East Kent Hospitals University NHS Foundation Trust

East Kent Hospitals University NHS Foundation Trust

Approved Clinical Guideline

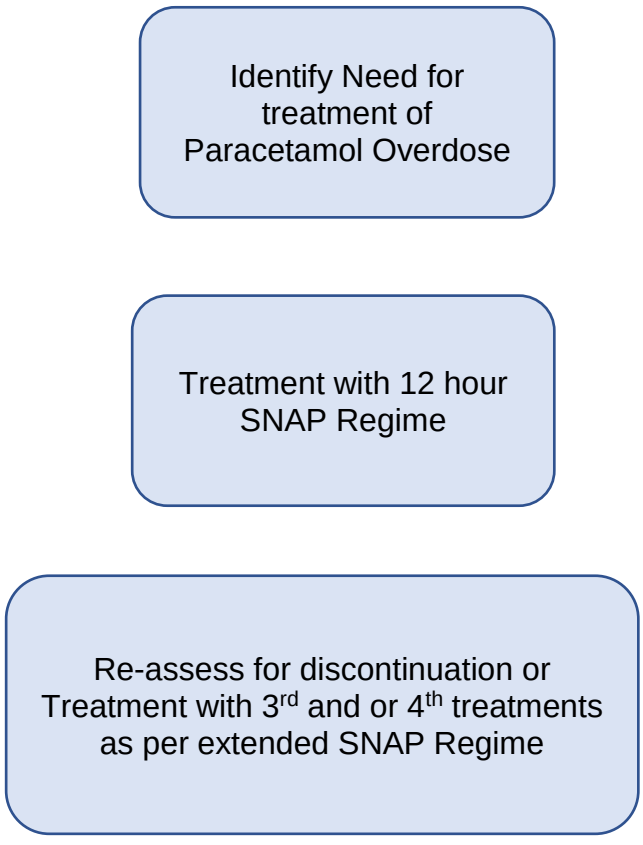
Title: SNAP Protocol: Clinical guideline for SNAP acetylcysteine regime in Paracetamol overdose WHH and QEQM

Date of publication: June 2024

Key words: SNAP, acetylcysteine, Paracetamol overdose

Target user Group: Emergency Department & Acute medical Clinical & nursing staff

Over view of process:



Guideline Development, Authorisation & Implementation

Version:	V1.7
Ratified by:	UEAM Triumvirates'
Date ratified:	October 2023
Name of originator/author:	Alison Brown Emergency care Nurse Consultant
Clinical lead	Dr D. Sharma Emergency Medicine Consultant
Director responsible for implementation:	Dr Tanwar UEAM clinical Director
Date issued:	20/06/2024
Review date:	April 2026

Contents

Note to Author: In the interest of quality and consistency, please do not make changes to the order of sections, contents of tables, or font.

1. Introduction, Background and Purpose

1.1. Paracetamol overdose is a common cause for emergency hospital admission and is the most common cause for acute liver failure in the UK. Annually in the UK, paracetamol overdose results in approximately 100,000 Emergency Department presentations and 50,000 acute hospital admissions and is the direct cause of death in around 150 people. Deaths or episodes of acute liver failure in patients who start treatment within 8 hours (h) of a single acute overdose are extremely rare because of the ease of availability of a highly effective antidote, acetylcysteine (NAC). This antidote replenishes cellular glutathione, which protects hepatocytes against injury from the toxic paracetamol metabolite N-acetyl-p-benzoquinone imine (NAPQI). Since 2012, revised guidelines for the NAC treatment of paracetamol poisoning have been implemented in the UK. The standard regimen for NAC treatment is 21-hours. The Scottish and Newcastle Acetylcysteine Protocol (SNAP) protocol is a shorter, 12-hour NAC regimen. The SNAP regimen has been shown to be as effective as the standard 21-hour regimen in preventing liver injury in paracetamol overdose and is associated with fewer adverse reactions. The SNAP protocol benefits patients with reduced side-effects, reduced treatment interruptions and reduced length of stay, and benefits the hospital with reduced length of stay for patients requiring treatment for paracetamol overdose.

1.2. The SNAP protocol follows the previous MHRA guidance on initiation of treatment from 4 hours post-ingestion. It is currently unlicensed by the MRHA but is being used in emergency departments and hospitals across the UK as evidence has shown it is a safe and effective alternative to the licenced 21-hour regimen. It is a clinical guideline in TOXBASE. The regimen is endorsed by National Poisons Information Service (NPIS) and The Royal College of Emergency Medicine (RCEM).

1.3. This guideline outlines the procedure for the safe and effective treatment for patients following paracetamol overdose at EKHUFT Emergency Departments, based on the SNAP protocol. TOXBASE should continue to be used as a clinical decision support resource in conjunction with the National Poisons Information Service (NPIS, 0344 892 0111)

2. Definitions

2.1. **Paracetamol overdose:** This refers to excessive ingestion of paracetamol over a period longer than one hour, usually in the context of self-harm.

2.2. **Paracetamol poisoning:** is also known as acetaminophen poisoning, is caused by excessive use of the medication paracetamol (acetaminophen).

2.3. **Acute Liver failure:** Acute liver failure is loss of liver function that occurs quickly — in days or weeks

3. Scope

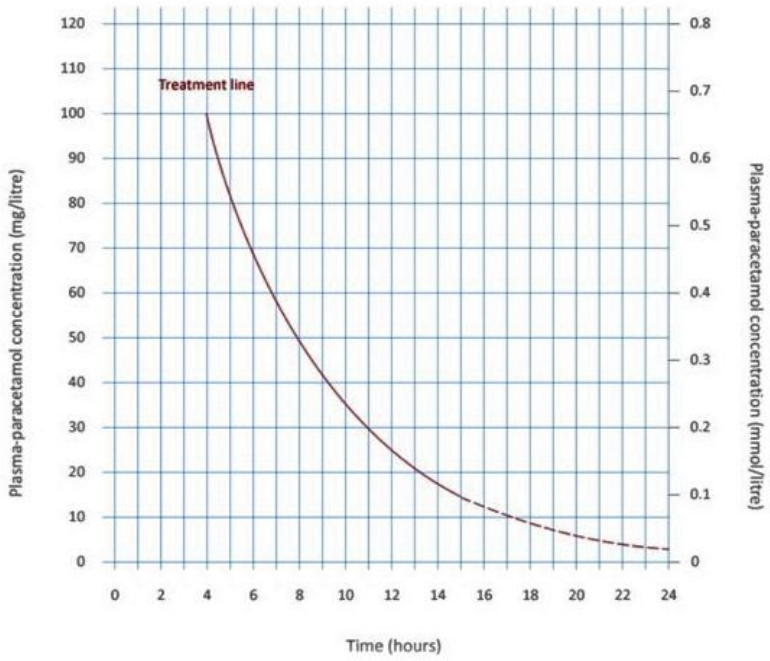
3.1. The policy applies to Emergency Department and Medical assessment/Acute medical unit staff.

3.2. Implementation of this policy will ensure that the SNAP protocol for NAC is safely and efficiently prescribed and administered, followed by ongoing administration in ED and if required, their ongoing phase of care.

3.3. This guidance is based on TOXBASE SNAP 12 hour regimen information. For further information please refer to TOXBASE https://www.toxbase.org/

3.4. This guideline is for all patients, adult and paediatrics, presenting to EKHUFT following paracetamol overdose who have concentration above a single treatment line on the paracetamol nomogram (the 100mg/L at 4 hr overdose treatment line). And treating all patients that have taken a staggered overdose, should have treatment started prior to Paracetamol level laboratory results.

WARNING: PLEASE CHECK THE UNITS CAREFULLY AND USE THE CORRECT SCALE



3.5. **It will be the responsibility of the treating clinician to assess the need for commencement of Acetylcysteine (NAC) treatment based on the TOXBASE guidelines for paracetamol overdose.**

3.6. The SNAP regime can be used in all types & duration of paracetamol overdose as per TOXBASE guidelines

3.7. For patients with very high level of ingestion and / or significantly deranged liver function, please refer to TOXBASE and consider early referral to specialist centres.

3.8. Please refer to TOXBASE for information on patients that have taken therapeutic overdoses.

4. Contraindications

4.1. Previous Anaphylaxis is no longer considered an absolute contraindication, TOXBASE must be consulted, and seek expert advice from NPIS

5. Special circumstances

5.1. For patients on renal replacement therapy the dose of acetylcysteine should be doubled. Discuss these patients with NPIS

5.2. Calculating paracetamol toxic doses and acetylcysteine doses in obesity, and pregnancy: SEE APPENDIX D

6. Procedure: SNAP Prescription and Administration for Adults & Children OVER 40kg (300mg/kg over 12 hours, as two separate prescriptions; table in Appendix A)

6.1. Prescription 1/ Bag 1:

100mg / kg NAC in 200ml 5% Glucose / 0.9% Saline over 2 hours

Preparation: Add the appropriate volume of acetylcysteine (100 mg/kg body weight, maximum 11 g) to 200 mL 5% glucose or 0.9% sodium chloride, infused **over 2 hours.**

Note that the 200 mL bags of 5% glucose or sodium chloride 0.9% required for the first infusion are not currently commercially available. For this infusion, the excess amount of fluid should be removed from a larger bag using a syringe and discarded, before adding the acetylcysteine, e.g. by removing and discarding 50 mL from a 250 mL infusion bag.

6.2. Prescription 2 / Bag 2: (or 3 & 4)

200mg / kg NAC in 1000ml 5% Glucose / 0.9% Saline over 10 hours

Preparation Add the appropriate volume of acetylcysteine (200 mg/kg body weight, maximum 22 g) to 1000 mL 5% glucose or 0.9% sodium chloride and infuse over the **next 10 hours.**

7. Procedure: SNAP Prescription and Administration for Children (and adults) UNDER 40kg (300mg/kg over 12 hours, as two separate prescriptions; table in APPENDIX B)

7.1. Prescription 1/ Bag 1:

100mg / kg NAC in 2ml/kg 0.9% Saline or 5% Glucose over 2 hours (gives concentration 50mg/ml)

Preparation: 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 stock solution.

Prepare the appropriate volume for the weight of the child. *(For example; 2 x 10 mL acetylcysteine plus 60 mL diluent = 80 mL stock solution. 54 mL stock solution required for a 25 kg child. See table for infusion volumes and rates)*. The dose is infused **over 2 hours** at the infusion rate stated in the table.

7.2. Prescription 2/ Bag 2 (or 3 & 4 If needs Extended Regime):

200mg / kg NAC in 20mg/kg 0.9% Saline or 5% Glucose over 10 hours (gives concentration 10mg/ml)

Preparation: Prepare a 10 mg/mL solution by diluting each 10 mL ampoule of acetylcysteine (200 mg/mL) with 190 mL glucose 5% or sodium chloride 0.9% to give a total volume of 200 mL stock solution.

Prepare the appropriate volume for the weight of the child. *(For example; 3 x 10 mL acetylcysteine plus 570 mL diluent = 600 mL stock solution. 540 mL stock solution required for a 25 kg child. See table for infusion volumes and rates).* The dose is infused **over 10 hours** at the infusion rate stated in the table.

8. Guidance for the end of the modified 12-hour IV acetylcysteine regimen (SNAP)

8.1. **Staggered overdose:** decision for discontinuation of NAC: Clinically significant hepatotoxicity is unlikely if at least 4 hours or more after the most recent paracetamol ingestion:

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

Acetylcysteine can be discontinued in patients not considered to be at risk of clinically significant liver damage. They can be considered for discharge.

8.2. **In all non-staggered overdose:** Obtain Bloods for Paracetamol levels, INR, U&E's, & LFT's at 10 hours from starting treatment. (This should be 2 hours from the end of the 2nd bag).

Acetylcysteine (NAC) **should be discontinued if all** of the following criteria are met:

- the paracetamol concentration is less than 10 mg/L, **AND**
- the ALT is within the normal range, and not doubled from Admission ALT (within the normal range) **AND**
- the INR is 1.3 or less*, **AND**
- the patient has no symptoms suggesting liver damage.

8.3. If these are **NOT** met, then Continue at the dose and infusion rate used in the 2nd treatment bag (10-hour). It is not necessary to give a further loading dose unless a second overdose has been taken.

*The decision regarding whether more acetylcysteine is required at end of 12-hours is dependent on the ALT and paracetamol. The INR does not influence this decision at this specific time point. However, in cases of ALT rise then the INR is a necessary marker of severity.

8.4. **For increase in INR, in absence of liver injury (normal ALT) (see Appendix C)**

8.5. 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. Discuss with your local poisons' information service: in the UK NPIS 0344 892 0111, in Ireland NPIC (01) 809 2566.

9. Guidance for an extended infusion (3rd or 4th Bag/prescriptions of Acetylcysteine)

9.1. As per 8.3, Continue subsequent doses if Criteria for continuation is met, by prescribing a **3rd bag at a dose of 200mg/kg over 10 hours**

Obtain bloods, INR, U&E's, & LFT's just before the end of the 3rd bag which should be just before 22 hours into the regime) Paracetamol concentration should only be re-checked at the end of the 22-hour infusion if the paracetamol concentration at the end of the 12-hour infusion was above 10 mg/L.

9.2. Acetylcysteine (NAC) **3rd treatment bag should be discontinued if all** of the following criteria are met:

- the paracetamol concentration is less than 10 mg/L, **AND**
- the ALT is within the normal range, and not doubled from Admission ALT (within the normal range), or increased from last value, or two times the upper limit of normal **AND**
- the INR is 1.3* or less, **AND**
- the patient has no symptoms suggesting liver damage.

If these are **NOT** met, then continue the dose and infusion rate used in the 3rd treatment bag. (section 10) It is not necessary to give a further loading dose unless a second overdose has been taken.

9.3. 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. Discuss with your local poison's information service: in the UK NPIS 0344 892 0111, in Ireland NPIC (01) 809 2566.

9.4. Patients who do not meet the criteria for continuing acetylcysteine and have no symptoms suggestive of liver injury can be considered medically fit for discharge.

10. Guidance for an extended infusion 4th bag (200mg/kg as per 2nd & 3rd bag dosing)

10.1. Obtain bloods, INR, U&E's, & LFT's every 10 hours This allows for assessment of liver toxicity progression, there is no need to take paracetamol levels unless a second overdose has been taken.

Acetylcysteine (NAC) **should be continued 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.

NB: consider other causes of elevated INR e.g. warfarin therapy.

10.2. For those patients receiving a 5th bag or more the dose and infusion rate in the last treatment bag should be used.

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

10.4. Patients who do not meet the criteria for continuing acetylcysteine and have no symptoms suggestive of liver injury can be considered medically fit for discharge.

11. Cautions

11.1. The Warning by TOXBASE of paracetamol concentrations that are checked during acetylcysteine infusion, states that some chemical analysers may significantly underestimate paracetamol concentrations by as much as 40% depending on serum acetylcysteine concentrations. NPIS recommends that clinicians ensure results provided by their lab are not affected in this way.

11.2. EKHUFT have confirmed that the assay used would be unlikely to cause this underestimation in paracetamol result, and there is sufficient clearance of Acetylcysteine. See report in **APPENDIX E.**

12. Adverse reactions

12.1.1. Acetylcysteine is more likely to cause adverse effects if paracetamol concentrations are low or absent. Adverse effects are also more likely in women, in asthmatics, and in patients with a family history of allergy. Visit Toxbase & NPIS for management of patients experiencing an adverse reaction to acetylcysteine.

12.1.2. A previous anaphylactoid reaction to acetylcysteine is **NOT** a contraindication for a further treatment course.

13. Consultation & Approval: Refer to table in section 21 pages 15 & 16.

14. Review & Revision Arrangements

14.1. This clinical guideline will be reviewed as scheduled in three years' time unless legislative or other changes necessitate an earlier review.

14.2. It will be ratified by the Clinical Guideline Authorisation Group every three years, or when there are significant changes and/or changes to underpinning legislation in accordance with the Policy for the Development and Management of Trust Clinical Guidelines.

15. Document Control including Archiving Arrangements

15.1. Document will be held on MICRO GUIDE, My Emergency Department APP, and department PROMT cards.

15.2. Consultation & Approval The clinical guideline was developed in consultation with the hospital supporting team, Children and young People Care Group and UEC Care group.

15.3. This clinical guideline was approved by the UEC Governance board.

15.4. This clinical guideline will be ratified by the Clinical Guideline Authorisation Group.

16. Training

16.1. Training will be undertaken by the ED Medical Clinical staff, Nursing Practice development team across sites for Urgent, Emergency and Acute Medicine (UEAM) care group

17. Monitoring

17.1. Compliance with SNAP protocol.

17.2. Audit to monitor rate of adverse drug reactions, length of stay, rate of liver injury and need for further treatment.

17.3. Staff survey to assess ease of use of SNAP protocol.

18. References & Associated Documents

TOXBASE: Paracetamol

Paracetamol (toxbase.org)

TOXBASE Staggered overdose

Paracetamol - staggered overdose (toxbase.org)

Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning study (SNAP):
https://bmcpharmacoltoxicol.biomedcentral.com/articles/10.1186/2050-6511-14-20

Pettite, J, et al (2019), Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose. *The Lancet*, eClincal medicine Vol 11. Pg 11-17. Open access Via eClinical-Medicine
https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30066-5/fulltext#secst0160

Royal College of Emergency Medicine (RCEM) Position Statement

https://rcem.ac.uk/wp-content/uploads/2021/11/Use_of_SNAP_for_Treatment_of_Paracetamol_Toxicity_Nov_2021.pdf

19. Equality Analysis.

An Equality Analysis not just about addressing discrimination or adverse impact; the guideline should also positively promote equal opportunities, improved access, participation in public life and good relations.

Person completing the Analysis		
Name	Alison Brown	
Job title	Advanced Care Practitioner	
Care Group / Department	UEAM	
Date completed	June 2024	
Who will be impacted by this clinical guideline?	☒ Staff (EKHUFT) ☐ Staff (Other) ☐ Service Users	☐ Carers ☒ Patients ☐ Relatives

Assess the impact of the guideline on people with different protected characteristics. When assessing impact, make it clear who will be impacted within the protected characteristic category. For example, it may have a positive impact on women but a neutral impact on men.		
Protected characteristic	**Characteristic Group**	**Impact of decision** Positive/Neutral/Negative
Example: Sex	Women Men	Positive Neutral
Age	All age	Positive
Disability (please see additional information below)	All	Positive
Gender reassignment	All	Positive
Marriage and civil partnership	All	Positive

Pregnancy and maternity	All	Positive
Race	All	Positive
Religion or belief	All	Positive
Sex	All	Positive
Sexual orientation	Positive	Positive

If there is insufficient evidence to plan about the impact of the guideline it may be necessary to consult with members of protected characteristic groups to establish how best to meet their needs or to overcome barriers.	
Has there been specific consultation on this guideline?	Treatment model is recommended by the Royal College of Emergency Medicine Consultation was completed within UEAM Care group and included nursing, medical Pharmacy and operational teams
Did the consultation analysis reveal any difference in views across the protected characteristics?	No
Disability Protected Characteristic	
We need to ensure that we meet the Accessible Information Standard (AIS) which aims to support people with a disability, sensory loss or impairment to receive information they can understand and any communication support they need. For more information: https://www.ekhuft.nhs.uk/staff/clinical/accessible-information-standard-ais/ https://www.england.nhs.uk/ourwork/patients/accessibleinfo/	

Mitigating negative impact: Where any negative impact has been identified, outline the measures taken to mitigate against it.	No negative impact

Conclusion: Advise on the overall equality implications that should be taken into account by the guideline approving committee.	None, consensus was reached and approved through UEAM governance meeting, Medication Safety Assurance group.

20. Checklist for Authorisation & Publication Please check

		Please tick to confirm as complete
1.	Appropriate and relevant title	✓
2.	Key words for MicroGuide search options	✓
3.	Overview of process with process map/flow chart	
4.	Guideline Development, Authorisation & Implementation table	✓
5.	Table of Contents	✓
6.	Sections 1 to 10 of the clinical guideline template	✓
7.	References including functional links to all referenced online sources	✓
8.	Equality Analysis (any areas with negative impact as a result of the implementation of this clinical guideline will require resolution prior to authorisation)	✓
9.	Version Control Schedule table	✓
10.	Consultation and Ratification Schedule tables Note: if guideline applies to paediatric patients and/or Young Persons, specialists in this area of care **must** be consulted.	✓
Checklist completed by: Alison Brown Consultant Nurse in Emergency Care		**Date:** **June 2024**

21. Version Control Schedule

Version	Date	Author	Status	Comment
DRAFT V1	29/3/2023	Alison Brown	ED Nurse Consultant	Sent for first comments
Draft V1.2	6/06/2023	Alison Brown	ED Nurse Consultant	Adjustment following comments from Dr Lamb, Dr Jenkinson, Dr Sharma
Draft V1.3	7/7/2023	Alison Brown	ED Nurse Consultant	Editorial adjustment
Draft 1.4	29/09/2023	Alison Brown	ED Nurse Consultant	Final review and agreement for sign off from QEQM
Draft for Final Version 1.4-1.6	October -December 2023	Alison Brown Ruth mount	ED Nurse Consultant Improvement team	Review and edits after feedback from DTAG MSAG, and Clinical guideline authorisation group
Final Version 1.7	June 2024	Alison Brown	ED Nurse Consultant	Edits in spelling, and wording for ALT as per Toxbase. Anaphylactoid reaction update as per TOXBASE

Consultation and Ratification Schedule

Name and Title of Individual	**Date Consulted**
Dr Diwakar Sharma Consultant ED & Clinical Lead WHH	**29/03/2023**
Dr Thomas Boon Consultant ED & Paediatrics	**29/03/2023**
Dr Hiten Tanwar Clinical Director UEC	**29/03/2023**
Dr W Kisson Consultant ED clinical lead QEQM	**29/03/2023**
Eno-Asabi Ente Acute medical Pharmacist	**20/04/2023**
Sairah Mukhtar UEC Pharmacist	**20/04/2023**

Dr Edmund Lamb Consultant Clinical scientist & Clinical Director of Pathology.	**20/04/2023**
Michael Jenkinson Consultant Physician, and Medical Examiner, Lead Clinician for Drugs & Therapeutics	**20/04/2023**
Will Wilson Director of Pharmacy	**20/04/2023**
Gifty George Clinical Scientist	**20/04/2023**

Name of Committee	**Date Reviewed**
UEC Governance and Patient Safety WHH	25/7/2023
UEC Governance and Patient Safety QEQM	29/9/2023
Drugs & Therapeutics by Dr Jenkinson	20/4/2023
Clinical Guideline Authorisation group	21/11/ 2023
Drugs and Therapeutics Authorisation Group	22/11/2023
Medication Safety Advisory group	12/12/2023

Appendix A:

N- Acetylcysteine doses 40kg Or Over

Bag 1 100mg/kg acetylcysteine in 200ml 0.9% Saline or 5% Glucose **over 2 hours**

Bag 2 200mg/kg acetylcysteine in 1000ml 0.9% Saline or 5% Glucose **over 10 hours**

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

[1] Dose calculations are based on the weight in the middle of each band. If the patient weighs less than 40 kg use the paediatric dose table.

[2] Ampoule volume (volume of concentrated NAC [200 mg/mL] extracted from ampoules) has been rounded up to the nearest whole number.

APPENDIX B: N-Acetylcysteine doses <40kg

Bag 1 Dose: - 100mg/kg acetylcysteine in 0.9% saline or 5% glucose. Volume: - 2ml/kg (gives a concentration of 50mg/ml) **over 2 hours**

Bag 2 Dose: - 200mg/kg acetylcysteine in 0.9% saline or 5% glucose. Volume: - 20ml/kg (gives a concentration 10mg/ml) **over 10 hours**

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]	Infusion Rate	Total infusion volume[2]	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

[1]Dose calculations are based on the weight in the middle of each band. If the patient weighs 40 kg or more use the adult dosage table.

[2]Figures have been rounded up to the nearest whole number.

APPENDIX C: Patients with an increase in INR and normal ALT

Both paracetamol and acetylcysteine treatment may cause an increase in INR in the absence of liver injury.

Patients who do not meet any of the criteria for continuation of acetylcysteine treatment but have an increase in INR of 0.4 or less (e.g. 1.1 to 1.5) and have a normal ALT can be considered for discharge.

For patients who have an increase in INR of 0.5 or more (e.g. 1.1 to 1.6) in the absence of an ALT rise, 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

If the criteria above are not met - restart acetylcysteine at the dose and infusion rate used in the last treatment bag (10-hour bag if using SNAP or 16-hour bag if using standard 21-hour regimen).

APPENDIX D: Calculating paracetamol toxic doses and acetylcysteine doses in obesity, and pregnancy.

1.1. **Calculating doses in pregnant patients:** NPIS advises that for pregnant patients the toxic dose should be calculated using the patient's pre-pregnancy weight and the acetylcysteine dose (both regimens) should be calculated using the patient's actual pregnant weight.

1.2. **Calculating doses in obese adults:** NPIS advises that for any adult patient weighing more than 110 kg the toxic dose and the acetylcysteine dose (both regimens) should be calculated using a maximum of 110 kg, rather than the patient's actual weight.

1.3. **Calculating doses in obese children:** NPIS advises that the child's actual weight should be used for calculating both the toxic dose and the acetylcysteine dose (both regimens), up to a maximum of 110 kg.

1.4. **Acetylcysteine doses for oral administration:** Very rarely, oral therapy is required (e.g. complete absence of venous access in an intravenous drug abuser). Oral therapy using the IV preparation may be used (not licensed in UK). Check TOXBASE link for oral dose advice

APPENDIX E: **Biochemistry report** By Gifty George Clinical scientist EKHUTF

Use of the SNAP Regime for the Treatment of Paracetamol Toxicity

Paracetamol toxicity has traditionally been treated by a 21-hour infusion (3 separate infusions) of N-Acetylcysteine (NAC). Emergency department at EKHUFT would like to implement the Scottish and Newcastle Acetylcysteine Protocol (SNAP) protocol for paracetamol overdose, which only requires a 12-hour infusion (*2 separate infusions consisting of intravenous NAC 100 mg/kg over 2 h then 200 mg/kg over 10 h*), and is recommended by the Royal College of Emergency Medicine (RCEM). The SNAP regime offers significant benefits to patients in terms of fewer side effects and reduced length of stay in hospital.

One of the criteria for stopping NAC treatment at 12 h is if paracetamol concentration is <10 mg/L when bloods are taken 2hrs before the end of infusion 2 (i.e. 10 h). Abbott kit insert says that no interference from NAC up to concentration 1660 mg/L. Therefore, there was a risk that with the new SNAP protocol, the infusion might reach this concentration when the sample is taken at 10 h for paracetamol concentration, and potentially interfere with our assay.

Clearance and volume of distribution are from Prescott et al (1989).

Steady state concentrations on infusion:

Clearance (CL) = 0.1908 L/h/Kg

First Infusion rate = 100 mg/Kg over 2 h i.e. 50 mg/Kg/h

Second Infusion rate = 200 mg/Kg over 10 hours i.e. 20 mg/Kg/h

Concentration at steady state (Cpss) = Infusion rate/CL

Cpss during first infusion = 50/0.1908 = 262 mg/L

Cpss during second infusion = 20/0.1908 = 105 mg/L

Concentration after 10 hours of second infusion:

Vd = 0.536 L/Kg

Cp0 = Cpss during first infusion i.e. concentration in plasma at end of first infusion

lnCp0 = ln262 = 5.57

t = time point = 10 h

Elimination rate constant (Ke) = CL/Vd = 0.1908/0.536 = 0.356 h

lnCpt = lnCp0 – (Ke x t) = 5.57 – (0.356 x 10) = 2.01

antiloge 2.01 = 7.5 mg/L (this is the conc. remaining from the first infusion)

105 + 7.5 = 112.5 mg/L (adding steady state conc. from second infusion to remaining conc. from first infusion)

Estimated concentration at 10 hours of second infusion = 113 mg/L

This assumes first order kinetics and a one compartment model. It also assumes clearance is unaffected by liver dysfunction or renal insufficiency. However, even if there was no clearance at all the maximum concentration after 10 hours of the second infusion would be 485 mg/L (Concentration = dose/Vd, dose at 10 hours of second bag is 100 mg/L + 160 mg/L = 260 mg/L, Concentration = 260/0.536 = 485 mg/L).

Additionally, Thanacoody et al., (2013) performed a Monte Carlo simulation using pharmacokinetic data derived from Prescott, to derive expected NAC plasma concentrations, based on a 1-compartment model, using a new shorter SNAP regimen. They estimated that at the modified infusion regimen would give rise to a mean NAC plasma concentrations of 225 mg/L at 10 h, which is less than the NAC concentration at which Abbott states there is

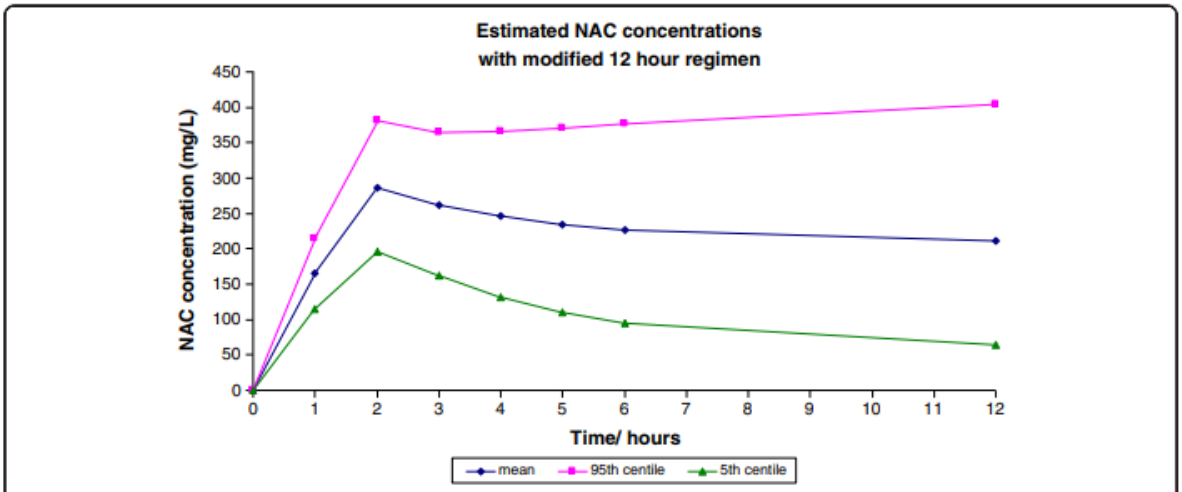


Figure 1 Monte Carlo calculations of proposed modified acetylcysteine regimen.

an interference.

In summary, potential NAC plasma concentration reached at 10 hours on second infusion is lower than what Abbot have tested at, so it seems unlikely that there would be any interference. Even if criteria for discontinuing NAC at 12 h has not met and has proceed to infusion 3, paracetamol concentration does not need to be measured again, as it is not one of criteria for assessing if any further infusion is required.

References;

Biochemistry report By Gifty George Clinical scientist EKHUFT

Pettie, J. M., Caparrotta, T. M., Hunter, R. W., Morrison, E. E., Wood, D. M., Dargan, P. I., Thanacoody, R. H., Thomas, S. H. L., Elamin, M. E. M. O., Francis, B., Webb, D. J., Sandilands, E. A., Eddleston, M., & Dear, J. W. (2019). Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose. EClinicalMedicine, 11, 11–17.

Prescott LF, Donovan JW, Jarvie DR, Proudfoot AT: The disposition and kinetics of intravenous N-acetylcysteine in patients with paracetamol overdosage. Eur J Clin Pharmacol 1989, 37:501–506.

Thanacoody, H. K., Gray, A., Dear, J. W., Coyle, J., Sandilands, E. A., Webb, D. J., Lewis, S., Eddleston, M., Thomas, S. H., & Bateman, D. N. (2013). Scottish and Newcastle antiemetic pre-treatment for paracetamol poisoning study (SNAP). *BMC pharmacology & toxicology*, *14*, 20.