

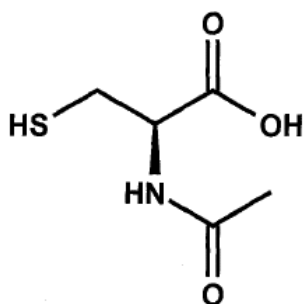
ACETADOTE[®] INJECTION

NAME OF THE MEDICINE

Acetylcysteine

Chemical Name: (2R)-2-(acetylamino)-3-sulphonylpropanoic acid.

Structural Formula:



Molecular Formula: C₅H₉NO₃S

Molecular Weight: 163.2

CAS Registry Number: 616-91-1

DESCRIPTION

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.

Acetadote[®] Injection contains acetylcysteine, Water for Injections and sodium hydroxide for pH adjustment.

PHARMACOLOGY

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.

Pharmacodynamics

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.

CLINICAL STUDIES

Observational Study – paediatric patients

An open-label, observational study conducted in the greater Newcastle area, New South Wales, Australia, documented treatment for paediatric patients who presented with a paracetamol overdose during a 16 year period from January 1987 to January 2003. This study was primarily considered a safety study.

Data from 148 paediatric patients, with an age range of 2 months to 15 years (this corresponds to 186 cases) were evaluated. Twenty three (23) out of 148 paediatric patients were given intravenous acetylcysteine treatment on at least one admission. Of these, 14 paediatric patients in the age group 12 to < 16 years (9.5% of the group), received acetylcysteine within 8 hours of ingesting paracetamol on at least one admission. There was a delay of at least 8 hours for 9 paediatric patients in this age group (6.1% of the group). One other paediatric patient in the age group 2 to < 5 years of age (0.7% of the group), received acetylcysteine with a delay of at least 8 hours on at least one admission.

Of the 23 patients who received intravenous acetylcysteine treatment, 3 patients (13%) experienced an adverse reaction (anaphylactoid reaction, rash and flushing, transient erythema). There were no deaths of paediatric patients. None of the paediatric patients receiving intravenous acetylcysteine developed hepatotoxicity, whilst two patients not receiving intravenous acetylcysteine did develop hepatotoxicity. The number of paediatric patients examined in this study is too small to provide a statistically significant finding for efficacy, however, the results appear to be consistent to those observed in adults.

Safety Study

A randomized, open-label, multi-centre clinical study was conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the intravenous acetylcysteine loading dose. One hundred and nine subjects were randomized to a 15 minute infusion rate and 71 subjects were randomized to a 60 minute infusion rate. The loading dose was 150 mg/kg, followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. Of the 180 patients examined in this study, 27% were male and 73% were female. Ages ranged from 15 to 83 years, with the mean age being 29.9 years (+13.0).

Within the first 2 hours following intravenous acetylcysteine administration, 17% of all patients developed an anaphylactoid reaction (18% in the 15-minute treatment group; 14% in the 60-minute treatment group) (See PRECAUTIONS). A subgroup of 58 subjects (33 in the 15-minute treatment group; 25 in the 60-minute treatment group) was treated within 8 hours of paracetamol ingestion. No hepatotoxicity occurred

within this subgroup; however with 95% confidence, the true hepatotoxicity rates could range from 0% to 9% for the 15-minute treatment group and from 0% to 12% for the 60-minute treatment group.

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

Acetadote Injection should be used with caution in patients with 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. Acetadote Injection can be used satisfactorily with silicone rubber and plastic.

Effects on 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.

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 fetus.

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 fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

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.

Use in Children

While the safety and effectiveness of Acetadote Injection in children has not been established, there is some limited clinical data in the use of acetylcysteine injection in children. (See also CLINICAL STUDIES).

No paediatric specific adverse reactions 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 Acetadote Injection in the elderly has not been established.

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 minimize 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 minimize the risk of of hyponatraemia, seizure and death.

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.

Genotoxicity

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.

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 acetylcysteine 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.

Interactions with Other Medicines

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

Effect on Laboratory tests

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

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 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 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 associated with the use of intravenous acetylcysteine.

Adverse reactions reported are summarized in the table below.

	<i>Adverse Event</i>
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Anaphylactoid reaction
Metabolism and nutritional disorders	Acidosis
Psychiatric disorders	Anxiety
Nervous system disorders	Syncope, generalised 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 macula-papular), 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 electrocardiograph (ECG) changes have been noted in patients with paracetamol poisoning irrespective of the treatment given. Monitoring of plasma potassium concentration is therefore recommended.

DOSAGE AND ADMINISTRATION

To be most effective in protecting against liver damage, therapy with Acetadote should be started within 10 hours of paracetamol ingestion. Although the role of Acetadote 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** of paracetamol ingested and the time of ingestion. Hepatic necrosis is preventable if treatment can be instituted within 10 to 12 hours of paracetamol ingestion.

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

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

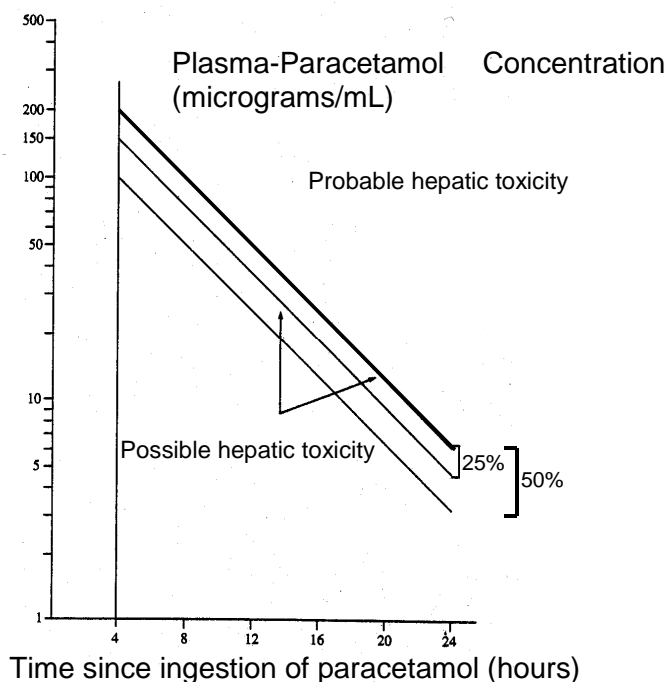
A. Patient presenting within 15 hours of ingestion

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 micrograms/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 the 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 Acetadote Injection.

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. Acetadote Injection may be beneficial in patients presenting later than 15 hours after ingestion. The use of Acetadote Injection 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

Acetadote Injection should be administered if appropriate (see A and B above). Acetadote Injection should be diluted in 5% glucose solution ~~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

Acetadote Injection 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~~ solution 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~~ solution 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~~ solution over the next 16 hours.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2° to 8°C for not more than 24 hours.

Acetadote Injection intravenous infusion dosage guide

Acetadote Injection is supplied in vials containing 30 mL of 200 mg/mL acetylcysteine for intravenous administration. **While the concentration of acetylcysteine in Acetadote Injection is exactly the same as in other acetylcysteine injectable products, each vial does contain three times the quantity of the active ingredient; that is, 6 g in 30 mL for Acetadote Injection, as compared to 2 g in 10 mL for other acetylcysteine injectable products.**

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

Note - The color of Acetadote may turn from essentially colorless to a slight pink or purple once the stopper is punctured. The color change does not affect the quality of the product.

The following table is intended as a guide on the volume (mL) of Acetadote Injection 200 mg/mL that is required to be added to 5% glucose ~~or 0.9% sodium chloride~~ solution 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 Acetadote Injection 200 mg/mL that should be added to 5% glucose ~~or 0.9% sodium chloride~~ solution 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 Acetadote Injection to be added to 200 mL of 5% glucose or 0.9% sodium chloride solution. Infusion over 15 to 60 minutes	SECOND INFUSION Volume (mL) of Acetadote Injection to be added to 500 mL of 5% glucose or 0.9% sodium chloride solution. Infusion over 4 hours	THIRD INFUSION Volume (mL) of Acetadote Injection to be added to 1000 mL of 5% glucose or 0.9% sodium chloride solution. Infusion over 16 hours	TOTAL Volume (mL) of Acetadote Injection Given over 20-21 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 Acetadote Injection in millilitres will be:

Initial infusion: 0.75x mL of Acetadote Injection 200 mg/mL to be added to 200 mL of 5% glucose

~~or~~
~~0.9% sodium chloride~~ solution

Second infusion: 0.25x mL of Acetadote Injection 200 mg/mL to be added to 500 mL of 5% glucose

~~or~~
~~0.9% sodium chloride~~ solution

Third infusion: 0.5x mL of Acetadote Injection 200 mg/mL to be added to 1000 mL of 5% glucose
~~or~~
~~0.9% sodium chloride~~ solution
Total: 1.5x mL of Acetadote Injection 200 mg/mL given over 20-21 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.

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.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Acetadote Injection is a clear, colourless, sterile, pyrogen free aqueous solution of acetylcysteine (N-acetyl-mercapto-alanine) with a pH of approximately 6.0 to 7.5.

Acetadote Injection is supplied in vials containing 6g of acetylcysteine in 30 mL (acetylcysteine 200 mg/mL) for intravenous administration. It is available in packs of 4 vials.

AUST R number 159242
Phebra code: INJ159

Acetadote Injection is intended for intravenous administration, following dilution in 5% glucose ~~or 0.9% sodium chloride~~ solution.

Each vial contains acetylcysteine 6 g in 30mL. **While the concentration of acetylcysteine in Acetadote Injection is exactly the same as in other**

acetylcysteine injectable products, each vial does contain three times the quantity of the active ingredient; that is, 6 g in 30 mL for Acetadote, as compared to 2 g in 10 mL for other acetylcysteine injectable products.

In addition, each vial contains the following inactive ingredients: sodium hydroxide (pH adjustment), and Water for Injections.

Product is for single use in one patient only. Discard any residue.

Store the unopened vial below 25°C. Protect from light.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

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DATE OF PREPARATION

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