
DBL™ ACETYL-CYSTEINE INJECTION CONCENTRATE

Name of medicine

Acetylcysteine

Presentation

DBL™ Acetylcysteine Injection Concentrate is a clear, colourless, sterile, pyrogen free aqueous solution of acetylcysteine (N-acetyl-mercapto-alanine) with a pH of approximately 7.0.

Each ampoule contains 200 milligrams/mL of acetylcysteine as well as sodium hydroxide, disodium edetate and water for injections.

Uses

Actions

Paracetamol is metabolised in the liver, mainly by conjugation with glucuronide and sulphate. It is also metabolised by cytochrome P450 to form a reactive, potentially toxic metabolite. This metabolite is normally detoxified by conjugation with hepatic glutathione, to form non-toxic derivatives. In paracetamol overdose, the glucuronide and sulphate conjugation pathways are saturated, so that more of the toxic metabolite is formed. As hepatic glutathione stores are depleted, this toxic metabolite may bind to hepatocyte proteins, leading to liver cell damage and necrosis. Acetylcysteine is a sulphhydryl (SH) group donor, and may protect the liver from damage by restoring depleted hepatic-reduced glutathione levels, or by acting as an alternative substrate for conjugation with, and thus detoxification of, the toxic paracetamol metabolite.

Pharmacokinetics

Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine, and is deacetylated in the liver to cysteine, or oxidised to other metabolites such as N-acetylcystine or N,N-diacetylcystine. The parent compound and metabolites may be present in the plasma either free or protein bound. Renal clearance accounts for about 30% of total body clearance. Following intravenous administration, mean terminal half lives have been calculated to be 1.95 and 5.58 hours respectively for reduced and total acetylcysteine.

Indications

As an antidote for paracetamol poisoning: DBL™ Acetylcysteine Injection Concentrate is indicated in the treatment of paracetamol overdose to protect against hepatotoxicity.

Dosage and administration

To be most effective in protecting against liver damage, therapy with DBL™ Acetylcysteine Injection Concentrate should be started within 10 hours of paracetamol ingestion. Although the role of DBL™ Acetylcysteine Injection Concentrate therapy in patients presenting later than 15 hours after paracetamol ingestion is not established, it may be considered as a clinical option in high risk patients.

Management of Paracetamol Overdosage

It should be noted that, after an ingestion of a potentially fatal dose of paracetamol, the patient may appear relatively well initially and may even continue normal activities for a day or two before the onset of hepatic failure. Hepatic damage is more likely to occur with a lower dosage of paracetamol in patients who have a history of chronic alcohol or enzyme-inducing drug ingestion (e.g. isoniazid, rifampicin, anticonvulsants including carbamazepine, phenytoin, phenobarbitone, primidone, sodium valproate).

Patients are notoriously unreliable as to the **amount** ingested and the **time** of ingestion. Hepatic necrosis is preventable if treatment can be instituted within 10 to 12 hours of ingestion.

Note: Liver damage may not be biochemically apparent for 24 to 48 hours after ingestion.

Hepatic necrosis has been seen with 6 grams of paracetamol, and death with 15 grams.

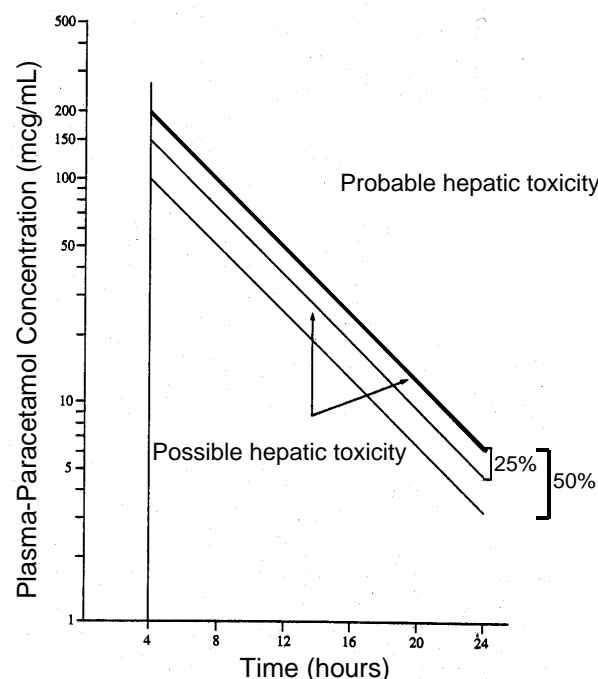
A. Patient presenting within 15 hours of ingestion

Give activated charcoal (1 to 2 grams/kg) if it is within 1 hour of paracetamol ingestion, and the patient's conscious state is not impaired.

Plasma paracetamol levels should be obtained no earlier than 4 hours after ingestion of the paracetamol overdose. Concentrations determined prior to this time are not reliable for assessing potential hepatotoxicity. If the time of ingestion is unknown, paracetamol levels should be measured immediately.

Measurements of plasma liver enzymes and bilirubin levels, and coagulation studies, should be performed as soon as possible after admission. Blood urea, electrolytes, glucose and blood gases should be obtained. The laboratory measurements are used to monitor hepatic and renal function and electrolyte balance. An ECG should also be performed.

Plasma paracetamol levels can be used to determine the likelihood of hepatic damage when compared with the nomogram below.



CAUTION: USE CORRECT UNITS FOR PARACETAMOL CONCENTRATION

Note: To convert paracetamol concentrations from micromol/L to mcg/mL, divide by 6.61

Do not delay acetylcysteine therapy while awaiting the results of plasma assays. Once the results become available, treatment may be discontinued if the initial concentration is below nomogram reference line.

Do not discontinue acetylcysteine therapy if the initial level is above the reference line and subsequent levels fall below the reference line.

The nomogram is designed to be used for single acute ingestions. It is not helpful in determining the need for acetylcysteine in multiple or chronic ingestions.

The nomogram may not be suitable for use when patients have taken sustained release preparations of paracetamol.

Patients whose plasma paracetamol level is above the solid line are at a high risk of developing hepatotoxicity.

The middle line (25% below the solid line) is included to allow for possible errors in plasma assays and estimated time from ingestion and should be used as a guide to treatment.

Patients who have a history of chronic alcohol abuse or are receiving enzyme-inducing drugs are at greater risk of developing hepatotoxicity and if their plasma paracetamol level is up to 50% below the solid line they may require treatment with DBL™ Acetylcysteine Injection Concentrate.

B. Patients presenting more than 15 hours after ingestion

Plasma paracetamol, bilirubin and AST levels should be determined on an urgent basis, and a clinical decision made on how to proceed. DBL™ Acetylcysteine Injection Concentrate may be beneficial in patients presenting later than 15 hours after ingestion. The use of DBL™ Acetylcysteine Injection Concentrate should therefore be considered in high risk patients who present late, but only after discussion with physicians with substantial experience in the management of patients with paracetamol poisoning.

C. General Management

DBL™ Acetylcysteine Injection Concentrate should be administered if appropriate (see **A** and **B** above). DBL™ Acetylcysteine Injection Concentrate should be diluted in 5% glucose or 0.9% sodium chloride solution, and administered by intravenous infusion. Nausea should be treated.

Daily liver function tests, and measurements of plasma urea, electrolytes, haemoglobin levels, white blood cell counts, platelets and prothrombin time should be made. Patients should be monitored for coagulation disorders, hepatic encephalopathy, renal failure and cardiac toxicity (minor ST changes are common). There is usually a mild metabolic acidosis. Hepatic encephalopathy is likely if bilirubin is above 60 millimoles per litre on days 3 to 5, or if the prothrombin time is prolonged.

Dosage in adults

DBL™ Acetylcysteine Injection Concentrate is infused in three intravenous infusions containing different doses. This will give a total dose of 300 milligrams/kg of acetylcysteine infused over 20 hours.

INITIAL INFUSION: An initial dose of 150 milligrams/kg of acetylcysteine diluted in 200 mL of 5% glucose or 0.9% sodium chloride and infused over 15 to 60 minutes.

SECOND INFUSION: The initial infusion is followed by a continuous infusion of 50 milligrams/kg of acetylcysteine in 500 mL of 5% glucose or 0.9% sodium chloride over the next 4 hours.

THIRD INFUSION: The second infusion is followed by a continuous infusion of 100 milligrams/kg of acetylcysteine in 1000 mL of 5% glucose or 0.9% sodium chloride over the next 16 hours.

DBL™ Acetylcysteine Injection Concentrate intravenous infusion dosage guide

DBL™ Acetylcysteine Injection Concentrate is supplied in ampoules containing 10 mL of 200 mg/mL acetylcysteine for intravenous administration.

Since DBL™ Acetylcysteine Injection Concentrate does not contain an antimicrobial preservative, use in one patient on one occasion only and discard any residue.

The following table is intended as a guide on the volume (mL) of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL that is required to be added to 5% glucose or 0.9% sodium chloride to prepare the initial, second and third infusion solutions. In order to use this table, the patient's weight in kilograms should be determined. The **volume (mL)** of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL that should be added to 5% glucose or 0.9% sodium chloride to prepare the initial, second and third infusion solutions is shown in the three columns next to the patient's weight.

PATIENT'S BODY WEIGHT (kg)	INITIAL INFUSION Volume (mL) of Acetylcysteine Injection Concentrate to be added to 200 mL of 5% glucose or 0.9% sodium chloride	SECOND INFUSION Volume (mL) of Acetylcysteine Injection Concentrate to be added to 500 mL of 5% glucose or 0.9% sodium chloride	THIRD INFUSION Volume (mL) of Acetylcysteine Injection Concentrate to be added to 1000 mL of 5% glucose or 0.9% sodium chloride	TOTAL Volume (mL) of Acetylcysteine Injection Concentrate Given over 20 hours
x*	0.75x	0.25x	0.5x	1.5x
50	37.5	12.5	25	75
60	45.0	15.0	30	90
70	52.5	17.5	35	105
80	60.0	20.0	40	120
90	67.5	22.5	45	135

* If the patient's body weight is x kilograms, then the infusion volumes of DBL™ Acetylcysteine Injection Concentrate in millilitres will be:

- Initial infusion: 0.75x mL of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL to be added to 200 mL of 5% glucose or 0.9% sodium chloride
- Second infusion: 0.25x mL of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL to be added to 500 mL of 5% glucose or 0.9% sodium chloride
- Third infusion: 0.5x mL of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL to be added to 1000 mL of 5% glucose or 0.9% sodium chloride
- Total: 1.5x mL of DBL™ Acetylcysteine Injection Concentrate 200 mg/mL given over 20 hours

Dosage and Administration in Children

Children should be treated with the same doses and regimens as adults. However the quantity of intravenous fluid should be modified to take into account age and weight, as fluid overload is a potential danger.

Contraindications

Acetylcysteine is contraindicated in patients with hypersensitivity or previous anaphylactic reaction to acetylcysteine or any component of the preparation.

Warnings and precautions

Acetylcysteine should be used with caution in asthma or where there is a history of bronchospasm. It should also be used with caution with patients with a past history of oesophageal varices and peptic ulceration (acetylcysteine induced vomiting may increase the risk of haemorrhage).

Acetylcysteine is not compatible with rubber and some metals, particularly, iron, copper and nickel. Acetylcysteine can be used satisfactorily with silicone rubber and plastic.

Carcinogenicity

Carcinogenicity assays have not been performed with acetylcysteine. In rats, no evidence of carcinogenicity was reported following 18 months of daily dietary administration of acetylcysteine at 60% of the maximum clinical dose, on a body surface area basis.

No evidence of mutagenicity was obtained in limited gene mutation assays with acetylcysteine. The potential for acetylcysteine to cause chromosomal damage has not been investigated.

Impairment of fertility

There was evidence of effects on fertility in male rats given acetylcysteine at doses up to 60% of the maximum clinical dose, on a body surface area basis. No effects were observed at doses 15% the maximum clinical dose, on a body surface area basis.

Pregnancy and Lactation

Use in Pregnancy

Category B2[†]

There was no evidence of teratogenicity in limited studies in rats and rabbits following administration of acetylcysteine during the period of gestation at doses up to 1.2 times the maximum clinical dose, on a body surface area basis. There are no well controlled studies in pregnant women but experience does not include any positive evidence of adverse effects to the foetus.

Use in Lactation

There was no evidence of adverse effects in a limited study in rats following administration of acetylcysteine during late gestation and lactation at 60% of the maximum clinical dose, on a body surface area basis. It is not known whether acetylcysteine and/or its metabolites are excreted in milk. There are no data on the use of acetylcysteine in lactating women and therefore breastfeeding is not recommended during treatment.

Paediatric use

The safety and effectiveness of acetylcysteine in children has not been established. No paediatric specific adverse effects have been documented.

Use in the Elderly

There are no adequate or well controlled studies in elderly patients. For this reason, the safety and effectiveness of acetylcysteine in the elderly has not been established.

Use in Renal/Hepatic impaired patients

Caution should be taken when administering acetylcysteine in patients with hepatic or renal failure, since there is little data relating to the effects of acetylcysteine in impaired renal and/or hepatic function. The decision to administer should be passed on a risk/benefit assessment for the individual subject.

In the presence of hepatic failure due to paracetamol overdose the degree of existing liver damage and the possible risk associated with the administration of acetylcysteine should be considered.

Patients with body weight less than 40 kg

For patients weighing less than 40 kg, adjustment of total volume is recommended when administering acetylcysteine, to minimise the risk of hyponatraemia, seizure, and death.

Patients on fluid restriction

For patients on fluid restriction, adjustment of total volume is recommended when administering acetylcysteine, to minimise the risk of hyponatraemia, seizure, and death.

Effects on ability to drive and use machines

Acetylcysteine is presumed to be safe since it is unlikely to produce an effect that may impair the patient's ability to concentrate and react and therefore not constitute a risk in the ability to drive and use machines.

Adverse effects

Intravenous administration of acetylcysteine, especially in the large doses needed to treat paracetamol overdose, may result in nausea, vomiting and other gastrointestinal symptoms. Hypersensitivity reactions have been reported following intravenous administration of acetylcysteine. Bronchospasm may occur in

[†] *Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.*

conjunction with a generalised anaphylactoid reaction. The symptoms of the anaphylactic-like reaction to acetylcysteine include airway obstruction (bronchospasm), angioedema, dyspnoea, hypotension, shock, tachycardia, urticaria, and injection site reaction (including rash). These reactions occur most commonly either during, or at the end of the period of the loading dose infusion, and may in fact be dose related. Since these anaphylactic-like reactions usually occur following the loading dose, careful monitoring is recommended.

There have been rare instances of death.

The following adverse effects have been reported:

Blood and lymphatic system disorders: Thrombocytopenia

Immune system disorders: Anaphylactoid reaction

Metabolism and nutrition disorders: Acidosis

Psychiatric disorders: Anxiety

Nervous system disorders: Syncope, generalized seizure

Eye disorders: Blurred vision, eye pain

Cardiac disorders: Cyanosis, tachycardia, bradycardia, cardiac arrest, extrasystoles

Vascular disorders: Flushing, hypotension, hypertension, vasodilation

Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory arrest, bronchospasm, coughing, stridor

Gastrointestinal disorders: Vomiting, nausea

Hepatobiliary disorders: Deterioration of liver function

Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash (erythematous and maculopapular), sweating, oedema periorbital

Musculoskeletal and connective tissue disorders: Arthralgia

General disorders and administration site conditions: Malaise, rigors, injection site reaction, chest pain, facial pain, face oedema

Investigations: Raised temperature

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

Interactions

Interactions with other medicines

No information is available on the interaction of acetylcysteine with other medicines.

Effects on laboratory tests

Acetylcysteine may cause a false-positive reaction with reagent dipstick tests for urinary ketones.

Overdosage

Symptoms

Symptoms following overdosage with acetylcysteine have been similar to those of anaphylactoid reactions noted under "**Adverse Effects**", but they may be more severe. Hypotension appears to be especially prominent. There is also a theoretical risk of hepatic encephalopathy.

Treatment

There is no specific treatment. General supportive measures should be carried out.

It has been suggested that generalised reactions to acetylcysteine can be treated with intravenous injection of an antihistamine, and infusion of acetylcysteine should be temporarily stopped but can be restarted at a slower rate without further reaction.

In case of overdose, immediately contact the Poisons Information Centre for advice on management. (In New Zealand call 0800 764 766).

Pharmaceutical precautions

Store below 25°C. Protect from light.

Medicine classification

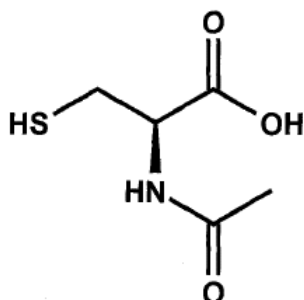
Prescription Medicine.

Package quantities

DBL™ Acetylcysteine Injection Concentrate is supplied in ampoules of 10 mL (acetylcysteine 200 mg/mL) for intravenous administration. It is available in packs of 10 ampoules.

Further information

The chemical structure of acetylcysteine is shown below:



The chemical name of acetylcysteine is (2R)-2-(acetylamino)-3-sulphanylpropanoic acid. Molecular Formula: C₅H₉NO₃S. Molecular Weight: 163.2. CAS Registry Number: 616-91-1. Acetylcysteine is a white, crystalline powder with a slight acetic odour. It is soluble in water and alcohol and practically insoluble in chloroform, dichloromethane and ether.

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