group
Controlled Document Lead (Author):	Consultant Emergency Department JSD
Approved By:	Clinical Guidelines Group
On:	January 2015
Review Date:	January 2018

PARACETAMOL OVERDOSE

Please note that EVERY patient with a DELIBERATE overdose needs RAID referral and an assessment before discharge

RECOGNITION AND ASSESSMENT

Symptoms and signs

- Usually none
- Extremely common: nausea and vomiting (occur within a few hours of ingestion of a hepatotoxic dose)
- Very rarely: coma and severe metabolic acidosis in patients who have extremely high plasma paracetamol concentrations (usually greater than 800 mg/L). Drowsiness in the first 1-2 days after a single paracetamol overdose is unlikely to be due to liver failure, so consider other causes.
- In those presenting late, loin pain, haematuria and proteinuria after 24 hours suggest incipient renal failure, whereas right subcostal pain and tenderness with recurrent nausea, vomiting and jaundice after 2 to 3 days are features of hepatic necrosis.
- Later features in severe cases (12-36 hours): abdominal pain.

Investigations – to be perform in ALL patients

- Patient's weight – this should be recorded clearly in patient's notes as this would guide further assessment and treatment.
- Plasma paracetamol 4 hours after ingestion (but not before).
- Compare plasma paracetamol levels with treatment graph (**figure 1**)
- Baseline:
    - FBC, INR
    - U&E, LFTs (ALT - most sensitive marker for liver injury), phosphate
    - Acid-base (venous sample) and venous blood lactate, bicarbonate, glucose.

IMMEDIATE TREATMENT

When using body weight to estimate dose ingested or antidote dose, allow maximum body weight 110 kg even in very obese patients weighing > 110 kg.

In pregnant patients the toxic dose should be calculated using the patient's pre-pregnancy weight and the antidote dose should be calculated using the patient's actual pregnant weight (to a max 110kg).

Activated Charcoal

If patient is thought to have taken **>12g or 150 mg/kg and presents within 1 hour** of ingestion, give activated charcoal 50 g (1 g/kg for children) orally or via nasogastric tube.

Acetylcysteine (standard regimen) - Adults

Acetylcysteine should be administered by intravenous infusion preferably using Glucose 5% as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.

- The full course of treatment comprises of **3 consecutive intravenous infusions**. Doses should be administered sequentially **with no break** between the infusions. The patient should receive a total dose of 300 mg/kg body weight over a 21 hour period. As per shown in **table 1**.
- If **<8 hours** from ingestion the use of acetylcysteine should be avoided until plasma paracetamol concentrations are known.
- Acetylcysteine efficacy declines rapidly **after 8 hours** so treatment shouldn't be delayed during this period.
- However, in patients who present **more than 24 hours** after the overdose, there is no evidence that treating with acetylcysteine before blood test are available confers benefit or that delaying treatment for a short period while waiting for blood results worsen prognosis.
- **Staggered overdose** treatment should be started within one hour of the patient arriving to the department.

Adverse reaction to acetylcysteine & management

- Can occur **in up to 15% of patients**, usually within first 30 minutes of administration when large amounts are given rapidly.
- Nausea, vomiting, flushing, urticarial rash, angioedema, tachycardia, bronchospasm are relatively common. Hypotension and collapse are rare. Very rarely, in severe cases, respiratory depression, renal failure and DIC.

1. Stop the infusion (usually this is all that is required).
2. Give an H1 antihistamine if necessary (e.g. chlorphenamine 10 mg IV).
3. Give nebulised salbutamol if bronchospasm is significant.
4. Other measures as indicated by the patient's clinical condition (e.g. hydrocortisone 100mg IV if the reaction is severe).
5. Restart treatment when the reaction has settled

Previous reaction to acetylcysteine

- Is **NOT** a contraindication for a further treatment course.
- Acetylcysteine is more likely to cause adverse effects if paracetamol concentrations are low or absent. Adverse effects are also more likely in women, asthmatics and in patients with a family history of allergy.
- **Prophylactic treatment** with H1 and H2 antihistamines should be considered (e.g. chlorphenamine 10 mg IV and ranitidine 50 mg diluted to 20 mL and given intravenously over at least 2 minutes).
- Pretreatment with nebulised salbutamol may be considered in those patients with a history of bronchospasm following acetylcysteine.
- Consider giving the first bag more slowly than normal, e.g. over 2 hours, if the patient has had a previous severe reaction to NAC.

MANAGEMENT

Time from OD (hours)		Management	Discharge policy and subsequent management
SINGLE ACUTE OD	**0 - 8**	• Consider activated charcoal if presentation within 1 hour from ingestion. • **Take bloods 4 hours after** ingestion **and await plasma paracetamol levels.** • Treat if above, on, or slightly below the appropriate treatment line (**figure 1**).	If the paracetamol concentration is below the treatment line; the INR and ALT are normal[#]; the patient is asymptomatic and has a normal serum creatinine s/he can be discharged with **advice to return to hospital if vomiting or abdominal pain occurs**.
	8- 24	• Take bloods • If **>150 mg/kg** give acetylcysteine immediately. • If **< 150 mg/kg**, wait for blood results before considering treatment.	**If 24hours after overdose or after antidote treatment complete**: ➢ Paracetamol concentration is not detectable ➢ INR ≤ 1.3 ➢ ALT < X2 the upper limit of normal ➢ Asymptomatic. ➢ Creatinine is normal. The patient is not considered to be at risk of liver damage and does not need treatment. If treatment has been started it can be discontinued. The patient can be discharged with advice to return if vomiting or abdominal pain occurs. **If after treatment blood results are abnormal:** ➢ the ALT has more than doubled since the admission measurement, **OR** ➢ the ALT is ≥ X2 the upper limit of normal , **OR** ➢ the INR ≥ 1.3 (in the absence of another cause, e.g. warfarin) **Continue acetylcysteine at**
	> 24	• Take bloods • If patient is jaundiced or has hepatic tenderness treat with acetylcysteine. • Otherwise wait for blood results before commencing treatment. **Treat if**: ➢ Paracetamol detected. ➢ INR >1.3 ➢ ALT > X2 times the upper limit of normal.	
Staggered Overdose (doses taken over >1 hour)		• Take bloods • Treat with acetylcystein	
Therapeutic excess (>than a licensed dose for that individual or **>75 mg/kg** in any 24hour period).		• Take bloods • **Treat if**: ➢ Jaundice or hepatic tenderness ➢ There is any uncertainty (dose or timing). ➢ Ingested **>150mg/kg** in any 24 hours. ➢ Abnormal ALT, INR or detectable paracetamol concentration more	

[#] If biochemical tests suggest acute liver injury (e.g. ALT above the upper limit of normal) consider acetylcysteine even if the plasma paracetamol is below the treatment line as in cases of severe poisoning the ALT rises rapidly and is commonly abnormal at first presentation to hospital.

<table>
<tr><td></td><td>than 24 hours after the last dose.
• If 75-150 mg/kg in any 24-hour period clinical judgement* should be used in determining the need for treatment. Discuss with senior.

❖ The underlying clinical reason for the chronic excess dosage should be considered.</td><td rowspan="2">the dose and infusion rate used in the 3rd treatment bag. Repeat all blood tests in a further 8-16 hours.
Acetylcysteine should be continued until:
➢ INR is ≤ 1.3, OR
➢ INR is falling towards normal on 2 consecutive blood tests and < 3.0.
Recheck U&Es, creatinine, ALT and INR every 8-16 hours to assess the course of liver injury.

There is no clinical advantage to treating ALT rises with acetylcysteine after normalisation in INR (indicating restoration of hepatic synthetic function). An isolated smaller (<X2 the upper limit of normal) rise in ALT in the presence of an INR ≤ 1.3 does not require further treatment. The patient can be discharged with advice to return if vomiting or abdominal pain occurs.

Liver failure and acute kidney injury should be managed conventionally.
If plasma creatinine is >10% greater than that at initial presentation after treatment, check renal function 12 hours later. Renal failure may occur as part of hepatorenal syndrome or, rarely, in the absence of hepatic injury (Acetylcysteine has not been tested as an antidote for this).</td></tr>
<tr><td>Uncertain time of ingestion
And the dose >75 mg/kg.</td><td>Take bloods and treat immediately if jaundice or hepatic tenderness.

If within the last 24 hours
• Take bloods
• Treat immediately if ≥150mg/kg.
• If 75-150mg/kg clinical judgement should be used. Discuss with senior.

If between 24-72 hours
• Take bloods.
• Treat immediately if ≥150 mg/kg in any 24 hour period within the last 72 hours.
• If between 75 - 150 mg/kg in any 24 hour period within the last 72 hours, clinical judgement should be used. Discuss with senior.

If >72 hours ago
• Take bloods

If >7 days
Asymptomatic patients, who have had no new symptoms since the time of ingestion, and who have no history of chronic kidney or liver disease, will not normally require further assessment, providing the timing of ingestion is certain.</td></tr>
<tr><td colspan="3">Other measures as indicated by patient's clinical condition.

Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.</td></tr>
</table>

* Clinical judgement should take into account the magnitude of the exposure, its duration, intent insofar as it relates to the reliability of the history, and any other relevant factors.

In case of uncertainty discuss with **National Poisons Information Service**
0844 892 0111

ALL ingestions of >75mg/kg are consider significant

LIFE-THREATENING FEATURES

A **poor prognosis** is indicated by:

- INR > 3.0
- Plasma creatinine > 200 micromol/L
- Blood pH < 7.3
- Signs of encephalopathy (mental confusion, drowsiness, spatial disorientation, asterixis)

If any of these features are present after overdose, seek advice from a consultant gastroenterologist

- Patients with **incipient or established hepatic failure may be candidates for liver transplantation. Please seek advice from liver team.**
- **Hypophosphataemia** usually occurs after paracetamol poisoning and correlates well with the degree of hepatic damage.
- Treat haemorrhage with fresh frozen plasma.

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an assessment before discharge

Figure 1 -Treatment Nomogram

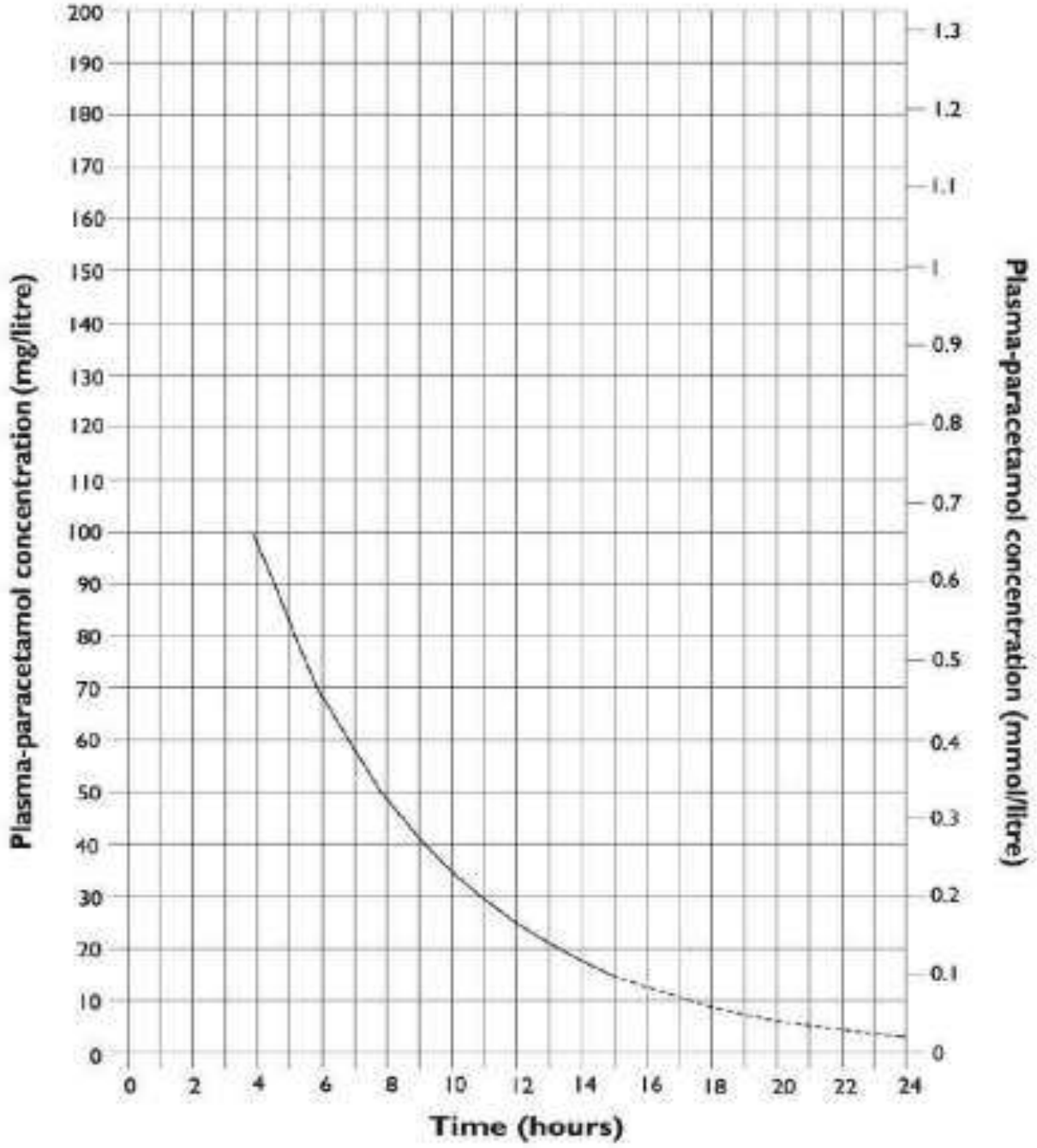

Table 1 – Adult dosage table

Adult acetylcysteine prescription (each ampoule = 200mg/mL acetylcysteine)					Please circle appropriate weight and volume.	
Regimen	**First Infusion**		**Second Infusion**		**Third Infusion**	
Infusion fluid	200 mLs 5% glucose or sodium chloride 0.9%		500 mLs 5% glucose or sodium chloride 0.9%		1000 mLs 5% glucose or sodium chloride 0.9%	
Duration of infusion	1 hour		4 hours		16 hours	
Drug dose	150 mg/kg acetylcysteine		50 mg/kg acetylcysteine		100 mg/kg acetylcysteine	
Patient Weight[1]	**Ampoule volume[2]**	**Infusion Rate**	**Ampoule volume[2]**	**Infusion Rate**	**Ampoule volume[2]**	**Infusion Rate**
kg	**mL**	**mL/h**	**mL**	**mL/h**	**mL**	**mL/h**
40-49	34	234	12	128	23	64
50-59	42	242	14	129	28	64
60-69	49	249	17	129	33	65
70-79	57	257	19	130	38	65
80-89	64	264	22	131	43	65
90-99	72	272	24	131	48	66
100-109	79	279	27	132	53	66
≥110	83	283	28	132	55	66

1 Dose calculations are based on the weight in the middle of each band. If the patient weighs less than 40kg use the paediatric dosage table.
2 Ampoule volume has been rounded up to the nearest whole number.

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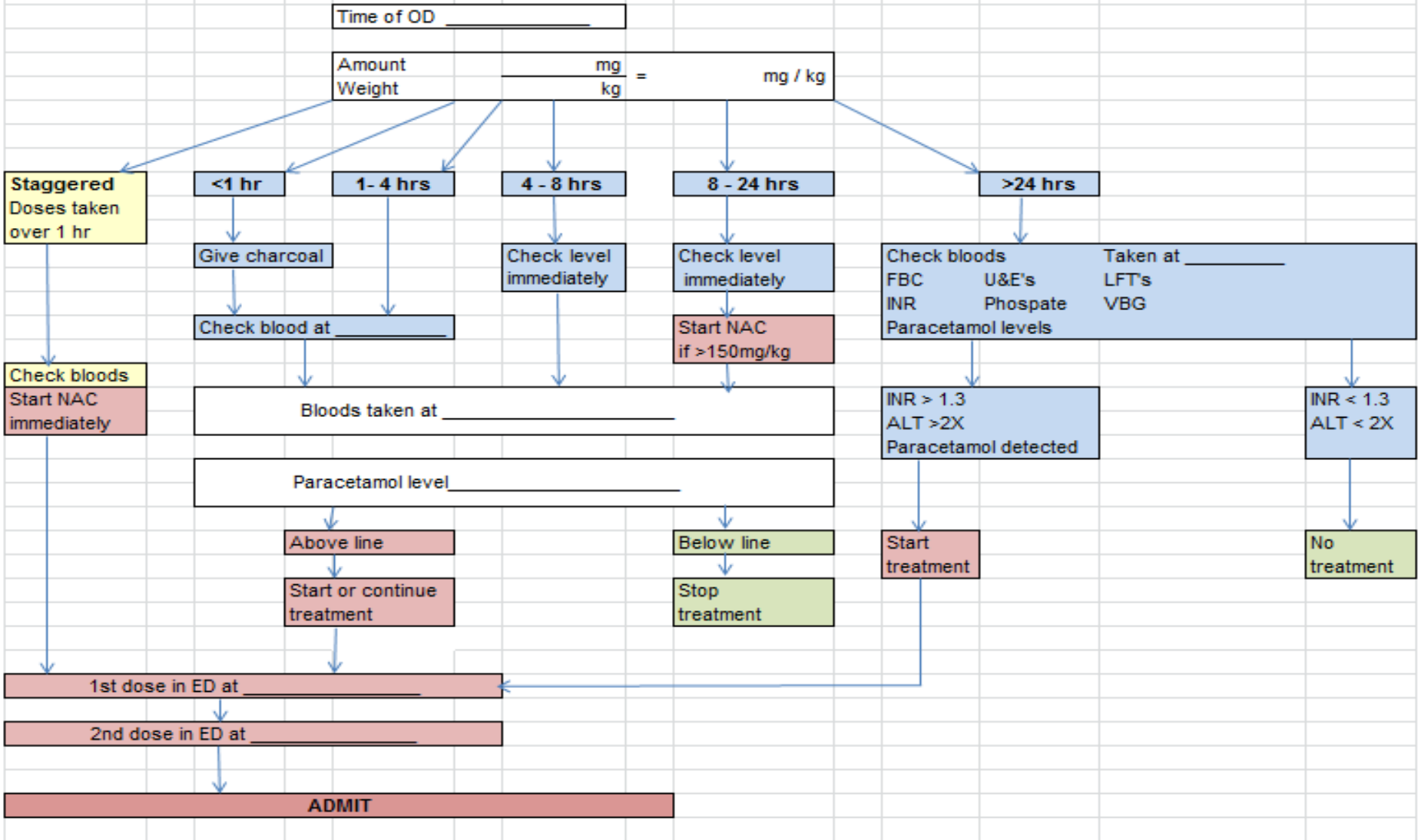
PARACETAMOL OD FLOWCHART



REFERENCES

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http://www.patient.co.uk/doctor/paracetamol-poisoning
http://www.uptodate.com/contents/acetaminophen-paracetamol-poisoning-in-adults-treatment
http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con178655.pdf

AUDITABLE OUTCOMES

http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Audit/Current%20Audits
http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Standards

CEM STANDARDS

1. Plasma levels should not be measured earlier than 4 hours after the estimated ingestion time.
2. Staggered overdoses - treatment started within one hour of arrival.
3. Patients arriving < 8 hours after ingestion - treatment given as per the 2012 MHRA guideline.
4. Patients arriving 8 to 24 hours after ingestion - treatment started before blood results available if there is a clear history of > 6 g ingestion (or 75 mg/kg whichever is the smaller).
5. Patients presenting > 24 hours. INR, urea and electrolytes bicarbonate & LFTs performed and recorded in the notes.