# PARACETAMOL OVERDOSE – ADULTS AND CHILDREN AGED 6 YEARS AND OVER

Ref No: 1297

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## CONTENTS

## FEATURES

**Early**

Common

Nausea and vomiting

Uncommon

Coma and severe metabolic acidosis

**Late**

Abdominal pain, features of hepatic necrosis (right subcostal pain and tenderness, nausea, vomiting, jaundice, renal failure and coma), abnormal LFTs, acidosis, hypoglycaemia, elevated creatinine, loin pain, haematuria, proteinuria and clotting abnormalities.

## GENERAL NOTES

If the patient is pregnant then the toxic dose should be calculated using the patient's pre-pregnancy weight and the anti-dote dose calculated using the patient's actual pregnant weight

In any patient weighing more than 110 kg the toxic dose in mg/kg should be calculated using a maximum of 110 kg, rather than the patient's actual weight. Similarly the antidote dose in an adult weighing more than 110 kg the anti-dote dose should be based on a maximum weight of 110 kg.

In patients with a history of repeated reactions to acetylcysteine, prophylactic treatment with chloramphenamine 10mg IV and ranitidine 50mg IV should be given.

This guideline is to be used within conjunction with Toxbase. User name and password can be obtained from Emergency Department.

## ASSESSMENT AND TREATMENT OF A SINGLE PARACETAMOL OVERDOSE

### PRESENTATION WITHIN 1 HOUR FROM INGESTION

If more than 75 mg/kg of paracetamol has been taken then administer activated charcoal PO or via NG tube. The dose is 50g for adults or 1g/kg in body weight in children.

### PRESENTATION 1-4 HOURS FROM INGESTION

Wait for 4 hours from ingestion from elapsed (see below)

### PRESENTATION 4-8 HOURS FROM INGESTION

Take a venous blood sample for measurement of:

- Paracetamol levels
- U&Es
- Creatinine
- LFTs
- INR
- FBC
- Glucose
- Blood gas for pH and Bicarbonate

NB: If the results are not available before 8 hours and the patient has taken more than 75 mg/kg then start treatment with IV acetylcysteine until the results are available

Once results available:

- Assess the risk of liver damage from the plasma concentration/time from ingestion graph (see appendix one)
- If the patient is not at risk i.e. below the treatment line then no anti-dote is required.
- If the patient is at risk i.e. above the treatment line or just below the treatment line then start IV acetylcysteine and continue treatment for 21 hours (see appendix two).

### ON-GOING TREATMENT

At 21 hours following the start of the course of IV acetylcysteine re-check

- U&Es
- Creatinine
- LFTs
- INR
- FBC
- Blood gas for pH and Bicarbonate

Continue the IV acetylcysteine if

- The transaminase has more than doubled since the admission measurement

OR

- The transaminase is more than three times the upper limit of normal

OR

- The INR is greater than 1.3

The IV acetylcysteine is continued at the dose and infusion rate as the 3$^{rd}$ treatment bag.

Repeat all blood tests in a further 8 hours.

An isolated smaller (less than x2) rise in transaminase in the presence of an INR of 1.3 or less does not require further treatment. The patient can be discharged with advice to return to hospital if

vomiting or abdominal pain occurs. If the blood tests are normal, the patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

**IN THOSE WITH LIVER TOXICITY RECEIVING ON-GOING TREATMENT WITH IV ACETYLCYSTEINE:**

The acetylcysteine should continue until:
- The INR is 1.3 or less

OR
- The INR is falling towards normal on two consecutive blood tests and less than 3

## PRESENTATION 8-24 HOURS FOLLOWING A SINGLE PARACETAMOL OVERDOSE

1. Give IV acetylcysteine immediately to all patients

2. Take venous blood for
   - Plasma paracetamol levels
   - U&Es
   - Creatinine
   - LFTs
   - INR
   - FBC
   - Blood gas for pH and bicarbonate

3. Assess the risk of liver damage from the plasma paracetamol/time from ingestion graph (see appendix one).

4. If the risk of liver damage is confirmed then continue the administration of antidote

**ON-GOING TREATMENT**

At 21 hours following the start of the course of IV acetylcysteine re-check
- U&Es
- Creatinine
- LFTs
- INR
- FBC
- Blood gas for pH and Bicarbonate

Continue the IV acetylcysteine if
- The transaminase has more than doubled since the admission measurement

OR
- The transaminase is more than three times the upper limit of normal

OR
- The INR is greater than 1.3

The IV acetylcysteine is continued at the dose and infusion rate as the 3rd treatment bag.

Repeat all blood tests in a further 8 hours.

An isolated smaller (less than x2) rise in transaminase in the presence of an INR of 1.3 or less does not require further treatment. The patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

If the blood tests are normal, the patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

**IN THOSE WITH LIVER TOXICITY RECEIVING ON-GOING TREATMENT WITH IV ACETYLCYSTEINE:**

The acetylcysteine should continue until:
- The INR is 1.3 or less

OR
- The INR is falling towards normal on two consecutive blood tests and less than 3

## PRESENTATION 24-36 HOURS POST A SINGLE PARACETAMOL OVERDOSE

1. Give IV acetylcysteine immediately to all patients

2. Take venous blood for
   - Plasma paracetamol levels
   - U&Es
   - Creatinine
   - LFTs
   - INR
   - FBC
   - Glucose
   - Blood gas for pH and bicarbonate

3. The plasma concentration more than 24 hours after overdose is likely to be below the limit of detection, even after a substantial overdose.

4. Blood tests should be monitored every 8 hours to assess progression of liver injury.

5. Acetylcysteine may be discontinued if the patient is not considered to be at risk of liver injury i.e. the paracetamol level is not detectable, the INR, creatinine and transaminase are normal and the patient is asymptomatic.

**ON-GOING TREATMENT**

At 21 hours following the start of the course of IV acetylcysteine re-check
- U&Es
- Creatinine
- LFTs
- INR
- FBC
- Blood gas for pH and Bicarbonate

Continue the IV acetylcysteine if
- The transaminase has more than doubled since the admission measurement

OR
- The transaminase is more than three times the upper limit of normal

OR
- The INR is greater than 1.3

The IV acetylcysteine is continued at the dose and infusion rate as the 3rd treatment bag.

Repeat all blood tests in a further 8 hours.

An isolated smaller (less than x2) rise in transaminase in the presence of an INR of 1.3 or less does not require further treatment. The patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

If the blood tests are normal, the patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

**IN THOSE WITH LIVER TOXICITY RECEIVING ON-GOING TREATMENT WITH IV ACETYLCYSTEINE:**

The acetylcysteine should continue until:

- The INR is 1.3 or less

OR

- The INR is falling towards normal on two consecutive blood tests and less than 3

## PRESENTATION MORE THAN 36 HOURS FOLLOWING A SINGLE PARACETAMOL OVERDOSE

1. Wait for results before commencing treatment UNLESS the patient is clearly jaundiced or has hepatic tenderness.

2. Take venous blood for
   - Paracetamol concentration
   - Clotting
   - FBC
   - Transaminase
   - Creatinine
   - Blood gas for pH and bicarbonate
   - Blood glucose

3. Paracetamol concentration more than 36 hours following an overdose is likely to below the limit of detection, even after a substantial dose. A full course of IV acetylcysteine should be given if paracetamol is detectable.

4. If the INR is greater than 1.3 and the transaminase is elevated e.g. ALT is 3 x above the upper limit then treat with acetylcysteine

5. If the INR is less than or equal to 1.3 but the transaminase is elevated e.g. ALT is 3 x above the upper limit then treat with acetylcysteine and repeat bloods at 8 hours. Acetylcysteine may be discontinued if the INR remains normal and the ALT has not substantially increased. Otherwise continue acetylcysteine and check bloods every 8 hours.

6. If the INR is greater than 1.3 and the transaminase is normal look for other causes of a raised INR.

7. If there is evidence of hepatic dysfunction at presentation below the levels above then the blood tests should be repeated at 12 hours following presentation.

**ON-GOING TREATMENT**

At 21 hours following the start of the course of IV acetylcysteine re-check

- U&Es
- Creatinine
- LFTs
- INR
- FBC
- Blood gas for pH and Bicarbonate

Continue the IV acetylcysteine if

- The transaminase has more than doubled since the admission measurement

OR
- The transaminase is more than three times the upper limit of normal

OR
- The INR is greater than 1.3

The IV acetylcysteine is continued at the dose and infusion rate as the 3rd treatment bag.

Repeat all blood tests in a further 8 hours.

An isolated smaller (less than x2) rise in transaminase in the presence of an INR of 1.3 or less does not require further treatment. The patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

If the blood tests are normal, the patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

**IN THOSE WITH LIVER TOXICITY RECEIVING ON-GOING TREATMENT WITH IV ACETYLCYSTEINE:**

The acetylcysteine should continue until:
- The INR is 1.3 or less

OR
- The INR is falling towards normal on two consecutive blood tests and less than 3

Assessment and Treatment of a staggered overdose or uncertain timing of ingestion

## STAGGERED OVERDOSE (DOSES TAKEN OVER MORE THAN ONE HOUR) OR UNCERTAIN TIMING OF INGESTION

1. For patients who have taken a staggered overdose or where there is doubt over the timing of the overdose then IV acetylcysteine must be given.

2. Take venous blood for
   - Paracetamol concentration
   - Clotting
   - FBC
   - Transaminase
   - Creatinine
   - Blood gas for pH and bicarbonate
   - Blood glucose

3. Acetylcysteine may be discontinued if ALL the following factors are reached
   - It is longer than 24 hours since paracetamol ingestion
   - The paracetamol level is not detectable
   - INR is normal
   - Creatinine is normal
   - Transaminases are normal
   - Patient is asymptomatic

**ON-GOING TREATMENT**

At 21 hours following the start of the course of IV acetylcysteine re-check
- U&Es
- Creatinine
- LFTs

- INR
- FBC
- Blood gas for pH and Bicarbonate

Continue the IV acetylcysteine if
- The transaminase has more than doubled since the admission measurement

OR
- The transaminase is more than three times the upper limit of normal

OR
- The INR is greater than 1.3

The IV acetylcysteine is continued at the dose and infusion rate as the 3rd treatment bag.

Repeat all blood tests in a further 8 hours.

An isolated smaller (less than x2) rise in transaminase in the presence of an INR of 1.3 or less does not require further treatment. The patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

If the blood tests are normal, the patient can be discharged with advice to return to hospital if vomiting or abdominal pain occurs.

**IN THOSE WITH LIVER TOXICITY RECEIVING ON-GOING TREATMENT WITH IV ACETYLCYSTEINE:**

The acetylcysteine should continue until:
- The INR is 1.3 or less

OR
- The INR is falling towards normal on two consecutive blood tests and less than 3

## REACTIONS TO ACETYLCYSTEINE

Intravenous acetylcysteine can cause an anaphylactoid reaction or local effects. Death has followed ten times the therapeutic dose. Toxicity would not be expected to arise from the use of eye drops.

It is reported that adverse effects with acetylcysteine are more likely in women, in patients with a family history of allergies and asthmatics.

Use of acetylcysteine before plasma paracetamol concentrations are known should be avoided unless more than 8 hours has elapsed since overdose. This is particularly important in patients with severe or brittle asthma, who should be monitored particularly carefully during acetylcysteine therapy, especially over the first few hours.

**FEATURES**

Anaphylactoid reactions to intravenous acetylcysteine occur in up to 20% of patients, usually during or soon after the first infusion, when large amounts are given rapidly. They are more likely in patients with lower paracetamol concentrations.

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 disseminated intravascular coagulation.

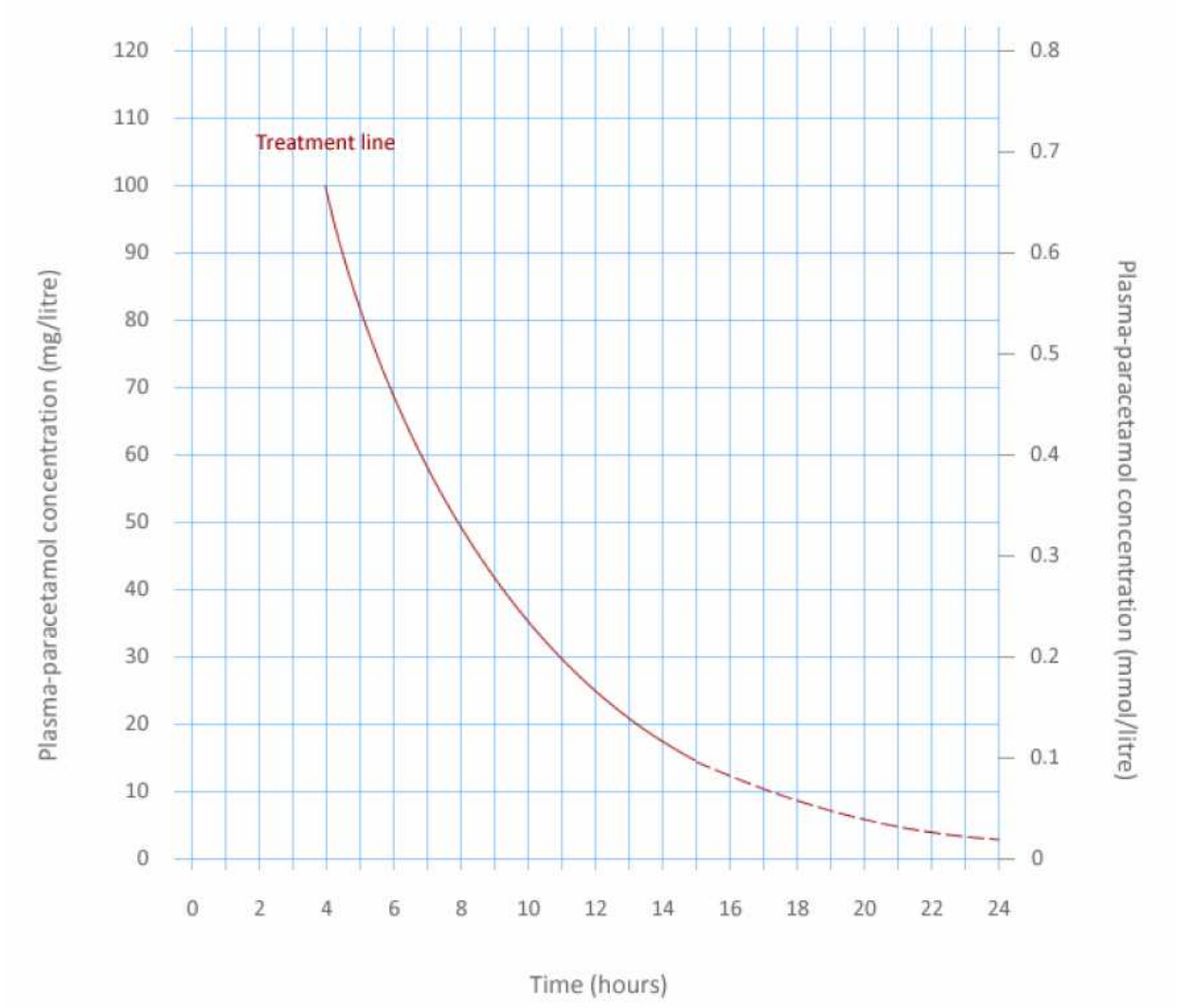
Severe adverse reactions to acetylcysteine should be reported to the MHRA via the yellow card scheme.

**MANAGEMENT**

1. Stop the infusion
2. Give 10mg chlorphenamine IV
3. Give 5mg of nebulised salbutamol if significant bronchospasm
4. In patients with a history of repeated reactions to acetylcysteine, prophylactic treatment with chloramphenamine 10mg IV and ranitidine 50mg IV should be given.
5. For adverse reactions developing during the first or second bag of the infusion regimen, it is essential that the acetylcysteine infusion should be started again once the reaction has settled. This should be at an infusion rate of 50 mg/kg over 4 hours, followed by the final 16 hour infusion (100 mg/kg over 16 hours). Further reactions are almost unknown.

## APPENDIX 1

### PLASMA PARACETAMOL/TIME FROM INGESTION GRAPH



# APPENDIX 2

## DOSING TABLES

### ACETYLCYSTEINE 200mg/mL INJECTION FOR INFUSION
### ADMINISTRATION INFORMATION FOR THE HEALTHCARE PROFESSIONAL

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 with acetylcysteine 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.

#### Adults

- Weigh the patient to determine the correct weight band.
- Use the adult dosage table to determine the appropriate volume of acetylcysteine (ampoule volume) to be added to the infusion fluid for each of the 3 infusion periods.

First infusion
Add the appropriate volume of acetylcysteine injection to 200 mL of infusion fluid and infuse over **1 hour**.

Second infusion
Add the appropriate volume of acetylcysteine injection to 500 mL of infusion fluid and infuse over the next **4 hours**.

Third infusion
Add the appropriate volume of acetylcysteine injection to 1 litre of infusion fluid and infuse over the next **16 hours**.

#### 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

## Children

Children are treated with the same doses and regimen as adults. However, the quantity of intravenous fluid used has been modified to take into account age and weight, as fluid overload is a potential danger. Doses should be administered sequentially using an appropriate infusion pump.

Preparation and administration of paediatric infusions

- Weigh the child to determine the correct weight band.
- Read off the table the total infusion volume required for each dose according to the weight of the child and make up the solutions according to the directions below.

First Infusion

- Prepare a 50 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 30 mL glucose 5% or sodium chloride 0.9% to give a total volume of 40 mL.
- **Prepare the appropriate volume for the weight of the child.**
- The dose is infused over **1 hour** at the infusion rate stated in the table.

Second Infusion

- Prepare a 6.25 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 310 mL glucose 5% or sodium chloride 0.9% to give a total volume of 320 mL.
- **Prepare the appropriate volume for the weight of the child.**
- The dose is infused over **4 hours** at the infusion rate stated in the table.

Third Infusion

- Prepare a 6.25 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 310 mL glucose 5% or sodium chloride 0.9% to give a total volume of 320 mL.
- **Prepare the appropriate volume for the weight of the child.**
- The dose is infused over **16 hours** at the infusion rate stated in the table.

*For example for a child weighing 12 kg, the first infusion would be 38 mL infused at 38 mL/h over 1 hour, the second infusion would be 100 mL infused at 25 mL/h over 4 hours and the third infusion is 208 mL infused at 13 mL/h over 16 hours.*

## Paediatric Dosage Table

| Paediatric acetylcysteine prescription (each ampoule = 200mg/mL acetylcysteine) | | | | | Please circle appropriate weight and volume. | |
|---|---|---|---|---|---|---|
| Regimen | First Infusion | | Second Infusion | | Third Infusion | |
| Infusion | 50mg/mL for 1 hour | | 6.25mg/mL for 4 hours | | 6.25mg/mL for 16 hours | |
| Infusion rate | 3mL/kg/h | | 2mL/kg/h | | 1mL/kg/h | |
| Patient Weight[1] | Total Infusion Volume | Infusion Rate | Total Infusion Volume | Infusion Rate | Total Infusion Volume | Infusion Rate |
| kg | mL | mL/h | mL | mL/h | mL | mL/h |
| 1 | 3 | 3 | 8 | 2 | 16 | 1 |
| 2 | 6 | 6 | 16 | 4 | 32 | 2 |
| 3 | 9 | 9 | 24 | 6 | 48 | 3 |
| 4 | 12 | 12 | 32 | 8 | 64 | 4 |
| 5 | 15 | 15 | 40 | 10 | 80 | 5 |
| 6 | 18 | 18 | 48 | 12 | 96 | 6 |
| 7 | 21 | 21 | 56 | 14 | 112 | 7 |
| 8 | 24 | 24 | 64 | 16 | 128 | 8 |
| 9 | 27 | 27 | 72 | 18 | 144 | 9 |
| 10-14 | 38 | 38 | 100 | 25 | 208 | 13 |
| 15-19 | 53 | 53 | 140 | 35 | 288 | 18 |
| 20-24 | 68 | 68 | 180 | 45 | 368 | 23 |
| 25-29 | 83 | 83 | 220 | 55 | 448 | 28 |
| 30-34 | 98 | 98 | 260 | 65 | 528 | 33 |
| 35-39 | 113 | 113 | 300 | 75 | 608 | 38 |

[1] Dose calculations are based on the weight in the middle of each band. If the patient weighs more than 40kg use the adult dosage table.
Figures have been rounded up to the nearest whole number

## APPENDIX 3

**REFERRAL CRITERIA TO A LIVER UNIT**

- pH <7.3
- PT >100 seconds
- INR >6.7
- Creatinine > 300 micromol/L in patients with grade 3 or 4 hepatic encephalopathy

## APPENDIX 4

### PARACETAMOL OVERDOSE IN PREGNANCY

Please report ALL cases of drug and/or chemical exposure in pregnancy to UKTIS by telephoning the service on 0844 892 0909 or by printing and completing a pregnancy reporting form, providing as many patient identifiers as possible to enable follow up of pregnancy outcome. This vital information enables UKTIS to provide evidence based advice for future enquiries and to conduct surveillance of potential and known teratogens.

**For case specific advice please contact UKTIS on 0844 892 0909.**

SUMMARY: There are limited published data on fetal outcome following paracetamol overdose during human pregnancy, however the information available does not suggest an increased risk of congenital malformations or fetal loss in the absence of severe maternal toxicity. There is evidence that the fetal liver begins to metabolise paracetamol from 18 weeks gestation onwards, therefore the fetus may also be at risk for hepatotoxicity following maternal paracetamol overdose.

Maternal treatment of paracetamol overdose should be as for the non-pregnant patient. There is evidence linking a delay in treating a pregnant patient with N-acetylcysteine with increased fetotoxic effects. Treatment with N-acetylcysteine should not be withheld on the basis of pregnancy. Pregnancy does not make a patient 'high risk' under the N-acetylcysteine treatment nomogram. Where treatment with N-acetylcysteine is clinically indicated, current weight up to a maximum of 110kg should be used to calculate dosing.

Maternal toxicity as a result of paracetamol overdose is likely to be a major determinant of the risk posed to a developing fetus. However, due to limitations in the available data, it is not currently possible to state that an absence of maternal toxicity excludes the possibility of adverse pregnancy outcomes.

In general, maternal paracetamol overdose would not usually be regarded as medical grounds for termination of pregnancy or any additional diagnostic tests. However, other risk factors may be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case specific risk assessments.

NOTE: This monograph refers only to paracetamol overdose in pregnancy. For therapeutic use of paracetamol in pregnancy, please refer to the 'USE OF PARACETAMOL IN PREGNANCY MONOGRAPH'.

This document is regularly reviewed and updated. Only use UKTIS monographs downloaded directly from TOXBASE.org or UKTIS.org, to be sure you are using the most up to date version.

Please report ALL cases of drug and/or chemical exposure in pregnancy to UKTIS by telephoning the service on 0844 892 0909 or by printing and completing a pregnancy reporting form, providing as many patient identifiers as possible to enable follow up of pregnancy outcome. This vital information enables UKTIS to provide evidence based advice for future enquiries and to conduct surveillance of potential and known teratogens.

For case specific advice please contact UKTIS on 0844 892 0909.

Paracetamol (acetaminophen) is an analgesic that appears to work by inhibiting prostaglandin synthesis in the central nervous system. It is often included with other preparations in over-the-counter medications and its use may be a marker for inflammatory or infectious disorders which may have independent effects on pregnancy outcome.[1] The recommended dose of oral paracetamol is 500-1000mg up to four times a day, with a maximum dose of 4g within a 24 hour period.[2]

There are no published guidelines concerning the management of paracetamol poisoning during pregnancy. Maternal toxicity as a result of acute exposure in pregnancy is likely to be a major

determinant of the risk posed to the developing fetus. It is therefore important to treat the mother appropriately to reduce the risk of maternal, and as a consequence fetal, toxicity. Pregnant women should be managed as for the non-pregnant patient. Treatment with the antidote N-acetylcysteine (NAC) should not be withheld on account of pregnancy. For current advice on management, readers are advised to consult TOXBASE or contact UKTIS. Because of the potentially severe consequences of under treatment, it may be advisable to use the patient's current weight (not pre-pregnancy weight) up to a maximum of 110kg when calculating NAC dosage.

Paracetamol is oxidised to an active metabolite that in high concentrations is hepatotoxic, but in low concentrations can be detoxified by conjugation with glutathione. The ability of the fetus to oxidise paracetamol begins at approximately 18 weeks, although oxidation by the fetal liver is approximately 10 times slower than by the adult liver.[3] The main pathway of paracetamol metabolism in the fetus is by sulphation[4] and the mixed function oxidase system appears to be active with glutathione available to conjugate the metabolites produced.[4,5]. Therefore, if fetal circulation becomes saturated with paracetamol as a result of maternal overdose, the developing fetal metabolism may produce sufficient toxic intermediary to cause hepatic injury in the neonate.[3, 6]

**Preclinical (animal) data**
There are reports of increased maternal hepatotoxicity in pregnant mice exposed to 300-400 mg/kg paracetamol when compared to non-pregnant mice.[7] The increased maternal toxicity could lead to adverse fetal effects and other studies have reported fetotoxic but not teratogenic effects at high doses (350 mg/kg).[8]

**Human data**
Often, data from observational sources or case reports, including data collected by UKTIS, may be confounded by maternal co-ingestion of a number of drugs, at varying doses, and for a range of indications. The severity of the underlying maternal condition, where relevant, is frequently unknown and information on other potential confounding variables may be incomplete. These factors should be considered when interpreting observational human pregnancy data.

***Studies***
An abstract of a prospective study of 604 pregnant women who had overdosed on paracetamol found no increased risk of congenital malformation (4.6%, 95%CI 2.9 to 7.1%) when compared to the expected background rate of 2-3%.[9] Twenty one infants were reported with malformations including five exposed in the first trimester. No pattern of malformation was observed. Malformations reported were forelimb phocomelia, talipes, diaphragmatic hernia, hypospadias and microphthalmus. No increase in spontaneous abortion (9.1%, 95%CI 6.5-12.7%) or late fetal death (1.7%, 95%CI 0.07-3.8%) were reported, and no causal relationship was identified between adverse fetal outcome and maternal plasma paracetamol concentration or treatment.[9] This study includes data on 300 pregnancy outcomes previously reported in McElhatton *et al* 1996.10© UKTIS 2012 [3]

Danish registry data reports 55 women who had taken a drug overdose (paracetamol n=4) during pregnancy and 67 women who had overdosed (paracetamol n=9) in the three months before conception. Across both cohorts of drug-exposed pregnancies, an increase in spontaneous abortion was noted when compared to the theoretical background risk of 10%, but no increase in malformations or neonatal problems were detected in live-born infants.[11]

A study of pregnancy outcomes following paracetamol overdose in 60 women found no increased risk of congenital malformation. One infant was born with talipes following exposure to paracetamol overdose in the third trimester, and no malformations were detected in electively terminated fetuses (n=9). A possible association was found between paracetamol overdose in the first trimester and increased risk of spontaneous abortion (p=0.014), however this should be interpreted with caution as the number of women exposed in the first trimester (n=19) was small.[12]

***Case reports***
Numerous case reports are available describing the outcome of paracetamol overdose during pregnancy.[4, 5, 13-17] Outcomes reported include intrauterine death in one case of third trimester exposure, emergency premature delivery and initial recovery and discharge from hospital followed by neonatal

death in two cases (one first trimester exposure, one third trimester exposure), occipital cephalohematoma and jaundice in one case of second trimester exposure, mild jaundice in two cases (one second trimester exposure, one third trimester exposure), and initial hypoglycaemia, respiratory illness and mild jaundice in one case of third trimester exposure.

***N-Acetylcysteine (NAC)***
NAC is the N-acetyl derivative of the amino acid L-cysteine and is used in the treatment of paracetamol poisoning. The benefit of maternal N-acetylcysteine treatment to the fetus is twofold: prevention of maternal toxicity prevents adverse effects on the fetus; and as NAC crosses the placenta it may detoxify the toxic metabolite N-acetyl-p-benzoquinoneimine formed by the fetal liver.

A study of pregnancy outcomes following paracetamol overdose in 60 women found an association between time of administration of the loading dose of NAC to the mother and spontaneous abortion or fetal death (p=0.002).[12] No association was found between the incidence of spontaneous abortion or fetal death and paracetamol levels above or below the nomogram for NAC treatment,[12] suggesting that delay in treatment with NAC, where clinically indicated, is associated with adverse pregnancy outcomes.
A case series of four infants born while their mothers were receiving N-acetylcysteine treatment for paracetamol overdose reported blood concentrations within the range associated with therapeutic doses of N-acetylcysteine typically administered to adults. One infant delivered at 22 weeks gestational age died 3 hours after birth. No adverse sequelae developed in the other three infants and all mothers recovered. None of the four infants had evidence of paracetamol-related toxicity.[18]

A case report of a first trimester pregnant patient receiving 20-hour IV NAC, after early presentation with paracetamol overdose, described no evidence of hepatotoxicity, fetal malformation, preterm delivery, or subsequent neonatal complications.[19]

A case report of a pregnant patient receiving NAC at 36 weeks gestation (loading dose 140 mg/kg, maintenance doses 70 mg/kg every 4 hr for 17 hr) for paracetamol overdose © UKTIS 2012 [4] resulted in discharge from hospital after three days followed by natural delivery six weeks later of a normal infant with no reported complications.[20]

Delay in NAC treatment has been reported to result in both infant and maternal death. A case report of late presentation (more than 26 hours) after paracetamol overdose (35g) at 31 weeks gestation resulted in emergency caesarean due to acute fetal distress. Maternal acidosis was noted along with hepatorenal failure 16 hours after admission. The infant required resuscitation at birth and died 34 hours after delivery. The mother died 40 hours after admission.[21] No autopsy was conducted.

**Paternal exposure**
There were no reports found regarding neonatal outcome following paternal paracetamol overdose.

**Lactation**
There were no reports found regarding neonatal toxicity following exposure to paracetamol overdose during lactation.

**Manufacturers data**
The manufacturers of paracetamol in the UK were contacted but provided no unpublished outcome data.

**UKTIS Data**
UKTIS data has been published by Lawler and McElhatton 2004.[9]

**Conclusions**
Paracetamol overdose can result in severe maternal hepatotoxicity and consequently adverse fetal effects. Fetal hepatotoxicity may also be possible. There is no evidence of increased risk of congenital malformations following maternal paracetamol overdose. Treatment with the antidote N-Acetylcysteine should be as for the non-pregnant patient if clinically indicated. Pregnancy alone does not make a patient ‘high risk’ under the N-acetylcysteine treatment nomogram. It may be advisable to use the patient’s current weight (not pre-pregnancy weight) up to a maximum of 110kg.

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## PARACETAMOL OVERDOSE – Read this before you leave hospital

You were seen today because you may have taken too much paracetamol.

Taking too much paracetamol can be particularly dangerous because it may cause damage to your liver.

## BEFORE YOU LEAVE HOSPITAL

**Please think again - is there anything you didn't tell us?**

If you have forgotten to tell us any of the information below, you may be at a greater risk of developing liver damage:

- Are you certain when you took the tablets?
- How many did you take?
- Did you take the tablets all at once?

If you have forgotten to tell us any of this information, **you MUST return to A&E at once**. Bring this leaflet with you.

We have assessed you and decided that you are not necessarily at risk of damage to your liver. However:

## Come back at once

**If you suffer from any of the following**:

- Stomach pains, nausea or vomiting
- Your skin or the whites of your eyes turn yellow
- You have not passed urine during the last 8 hours
- Have a severe headache, become confused or get very drowsy

Any of these conditions may mean that your liver has been damaged. **You must return to A&E at once.** Because paracetamol poisoning develops over a number of days if you begin to feel at all unwell you **must return to A&E**. Bring this leaflet with you.

If you have any questions or need further medical help call this number:

## PRH: 01952 641222

## RSH: 01743 261000