South Australian Paediatric Clinical Practice Guidelines

Paracetamol Poisoning

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate, and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:

The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horseshoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horseshoe shape depicts a pregnant woman. The smaller horseshoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Cultural safety enhances clinical safety.

To secure the best health outcomes, clinicians must provide a culturally safe health care experience for Aboriginal children, young people and their families. Aboriginal children are born into strong kinship structures where roles and responsibilities are integral and woven into the social fabric of Aboriginal societies.

Australian Aboriginal culture is the oldest living culture in the world, yet Aboriginal people currently experience the poorest health outcomes when compared to non-Aboriginal Australians.

It remains a national disgrace that Australia has one of the highest youth suicide rates in the world. The over representation of Aboriginal children and young people in out of home care and juvenile detention and justice system is intolerable.

The accumulated effects of forced removal of Aboriginal children, poverty, exposure to violence, historical and transgenerational trauma, the ongoing effects of past and present systemic racism, culturally unsafe and discriminatory health services are all major contributors to the disparities in Aboriginal health outcomes.

Clinicians can secure positive long term health and wellbeing outcomes by making well informed clinical decisions based on cultural considerations

The term 'Aboriginal' is used to refer to people who identify as Aboriginal, Torres Strait Islanders, or both Aboriginal and Torres Strait Islander. This is done because the people indigenous to South Australia are Aboriginal and we respect that many Aboriginal people prefer the term 'Aboriginal'. We also acknowledge and respect that many Aboriginal South Australians prefer to be known by their specific language group(s).

Government of South Australia
SA Health

Purpose and Scope of PCPG

The Paracetamol Poisoning Clinical Guideline is primarily aimed at medical staff working in any of primary care, local, regional, general or tertiary hospitals. It may, however, assist the care provided by other clinicians, such as nurses. The information is current at the time of publication and provides a minimum standard for the assessment (including investigations) and management of Paracetamol Poisoning. It does not replace or remove clinical judgement or the professional care and duty necessary for each specific case.

Table of Contents

Introduction

This guideline provides information on the assessment and initial management of children presenting with paracetamol poisoning. It is not intended to be a comprehensive source of information on the management of paracetamol poisoning.

Abbreviations

mg	milligram/s
g	gram/s
kg	kilogram/s
ALT	alanine aminotransferase
UEC	urea, electrolytes, creatinine
INR	international normalised ratio
BSL	Blood sugar level
VBG	Venous blood gases
LFT	Liver function test
L	litre
yrs	years
hr	hour
NABQI	N-acetyl-p-benzoquinoneimine

Detailed steps, Procedures and Actions

Patients Requiring Investigation, Observation and Possible Treatment

> Ingestion of unknown quantity or **ANY patient with intentional ingestion**

***NOTE: For obese children, the weight used should be based on an ideal body weight.**

Paracetamol dosing that may be associated with hepatic injury[1]

	Adults & children >6 years of age	**Children (aged 0-6 years) ***
Acute single ingestion	>200mg/kg or 10g (whichever is less) over a period of <8 hours	>200mg/kg over a period of <8 hours
Repeated supratherapeutic ingestion	>200mg/kg or 10g (whichever is less) over a single 24-hour period	>200mg/kg over a single 24-hour period
	>150mg/kg or 6g (whichever is less) per 24-hour period for the preceding 48 hours	>150mg/kg per 24-hour period for the preceding 48 hours
	>100mg/kg or 4g (whichever is less) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury (e.g. abdominal pain, nausea or vomiting	>100mg/kg per 24-hour period for more than 48 hours

Management

(See Flow diagrams & Investigation table)

- Ensure support of vital functions **(Airway, Breathing and Circulation)**
- **Activated charcoal** has limited utility and is generally not required. Exceptions are in the alert adolescent patient with sustained release ingestion within 4 hours. **Charcoal should NOT be given orally or via nasogastric tube in an uncooperative/drowsy patient.** Advice from a toxicologist via the Poisons Information Centre (131126) should be obtained prior to administering activated charcoal.
- Activated charcoal dose in children is 1g/kg (max 50g) and may be given orally or via a nasogastric tube
- Serum paracetamol level **at (or as soon as possible after) 4 hours post ingestion** will determine the need for **acetylcysteine** administration (see nomogram)

Consult toxicologist in massive dose ingestion (>30g) or if initial paracetamol level is over double the nomogram value.

- It is safe to wait for the paracetamol concentration to decide on the need for acetylcysteine in all cases that present within 8 hours of ingestion AND where paracetamol concentration result will be available for interpretation **within 8 hours** of ingestion
- Patient refusal to undergo paracetamol level may be grounds for application of the *Consent to Medical Treatment and Palliative Care Act 1995*.
- A general drug screen of urine or gastric aspirate may be indicated, particularly in adolescent patients who may have ingested other drugs
- Acetylcysteine treatment **must** be started if the nomogram indicates a potentially toxic paracetamol level or if otherwise indicated (see nomogram)
- Decision to discontinue treatment must be made by the treating consultant. Infusion must be continued beyond 20 hours if encephalopathic or LFT's deranged **(Gastroenterology referral mandatory)**
- A mental health assessment is required following any deliberate ingestion with self-harm intent.
- Mandatory notification is required if child abuse or neglect is suspected.

Recommended investigations according to time from paracetamol ingestion to acetylcysteine treatment (excluding multiple supra therapeutic and modified release ingestions)

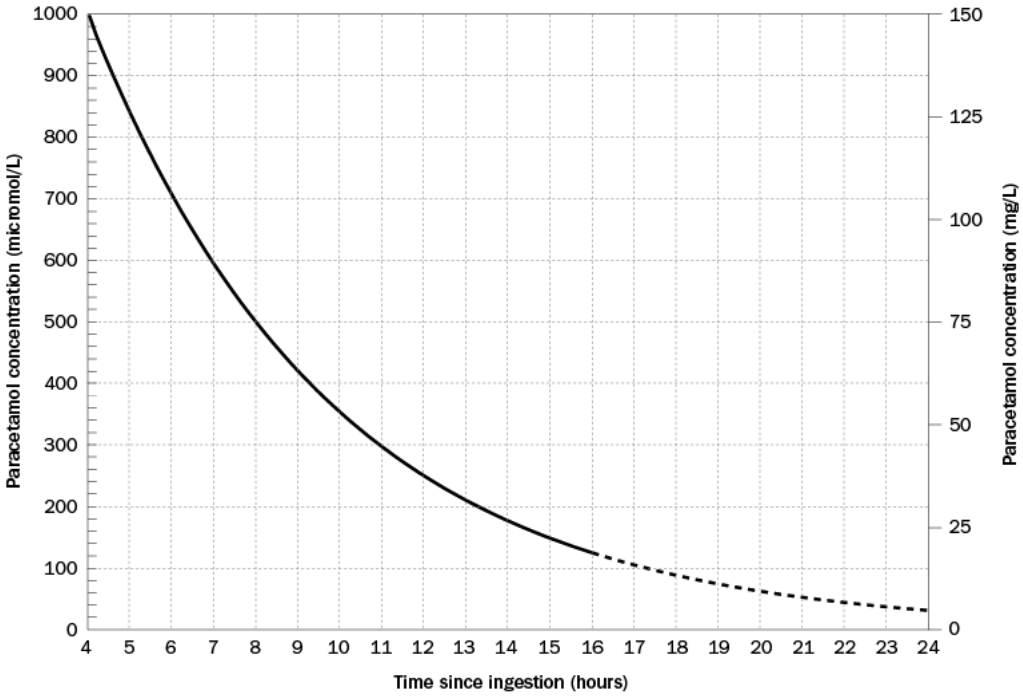
Time (hours from ingestion to acetylcysteine)	Investigations on admission	Investigations at the completion of acetylcysteine
Less than 8 hours	Serum paracetamol concentration	ALT*
8 – 24 hours	Serum paracetamol concentration and ALT	ALT and UEC
Greater than 24 hours	Serum paracetamol concentration, ALT and INR	ALT, INR and UEC
Patients who have an abnormal ALT	UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).	**Repeat investigations every 12 hours including:** UEC, LFTs, INR, BSL, phosphate and VBG (looking at the pH and lactate).

ALT = alanine aminotransferase, BSL = blood sugar level, INR = international normalised ratio, UEC = urea, electrolytes, creatinine, VBG = venous blood gas.

Investigations[1,4]

*Co-ingestion of other medications may require a different approach to investigation and treatment. Discuss with Emergency Department/responsible consultant and/or poisons centre.

Paracetamol treatment nomogram [3]



Ensure the units of measure are the same as the scale used on the nomogram

Paediatric Liquid Paracetamol Ingestion

In children suspected of ingesting >200 mg/kg of liquid paracetamol measure the serum paracetamol level at least 2 hours post ingestion:

- If the concentration 2-4 hours post ingestion is <1000 micromol/L, acetylcysteine is not required.
- If the 2 hour concentration is >1000 micromol/L measure again at 4 hours post ingestion. If the 4 hour concentration is still > 1000 micromol/L, then commence acetycysteine infusion
- For children presenting later than 4 hours post ingestion or ≥ 6 years refer to the flow diagram below.

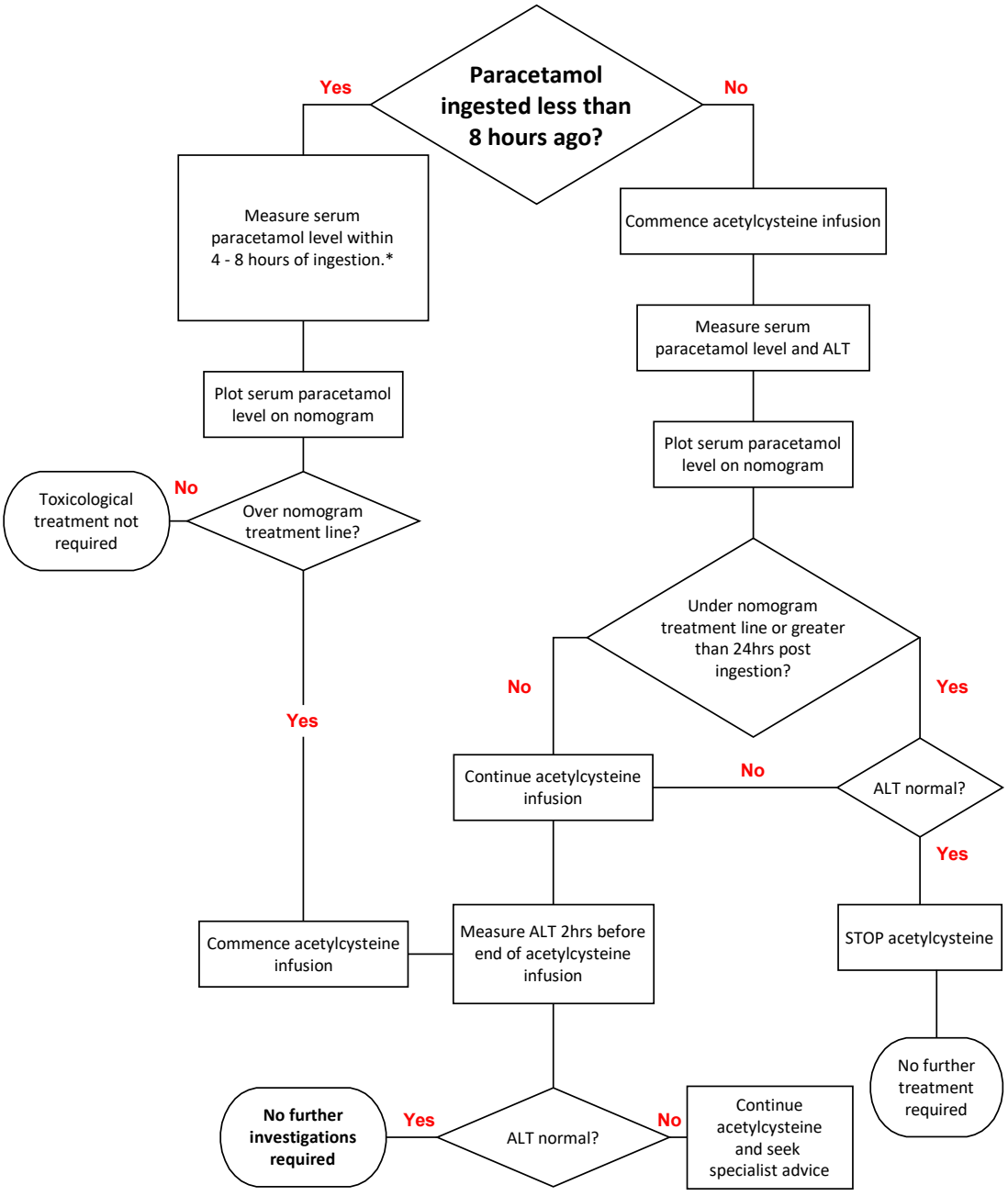
Indications for acetylcysteine[2,3]

- Single ingestion and paracetamol level (taken 4 – 8 hours post-ingestion) is above the nomogram line
- Ingestion of more than 200mg/kg or 10g of a sustained release paracetamol (whichever is less)
- Ingestion of sustained release paracetamol where either of the 2 levels (taken 4 hours apart) is above the nomogram line
- Repeated supratherapeutic ingestions – see flow diagram below
- Established hepatoxicity
- Patients who present >8 hours (or where level will not be known for >8 hours) after a toxic ingestion (>200mg/kg) or after an ingestion in association with symptoms of toxicity (right upper quadrant pain or tenderness, nausea, vomiting) should be commenced on acetylcysteine immediately. The decision to continue or cease treatment is then based on paracetamol concentration and alanine amino transferase (ALT)
- Patients with uncertain time of ingestion must be treated on a 'worst case basis' depending on ingestion dose or paracetamol level. If in doubt it is safer to treat than to withhold treatment
- Discuss other scenarios with toxicologist.

Flow Diagram Paracetamol exposure with known time of ingestion[1,2]

Consult toxicologist in massive dose ingestion (>30g) or if initial paracetamol level is over double the nomogram value.

Activated charcoal has limited utility and is generally not required. Exceptions are in the alert adolescent patient with sustained release ingestion within 2 hours. **Charcoal should NOT be given orally or via nasogastric tube in an uncooperative/drowsy patient**. Advice from a toxicologist via the Poisons Information Centre (131126) should be obtained prior to administering activated charcoal.



ALT = alanine amino transferase
*2 hr level for children < 6 yrs who have ingested liquid paracetamol

Ingestions that are staggered over a period under 8 hours should be treated as a single acute ingestion at the earliest time of ingestion.

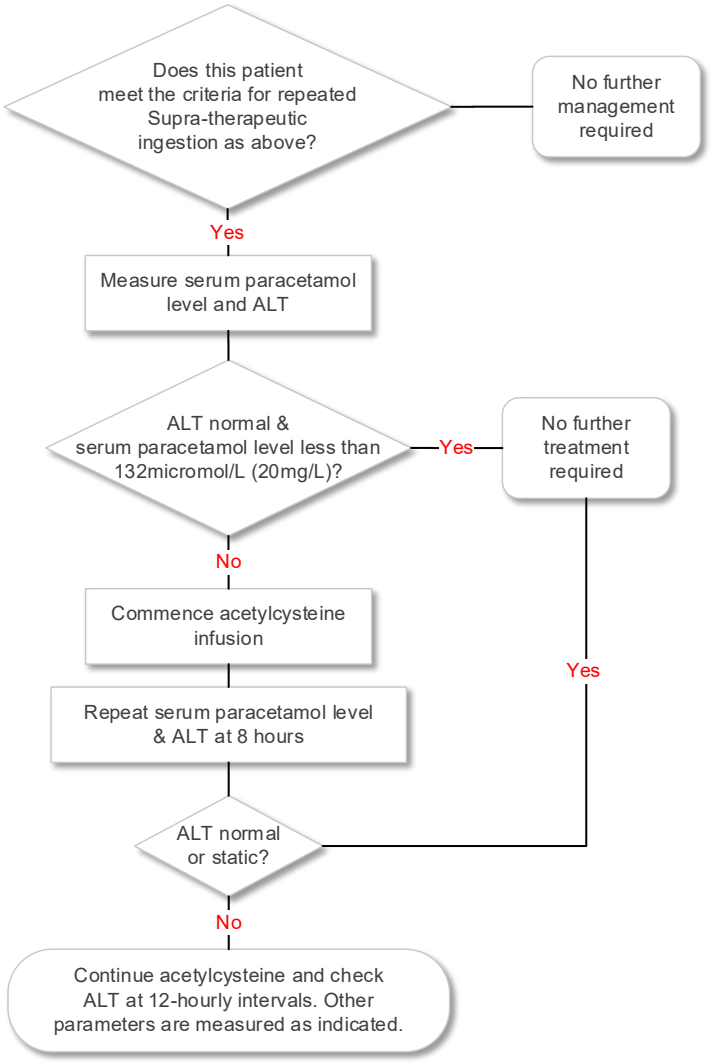
Flow Diagram for repeated supra-therapeutic overdose[1, 2]

Adults & children >6 years of age	Children (aged 0-6 years) *
At least 200mg/kg or 10g Paracetamol (whichever is less) over a single 24-hour period	200mg/kg or more over a single 24-hour period
At least 150mg/kg or 6g Paracetamol (whichever is less) per 24-hour period for the preceding 48 hours	150mg/kg or more per 24-hour period for the preceding 48 hours
More 100mg/kg or 4g Paracetamol (whichever is less) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury	100mg/kg or more per 24-hour period for more than 48 hours

***NOTE:** For obese children the weight used, should be based on an ideal body weight.

Consult toxicologist in massive dose ingestion (>30g) or if initial paracetamol level is over double the nomogram value.

Activated charcoal has limited utility and is generally not required. Exceptions are in the alert adolescent patient with sustained release ingestion within 2 hours. **Charcoal should NOT be given orally or via nasogastric tube in an uncooperative/drowsy patient**. Advice from a toxicologist via the Poisons Information Centre (131126) should be obtained prior to administering activated charcoal. Activated charcoal dose in children is 1g/kg – max 50g and may be given orally or via a nasogastric tube.

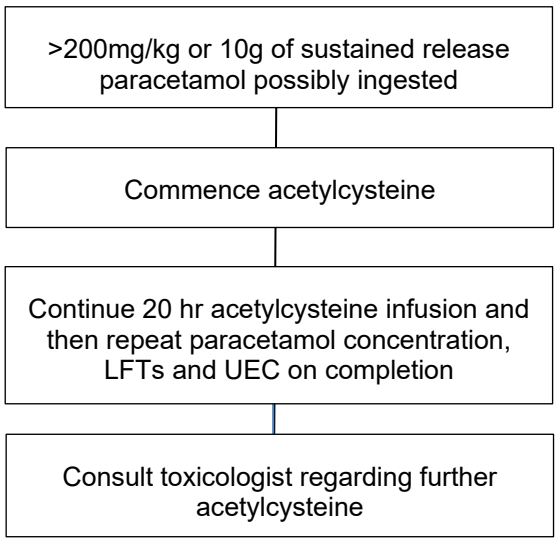


Flow Diagram for Sustained Release (SR) Paracetamol Overdose[4]

- Modified release paracetamol may be more slowly absorbed with delayed peak serum concentrations

Recommendations:

- **Activated charcoal** should be considered in the alert adolescent patient with sustained release ingestion within 4 hours. **Charcoal should NOT be given orally or via nasogastric tube in an uncooperative/drowsy patient**
- Ingestions of <4g or 60mg/kg, whichever is less are no risk with no investigation or treatment required
- Ingestions of 4g-10g or 60-200mg/kg, whichever is less are low risk. Obtain levels at 4hrs and 8hrs post ingestion. No Acetylcysteine needed if BOTH levels below nomogram line AND the second level is falling
- For unknown dose or ingestions >10g or 200mg/kg 20 hour Acetylcysteine infusion should be given as per the flow chart below unless paracetamol level is < 20 micromol/L.



LFT = liver function test

UEC = urea, electrolytes, creatinine

Acetylcysteine Infusion

The standard administration of Acetylcysteine is a 2 stage infusion (recently changed from 3 stage infusion) giving a total dose of 300 mg/kg:

200 mg/kg over 4 hours

100 mg/kg over the next 16 hours

DOSE Calculated based on actual body weight. For children >110 kg, calculate the dose based on 110 kg body weight.

Acetylcysteine may be diluted in 5% glucose or 0.9% sodium chloride (normal saline). It can also be diluted in combination glucose-sodium chloride solutions not exceeding these concentrations including 0.45% sodium chloride in 5% glucose, and 0.9% sodium chloride in 5% glucose.

The volume and choice of fluid for each stage of the infusion needs to be appropriate for the age and weight of the child and clinical circumstances.

The volume of Acetylcysteine needs to be included in the TOTAL volume of the infusion to avoid under-dosing (volumes specified in tables below are TOTAL volumes, ie: Acetylcysteine volume plus fluid volume combined).

For children >20 kg body weight:

Acetylcysteine Dose	Dilute to (using sodium chloride or glucose)	Rate and Duration
200 mg/kg	TOTAL volume **250 mL**	62.5 mL/hr for 4 hours Infuse entire bag
100 mg/kg	TOTAL volume **500 mL**	31.25 mL /hr for 16 hours Infuse the entire bag

NOTE: *this results in a total of 750 mL* ***o****f fluid which is inappropriate for smaller children.*

For children ≤20 kg body weight:

Acetylcysteine Dose	Dilute to (using sodium chloride or glucose)	Rate and Duration
200 mg/kg	TOTAL volume **250 mL****	62.5 mL/hr** for 4 hours Infuse entire bag
100 mg/kg	TOTAL volume **250 mL****	15 ml/hr** for 16 hours Infuse entire bag

****For infants**, even smaller volumes may be required. Doses can be diluted in 100 ml bags if available (note: the entire dose must be administered over the specified time.). For infants who are fluid restricted with concerns about fluid overload, a smaller total volume is required. Contact hospital pharmacist for advice.

Infant example

Acetylcysteine Dose	Dilute to (using sodium chloride or glucose)	Rate and Duration
200 mg/kg	TOTAL volume **100 mL**	25 mL/hr for 4 hours Infuse entire bag
100 mg/kg	TOTAL volume **250 mL**	15.7 mL/hr for 16 hours Infuse entire bag

In all cases, additional maintenance fluids can be given if required, or acetylcysteine may be administered in larger volume bags if more convenient.

Acetylcysteine dosing or administration errors should be discussed with a toxicologist.

Note: Anaphylactoid reactions to acetylcysteine may occur (wheeze, rash, mild hypotension): stop the infusion for 30 minutes, give oral cetirizine then recommence infusion at half the previous rate. Increase the rate slowly over time until the desired rate is again reached.

Very rarely, a more severe reaction can occur. If there are significant cardiovascular changes or respiratory distress, **escalate for urgent assessment per hospital procedure** and consider giving adrenaline 1:1000 (0.01 ml/kg) IM and hydrocortisone (4mg/kg) IV.

Nursing Observations during Acetylcysteine Infusion

- Observe for any side effects or allergic reaction to the acetylcysteine infusion: nausea, vomiting, rash, itch, wheeze, shortness of breath, hypotension. These generally occur within 60 min of commencing the infusion but may be delayed
- For the first hour of infusion, 15 minute observations for heart rate, respiration and blood pressure
- The first hour of infusion should take place in a monitored area
- If an infusion reaction occurs, the infusion should be stopped, and medical officer informed
- When recommenced, the infusion is started at half the previous rate and then increased slowly until the desired rate is reached
- Monitoring and 4 hourly observations for heart rate, respiration and blood pressure is required for 20 hours while the infusion is running.

Management of Specific Clinical Features

- A patient with a paracetamol-only overdose who is medically stable and only treated with acetylcysteine infusion should have cardiorespiratory monitoring for 1 hour after commencement of the infusion. During this period, the patient needs close observation for side effects and anaphylactoid reactions. After 1 hour of infusion, the patient can have routine 4 hourly observations and without continuous cardiorespiratory monitoring.
- For patients who are haemodynamically unstable from other co-ingestions, high dependency may be needed, and intensive care/toxicologist should be consulted in the ongoing care of these cases.
- Transfer to tertiary care should be considered by contacting MedSTAR Kids retrieval service on 13STAR (13 78 27)
- Risk factors for increased likelihood of hepatotoxicity include chronic ethanol abuse, chronic treatment with isoniazid or drugs which increase cytochrome P450 mixed function oxidase activity (e.g., barbiturates, phenytoin, carbamazepine and rifampicin). Known liver disease, Cystic Fibrosis, anorexia, or greater than 2 therapeutic doses of paracetamol within 24 hrs of toxic ingestion are also significant risk factors. Hepatotoxicity has been reported in patients with these risk factors who had 4 hour plasma paracetamol concentrations much lower than 1300 micromol/L. Early gastroenterology review should be considered for patients with risk factors.

General Background Information

Paracetamol is an effective, simple analgesic that is well tolerated by adults and children at therapeutic doses. It is inexpensive and readily available without prescription. Unfortunately, it is also the most common drug taken in overdose and is responsible for a considerable number of hospital admissions and deaths each year. Early symptoms are minimal, even in potentially fatal ingestions.

Because the amount of paracetamol ingested and absorbed by children is difficult to determine, treatment should be undertaken if the history suggests an acute ingestion of greater than 200mg/kg or 10g (whichever is less), or if the patient is symptomatic.

The lowest recorded acute ingestion where serious toxicity has occurred is 200mg/kg, although toxicity from repeated smaller ingestions is widely recognised.

Note: There are a wide range of paracetamol preparations available in varying pack sizes. Always clearly establish the exact strength and type of the preparation, in addition to the pack size before estimating the total amount of paracetamol ingested by the patient. Sustained release preparations may be absorbed more slowly and require a second paracetamol level 4 hours after the initial level. Liquid suspensions have a more rapid absorption and can reach peak levels at 2 hours post ingestion. There is some evidence that a level at 2 hours may be useful in this circumstance.

Following a normal therapeutic dose, paracetamol is primarily metabolised by sulfation and glucuronide formation, with only 5% oxidised to a reactive metabolite. N-acetyl-p-benzoquinoneimine (NABQI). This is rapidly detoxified by conjugation with glutathione. In toxic ingestions, however larger amounts are shunted through the P450 dependent oxidase, resulting in dangerously high NABQI production and glutathione depletion. Paracetamol induced hepato-renal damage is mediated by NABQI. There is some evidence to suggest that young children are less susceptible to hepatic injury because of more effective sulfation and greater glutathione stores.

Acetylcysteine is used in the treatment of paracetamol poisoning. In vivo, acetylcysteine forms l-cysteine, cystine, l-methionine, glutathione and mixed disulphides which allow the toxic metabolite to be metabolised to non-toxic metabolites.

Acetylcysteine may also have a secondary benefit as an antioxidant and as a free radical scavenger.

The risk of hepatotoxicity is best related to the plasma paracetamol concentration. Hepatotoxicity is more likely to occur if the plasma concentration 4-15 hours after ingestion is above the line joining 1000 micromol/L at 4 hours and 150micromol/L at 15 hours. (See nomogram for plot of plasma paracetamol levels vs time).

Major Clinical Features

In most cases, there are no signs in the first 24 hours. The early presence of sedation, miosis and respiratory changes may suggest the concurrent administration of other agents such as codeine, dextropropoxyphene, antihistamines, alcohol and salicylates.

Children may have episodes of vomiting earlier than in adults regardless of the amount of paracetamol ingested.

A poor prognosis in relation to hepatotoxicity is associated with any of the following:

- pH <7.3
- continued rise in INR on day 4 compared with day 3
- serum creatinine>300 micromol/L with INR>6 and hepatic coma grade 3 or 4 peak INR>10

Gastrointestinal

Nausea, vomiting, anorexia, abdominal pain and sweating may occur, generally in the first 2 to 14 hours after ingestion.

Hepatic

Paracetamol is hepatotoxic following overdose. Clinical and laboratory evidence of hepatotoxicity may be delayed for 24 to 36 hours post-ingestion. An increased ALT (SGPT), bilirubin, hypoglycaemia, abnormal clotting studies and right-sided abdominal pain and tenderness are indicative of onset of hepatotoxicity. Peak hepatotoxicity may not occur for up to 72 to 96 hours post-ingestion.

Renal

Renal insufficiency or damage may occur.

Endocrine

Pancreatitis

Acid-base

Metabolic acidosis

Haematologic

Thrombocytopaenia

Metabolism

Hypophosphataemia

Cardiovascular

Myocardial damage has been reported. It is unclear whether this is a direct effect of paracetamol or secondary to metabolic and vital sign abnormalities.

References

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2. Sydney Children's Hospitals Network. Guideline: Paracetamol Overdose – Assessment and Management.
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5. Chiew AL, Isbister GK, Page CB et al (2018): Modified release paracetamol overdose: a prospective observational study (ATOM-3), Clinical Toxicology

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7. New regimens for intravenous acetylcysteine, where are we now? (English) By: Bateman DN; Dear JW; Thomas SH, Clinical Toxicology (Philadelphia, Pa.) [Clin Toxicol (Phila)], ISSN: 1556-9519, 2016; Vol. 54 (2), pp. 75-8; Publisher: Informa Healthcare; PMID: 26666290.

Resources

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