TP Information on ANTIDOTES

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on

ANTIDOTES

Department of Medical Sciences, Ministry of Public Health

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FOREWORD

The *TP Information on Antidotes* has been initiated by the Thai Pharmacopoeia (TP) Committee with the intention to provide definitive and practical guidance on the use of antidotes to treat poisoning and drug overdose. It is aimed at assisting clinical toxicologists and all those involved in treatment and management of poisoning in the selection and administration of an appropriate antidote. The book covers antidote products which are available in the market or prepared extemporaneously in the pharmacy department. It offers their clinical uses, modes of action and detailed clinical information on routes of administration, contra-indications, warnings, precautions, and additional information. The text is complemented by information on proper handling of antidotes during storage and their stability to be aware of.

The success of the *TP Information on Antidotes* would not have been possible without the great efforts of the individual members from the Subcommittee on Drug Safety, the Subcommittee on Drug Stability and the Subcommittee on Editorial Style, under the supervision of the Thai Pharmacopoeia Committee. The committee is also indebted to the assistance and contributions from the following institutions: Ramathibodi Poison Center, Ramathibodi Hospital, Rajavithi General Hospital, Siriraj Hospital, Chulalongkorn Hospital, and the Food and Drug Administration.

PREFACE

The *TP Information on Antidotes* marks the first TP publication that compiles all evidence-based information on the treatment of poisoned patients with antidotes and therapeutic drugs. The book is designed to be used as a handy reference with a comprehensive index. The section of "Classification of Antidotes" is introduced to categorize the antidotes by their clinical uses and indications. The section of "Products" leads the reader through detailed information on administration and handling of about 40 antidotes arranged alphabetically.

For convenience of use, the relevant texts of general notices are reproduced with the kind permission of the Thai Pharmacopoeia Committee. When more in-depth information is required, the reader is encouraged to refer to the Thai Pharmacopoeia.

This book is expected to help the health care professionals to deliver the highest quality care to patients. Comments, criticisms, and suggestions are welcome for improvement in subsequent editions.

EDITORIAL BOARD

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GENERAL NOTICES

GENERAL NOTICES

Indication

A statement of indication usually is provided for each pharmaceutical product. It indicates the therapeutic purpose, clinical use and important information supporting rational use.

Strength(s) Available

Statements under the side-headings Strength or Strengths Available are included as a guide and are not necessarily comprehensive. For solid dosage forms such as Capsules and Tablets the strength is given as the amount of active ingredient in each unit. For liquid dosage forms such as Injections and semi-solid dosage forms such as Creams the strength is given as a concentration. For Powders for Injections the strength is given as the amount of active ingredient in each sealed container. Unless otherwise stated the strength is given in terms of the weight or concentration of the official medicinal substance used in making the formulation.

Doses

The statements given under "Dose" in the monographs of the Pharmacopoeia are primarily intended to serve only as a guide to the physician, who may vary it in the best interests of the patient and in accordance with the variables that affect the action of the drug.

The specific terms used to classify the age of the patients are as follows:

Adults: over 12 years of age
Adolescents: 12 to 15 years of age
Children: 1 to 12 years of age
Infants: 5 weeks to 1 year of age
Neonates: from newborn to 1 month of age

Unless otherwise specified, the route of administration is oral.

The statements of dosage in the case of Capsules and Tablets are expressed in terms of the content of active ingredient and seldom represent the total weight of the capsule contents or of the tablets.

In some instances, the dosage may be stated in terms of the pharmacologically active portion (moiety) of the molecule in order to permit the prescriber or dispenser to correlate the weight equivalent for salts, esters, or other chemical forms of the same drug moiety. However, it is not to be inferred that all chemical forms in which the active moiety may be presented are therapeutically equivalent.

Where the physician chooses to use the body surface area as a basis for the specified dose, the "Table of Body Surface Area from Height and Weight (m^2)" in Appendix 1.17 may be employed to simplify the calculation of square meters of body surface.

The dose given in each monograph is that which may ordinarily be expected to produce in the patients with normal renal/hepatic function, following administration in the manner indicated, at such time intervals as may be stated, the diagnostic, therapeutic or prophylactic effect for which the monograph is recognized.

Contra-indication

This section specifies those conditions in which the drug should NOT be used.

Warning and Precaution

Warnings of the possible risk of certain hazards from the use of a drug are to be observed and taken care of before prescribing or administering it to a patient. Caution and careful consideration on the drug's benefits and risk ratio should therefore be contemplated on an individual basis prior to the decision to use it.

On the other hand, important notes to be observed and carefully followed during and after the administration of a drug are described under the heading "Precaution".

Only the more important warnings and precautions are selected and included under the headings "Warning" and "Precaution" on the basis of their common or usual clinical significance to the population as a whole and it should not be assumed that the omission of a warning or a precaution in any particular monograph means that warning or precaution may not be of clinical significance for a specific patient.

Additional Information

The specific route of administration to be used for a particular drug, any pertinent personal observation or care on the part of the patient himself, and other special relevant information concerning an individual drug are to be grouped under the heading "Additional information".

Packaging and Storage

The substances and preparations described in the Pharmacopoeia are stored in such a way as to prevent contamination and, as far as possible, deterioration. Precautions that should be taken in relation to the effects of the atmosphere, moisture, heat, and light are indicated, where appropriate, in the monographs.

CONTAINERS

The container is the device that holds the substance, either in the form of the raw material or of the finished dosage-form preparation. The closure of the container, including the stopper, the cap, the attached dropper, etc., is considered as a part of the container.

The *immediate container* is the one which is in direct contact with the substance.

The container should be cleaned before use, and no extraneous matter should be introduced into it or into the substance placed in it. It must, likewise, not interact physically or chemically with the substance which it holds so as to alter the latter's quality, purity, or therapeutic potency to a level below its Pharmacopoeial requirements.

1. **Well-closed container**

A well-closed container must protect the contents from extraneous matter or from loss of the substance under ordinary or customary conditions of handling, shipment, storage, or sale.

2. **Tightly closed container**

A tightly closed container must protect the contents from contamination by extraneous matter or moisture, from loss of the substance, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, or

sale, and shall be capable of tight reclosure. Where a tightly closed container is specified, it may be replaced by a hermetically closed container for a single-dose of the substance.

3. Hermetically closed container

A hermetically closed container must be impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, or sale.

4. Light-resistant container

A light-resistant container is the one which prevents transmission of light, such as an opaque container or a bottle of black, dark red or dark brown glass.

5. Single-unit container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labelled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

6. Single-dose container

A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labelled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labelled.

7. Multiple-unit container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

8. Multiple-dose container

A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

9. Tamper-evident container

A tamper-evident container is a closed container fitted with a device that reveals irreversibly whether the container has been opened.

STORAGE

The following expressions are used in monographs under Packaging and storage with the meaning shown.

Protected from light means that the product is to be stored either in a light-resistant container or in a container enclosed in an outer cover that provides such protection or stored in a place from which all such light is excluded.

Protected from moisture means that the product is to be stored in a tightly closed container. Care is to be taken when the container is opened in a damp atmosphere. A low moisture content may be maintained, if necessary, by the use of a desiccant in the container provided that direct contact with the product is avoided.

Storage Temperatures

When special conditions of storage are necessary, including limits of temperature, they are prescribed in the monograph. Where, in a monograph, the storage conditions are mentioned using the general expressions "at room temperature", "in a cold place", and the like, these terms are generally defined as follows.

Freezing temperature Any temperature not higher than –10°. An article for which storage at Freezing temperature is directed may, alternatively, be stored in a freezer, unless otherwise specified in the individual monograph.

Very cold temperature Any temperature above –10° but not higher than 8°. A *refrigerator* is a very cold place in which the temperature is maintained thermostatically between 2° and 8°.

Cold temperature Any temperature above 8° but not higher than 16°.

Cool temperature Any temperature above 16° but not higher than 23°.

Room temperature Any temperature above 23° but not higher than 35°.

Controlled room temperature A temperature maintained thermostatically (30° ± 2°) that encompasses the usual and customary working environment of 23° to 35°; that results in a mean kinetic temperature calculated to be 30°.

Hot temperature Any temperature above 35° but not higher than 40°.

Very hot temperature or Excessive heat Any temperature higher than 40°.

Storage Under Nonspecific Conditions

For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution include protection from moisture, freezing and excessive heat.

CLASSIFICATION OF ANTIDOTES

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PRODUCTS

ACETYLCYSTEINE INJECTION or GRANULE FOR ORAL SOLUTION or EFFERVESCENT TABLETS

(*N*-Acetylcysteine, NAC)

Indication Antidote to paracetamol overdose.

Acetylcysteine is indicated in the treatment of paracetamol overdose to protect against hepatotoxicity.

Strengths available Injection: 100 mg per ml.
Granule: 100 and 200 mg.
Effervescent tablets: 600 mg.

Dosage and administration

Oral, 140 mg per kg of body weight followed by 17 doses of 70 mg per kg of body weight every 4 hours or until paracetamol assay reveals nontoxic levels.

Intravenous, 300 mg per kg of body weight administered over 20 hours and 15 minutes, divided as follows:

Initial loading dose, 150 mg per kg of body weight in up to 200 ml of 5 per cent dextrose injection, administered over 15 minutes.

Second infusion, 50 mg per kg of body weight in 500 ml of 5 per cent dextrose injection, administered over 4 hours.

Third infusion, 100 mg per kg of body weight in 1000 ml of 5 per cent dextrose injection, administered over the next 16 hours.

For oral solution: Dissolve the granule or effervescent tablets in soft drink to a final concentration of 5 per cent. If administered via gastric tube, water may be used as the diluent.

Warning

1. It should be used with caution in elderly patients with severe respiratory insufficiency and in patients with asthma or conditions predisposing to gastro-intestinal hemorrhage (such as esophageal varices and peptic ulcer).

2. It may cause bronchospasm, stomatitis, severe rhinorrhea, drowsiness, clamminess, nausea, vomiting, chills, fever, and hemoptysis.

3. With intravenous administration, anaphylactoid reactions (flushing, rash, angio-edema, hypotension and bronchospasm) may occur.

Precaution Discontinuation of acetylcysteine therapy should be considered if generalized urticaria or other symptoms of an allergic reaction occur and cannot be controlled by other means.

Patient monitoring The following are recommended:

1. The plasma paracetamol concentration, not less than 4 hours following ingestion of the overdose. Concentrations determined prior to this time are not reliable for assessing potential hepatotoxicity.

2. Liver function tests (serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), prothrombin time, and bilirubin), to detect hepatotoxicity, at 24-hour intervals for at least 96 hours postingestion. If no abnormalities are detected within 96 hours, further determinations are not needed.

3. Renal and cardiac function, monitored and appropriate therapy instituted if necessary.

Additional information

1. An initial dose of acetylcysteine should be administered immediately (within 24 hours), without waiting for the results of paracetamol determinations or other laboratory tests.

2. If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, repeat that dose.

3. Acetylcysteine solution must be diluted prior to oral administration because of its unpleasant odour and its irritating or sclerosing properties. Dilution may also reduce the risk of vomiting.

Packaging and storage Acetylcysteine Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light and stored at a temperature not exceeding 30°.

Granule for Oral Solution and Effervescent Tablets shall be kept in tightly closed containers or moisture-proof packs and may require the use of separate packages containing water-absorbent agents, such as silica gel.

Stability After exposure to air, the solution should be stored between 2° and 8°to retard oxidation and should be used within 4 hours.

AMYL NITRITE INHALATION SOLUTION

Indication Antidote to cyanide poisoning (adjunctive therapy).

Amyl nitrite is used as an adjunct in the treatment of cyanide poisoning. Nitrite ions react with hemoglobin to form methemoglobin, which combine with cyanide to form nontoxic cyanmethemoglobin.

Strengths available 0.18 and 0.3 ml per ampoule.

Dosage and administration

Inhalation, as necessary, administered for 30 to 60 seconds every 5 minutes until the patient is conscious, then repeated at longer intervals for 24 hours. (Onset: 30 seconds, Duration: 3 to 5 minutes).

Contra-indication It is contra-indicated in patients hypersensitive to nitrates.

Warning

1. It should be used with caution in patients with severe anemia, recent head trauma or cerebral hemorrhage, early myocardial infarction, hyperthyroidism, and glaucoma.
2. It may cause hemolytic anemia, severe headache, dizziness, weakness, restlessness, orthostatic hypotension, tachycardia, flushing of face and neck, sweating, nausea, vomiting, and skin rash.
3. High doses of nitrates may cause methemoglobinemia, especially

in individuals with methemoglobin reductase deficiency or other metabolic abnormality that interferes with the normal conversion of methemoglobin back to hemoglobin.

4. Tolerance and cross-tolerance with other nitrates may develop with repeated use over prolonged periods of time.

5. Caution should be exercised when it is to be used concomitantly with other hypotension-producing medications, alcohol, norepinephrine, and sympathomimetics (such as phenylephrine, ephedrine, or epine phrine).

6. Risk-benefit should be considered if it is to be used in pregnant or nursing women. Safety and efficacy for use in children have not been established.

Precaution It should be discontinued if blurred vision or dry mouth occurs.

Patient monitoring The following is recommended:

Blood pressure and cardiac function monitoring, at periodic intervals in patients using amyl nitrite regularly.

Additional information Amyl nitrite is very flammable. Do not use where it may be ignited.

Packaging and storage Amyl Nitrite Inhalation Solution shall be kept in tightly closed, unit-dose glass containers, wrapped loosely in gauze or other suitable material, protected from light and stored at a temperature between 8° and 15° .

ATROPINE SULFATE INJECTION

Indication Antidote to cholinesterase inhibitors, organophosphate or carbamate pesticides, and muscarine poisoning.

Atropine is indicated in the treatment of poisoning from cholinesterase inhibitors such as neostigmine, pilocarpine,

physostigmine, and methacholine, and in the treatment of the rapid type of mushroom (muscarine) poisoning. Atropine is also indicated in the treatment of poisoning caused by pesticides that are organophosphate cholinesterase inhibitors, chemical warfare, and "nerve" gases. In case of organophosphate cholinesterase inhibitors intoxication, 2-PAM must be administered immediately following atropine treatment (See dosage of 2-PAM under *Pralidoxime Chloride for Injection*, p. 72.).

Strengths available 0.6 and 1 mg per ml.

Dosage and administration

Adults—

Antidote to cholinesterase inhibitors: *Intravenous*, 2 to 4 mg initially, then 2 mg repeated every 5 to 10 minutes until muscarinic symptoms disappear or signs of atropine toxicity appear.

Antidote to muscarine in mushroom poisoning: *Intramuscular* or *intravenous*, 1 to 2 mg every hour until respiratory effects subside.

Antidote to organophosphate or carbamate pesticides: *Intramuscular* or *intravenous*, 1 to 2 mg, repeated in 20 to 30 minutes until muscarinic symptoms disappear or signs of atropine toxicity appear. Continue the dosage until definite improvement occurs and is maintained, sometimes for 2 days or more.

Children—

Antidote to cholinesterase inhibitors: *Intravenous* or *intramuscular*, 1 mg initially, then 0.5 to 1 mg every 5 to 10 minutes until muscarinic symptoms disappear or signs of atropine toxicity appear.

Contra-indication It is contra-indicated in narrow-angle glaucoma, pyloric or intestinal obstruction, intestinal atony of the elderly, paralytic ileus, asthma, achalasia (megaesophagus), prostatic hypertrophy, frank bladder neck obstruction, acute hemorrhage with unstable cardiovascular status, myasthenia gravis or hypersensitivity to any component of belladonna alkaloids.

Warning

1. Adults and children with Down's syndrome may develop increased susceptibility to atropine.
2. It should be used with caution in patients with cardiovascular disease, brain damage in children, autonomic neuropathy, renal or hepatic function impairment, hyperthyroidism, hiatal hernia, ulcerative colitis, urinary retention, reflux esophagitis, fever, or in those who are being treated with antihistamines, benzodiazepines, phenothiazines or other CNS depressants, monoamine oxidase inhibitors or other antidepressants, sympathomimetics, corticosteroids, digoxin, or other anticholinergics.
3. Infants and young children are especially susceptible to the toxic effects of anticholinergics.
4. Geriatric patients, particularly over the age of 60, frequently develop increased sensitivity to anticholinergic drugs. Thus, excitement, agitation, drowsiness, confusion, hallucination, blurred vision,tinnitus, dryness of skin and mouth, constipation, and/or urinary retention are more likely to occur, and lower doses may be required in those patients.
5. It may impair mental and/or physical abilities required for the performance of potentially hazardous tasks. The patients should observe caution while driving or performing other tasks requiring alertness.

Precaution

1. Close supervision is recommended for infants and children with spastic paralysis or brain damage, chronically ill patients, elderly; dosage adjustments are often required.
2. In dehydrated patients, such as those with diarrhea and vomiting, treatment with atropine should be initiated at a lower dosage.

Patient monitoring The following is recommended:

Intra-ocular pressure determinations, at periodic intervals. Atropine may increase the intra-ocular pressure by producing mydriasis.

Additional information

1. The intravenous injection of atropine should be administered slowly.

2. Doses of 0.5 to 1 mg of atropine are mild CNS stimulant. Larger doses may produce mental disturbances; very large doses have depressant effect.

3. The fatal dose of atropine in children may be as low as 10 mg.

Packaging and storage Atropine Sulfate Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass and protected from light.

BENTONITE ORAL SUSPENSION

Indication Antidote to paraquat poisoning (adsorbent).

Dosage and administration

Bentonite Oral Suspension should be freshly prepared from: Bentonite 7.0 g, Glycerol 20.0 ml, Paraben concentrate. 1.0 ml, Purified water to 100.0 ml.
(Paraben concentrate is a solution of 10 per cent w/v Methylparaben and 2 per cent w/v Propylparaben in Propylene Glycol)

Oral, 200 to 500 ml of a 7 per cent w/v suspension administered via a gastric tube every 2 hours for 3 doses, in association with 5 per cent w/v magnesium sulfate or mannitol to promote diarrhea and empty the gut.

Packaging and storage Bentonite Oral Suspension shall be kept in tightly closed containers.

BENZTROPINE MESYLATE INJECTION

Indication Antidote to relief parkinsonian signs induced by antipsychotics.

Benztropine is an antidyskinetic. It is indicated in the control of extrapyramidal disorders (*except tardive dyskinesia*) due to central nervous

system (CNS) drugs such as reserpine, phenothiazines, dibenzoxazepines, thioxanthenes, and butyrophenones.

Strength available 1 mg per ml.

Dosage and administration

Adults: *Intramuscular* or *intravenous*, 1 to 4 mg one or two times a day (Onset: within a few minutes. Duration: 24 hours.)

The maximum total dose should not exceed 6 mg daily.

Children 3 years of age and over: Dosage must be individualized by the physician.

Contra-indication It is contra-indicated in closed-angle glaucoma.

Warning

1. Concomitant administration of benztropine with drugs possessing anticholinergic effects may cause paralytic ileus that is sometimes fatal.
2. It should be used with caution in patients with cardiac arrhythmia, hypertension, hepatic impairment, glaucoma, tardive dyskinesia, mental disorder, gastro-intestinal obstruction, myasthenia gravis, genito-urinary retention, prostatic hypertrophy or renal function impairment.
3. Geriatric patients may be more sensitive to the effects of the usual adult dose.
4. When an antidyskinetic is to be discontinued, dosage should be reduced gradually.

Patient monitoring The following is recommended:

Intra-ocular pressure, at periodic intervals during therapy, especially in patients with angle-closure and open-angle glaucoma.

Additional information The need for benztropine should be re-evaluated after 1 to 2 weeks of therapy.

Packaging and storage Benztropine Mesylate Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, and stored at a temperature not exceeding 30°; avoid freezing.

BENZTROPINE MESYLATE TABLETS

Indication Antidote to relief parkinsonian signs induced by antipsychotics.

Benztropine is an antidyskinetic. It is indicated in the control of extrapyramidal disorders *(except tardive dyskinesia)* due to central nervous system (CNS) drugs such as reserpine, phenothiazines, dibenzoxazepines, thioxanthenes, and butyrophenones.

Strengths available 0.5, 1 and 2 mg.

Dosage and administration

Adults: *Oral*, 1 to 4 mg once or twice a day. Or, 1 to 2 mg two or three times a day if drug-induced extrapyramidal reactions develop soon after initiation of treatment with neuroleptic drugs (Onset: 1 to 2 hours. Duration: 24 hours.)

Children 3 years of age and over: Dosage must be individualized by the physician.

Contra-indication; Warning; Patient monitoring; Additional information See under *Benztropine Mesylate Injection*, p. 23.

Packaging and storage Benztropine Mesylate Tablets shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

BROMOCRIPTINE MESYLATE TABLETS

Indication Treatment of neuroleptic malignant syndrome caused by neuroleptic drugs (adjunctive therapy).

Neuroleptic malignant syndrome is resulted from the depletion of dopamine or blockade of dopamine receptors in the nigrostriatal, hypothalamic and mesolimbic cortical pathways. Bromocriptine stimulates these dopamine receptors. Thus, relieve the symptoms.

Strength available 2.5 mg.

Dosage and administration

Adults: Initial, 5 mg once a day taken at bedtime with a snack; dosage adjustment according to patient response by 2.5-mg increments a day as needed, taken in divided doses with meals or at bedtime with a snack.

Maintenance, up to 20 mg a day taken in divided doses with meals or at bedtime with a snack. (Onset: 30 to 90 minutes.)

The maximum total dose should not exceed 20 mg a day.

Warning

1. It should be used with caution in patients sensitive to ergot alkaloids or with hypertension or pregnancy-induced hypertension and psychiatric disorders.
2. It may cause confusion, dyskinesia, hallucinations, myocardial infarctions, seizures, strokes, sudden weakness, hypotension (especially orthostatic hypotension) and nausea.
3. High doses of bromocriptine may cause cerebrospinal fluid rhinorrhea, fainting, gastro-intestinal hemorrhage or peptic ulcer, retroperitoneal fibrosis, constipation, diarrhea, drowsiness or tiredness, dry mouth, leg cramps at night, loss of appetite, mental depression, Raynaud's phenomenon, stomach pain, stuffy nose, and vomiting.
4. Caution should be exercised when it is to be used concomitantly with alcohol.
5. Concurrent use of bromocriptine with levodopa, ritonavir, clarithromycin or erythromycin or troleandomycin and hypotension-producing medications will potentiate the effect of each other. Dosage adjustments are necessary.
6. It should not be administered to mothers who intend to breast-feed, since it interferes with lactation.

Packaging and storage Bromocriptine Mesylate Tablets shall be kept in tightly closed containers, protected from light and stored at a temperature not exceeding 30°.

CALCIUM POLYSTYRENE SULFONATE POWDER

Indication Antihyperkalemic.

Calcium polystyrene sulfonate is indicated in the treatment of hyperkalemia associated with anuria and severe oliguria.

Dosage and administration

Adults: *Oral*, 15 g three or four times a day. The resin given by mouth as a suspension in a small amount of water (3 to 4 ml per g of resin), or it may be mixed with some sweetened vehicle (but not fruit juices, which contain potassium).

Rectal, in case of vomiting or upper gastro-intestinal problems, including paralytic ileus. The resin may be given rectally as a suspension of 30 g of resin in 150 ml of water or 10 per cent dextrose in water, as a daily retention edema.

The enema should, if possible, be retained for at least 9 hours following which the colon should be irrigated to remove the resin. If both routes are used initially, it is probably unnecessary to continue rectal administration once the oral resin has reached the rectum.

Children: *Oral*, lower dose should be used; 1 mmol potassium per g of resin.

Initial dose: 1 g per kg of body weight daily in divided doses.

Maintenance dose: 0.5 g per kg of body weight daily in divided doses.

Rectal, resin may be given rectally using a dose at least as great as that which would be given orally, diluted in the same ratio as described for adults.

Neonate: Should not be given by the oral route.

Rectal, 0.5 to 1 g per kg of body weight would be employed.

Contra-indication It is contra-indicated in patients with obstructive bowel disease and conditions associated with hypercalcemia (e.g. hyperparathyroidism, multiple myeloma, sarcoidosis or metastatic carcinoma).

Warning

1. It may cause gastric irritation, anorexia, nausea, vomiting, fecal impaction, intestinal obstruction, hypokalemia, and hypercalcemia.
2. Caution should be exercised when it is to be used concomitantly with aluminium hydroxide and digoxin.

Precaution

1. In the event of clinically significant constipation, treatment should be discontinued until normal bowel movement has resumed. Magnesium containing laxatives should not be used.
2. With oral administration, care should be taken to avoid aspiration, which may lead to bronchopulmonary complication.
3. Since effective lowering of serum potassium with calcium resin may take hours to days, treatment with this drug alone may be insufficient to rapidly correct severe hyperkalemia.

Patient monitoring The following are recommended:

1. Serum calcium level, to detect the early development of hypercalcemia, weekly intervals. The dose of resin is adjusted to prevent hypercalcemia and hypokalemia.
2. Serum magnesium levels, to detect hypomagnesemia.

Additional information Treatment with calcium polystyrene sulfonate may be discontinued when the serum potassium concentrations have been reduced to 5 mEq (mmol) per litre.

Packaging and storage Calcium Polystyrene Sulfonate Powder shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

CHARCOAL ORAL POWDER, ACTIVATED

Indication Nonspecific antidote (adsorbent).

Activated charcoal adsorbs the toxic substance ingested, thus inhibiting gastro-intestinal absorption. It also adsorbs many toxic irritants that cause diarrhea and gastro-intestinal discomfort and its antiflatulent effect is resulted from the absorption of intestinal gas.

Not to be used in the treatment of poisoning caused by caustic alkalis, boric acid, lithium, petroleum distillates (e.g. kerosene, gasoline, coal oil, fuel oil, paint thinner, cleaning fluid), ethanol, methanol, iron salts, and mineral acids.

Dosage and administration

Initial dose, 1 g per kg of body weight or 25 to 100 g orally or via gastric tube (as a slurry in water) or if the quantity of toxin ingested is known, 10 times the amount of ingested toxin by weight is given.

Repeat-dose, 0.25 to 0.5 g per kg of body weight (15 to 30 g) every 2 to 4 hours is given orally or by gastric tube.

Following administration of activated charcoal, it is recommended that a cathartic be administered to enhance removal of the drug-charcoal complex since failure to excrete the drug-charcoal complex promptly may result in enhanced toxicity. When multiple doses of activated charcoal are required, administration of a small dose of cathartic with every second or third charcoal dose is recommended. Do not use cathartic with every activated charcoal dose.

Warning

1. It should be used with caution in patients with absence of bowel sounds.
2. It may cause swelling of abdomen or pain and black stools.
3. The effectiveness of oral acetylcysteine and other oral medications may be decreased when used concurrently with activated charcoal.
4. Chocolate syrup or ice cream or sherbet should not be used as vehicles for the administration of activated charcoal since they will decrease the adsorptive capacity of the activated charcoal.

5. When both ipecac and activated charcoal are to be used in the treatment for oral poisoning, it is generally recommended that the charcoal be administered only after vomiting has been induced and completed.

Additional information

1. Activated charcoal is most effective when it is administered early in acute poisoning, preferably within 30 minutes following ingestion of the poison.
2. Tablets or granules of activated charcoal are less effective than the powder form of the medication and should not be used in the treatment of poisoning.

Packaging and storage Activated Charcoal Oral Powder shall be kept in well-closed containers.

DANTROLENE SODIUM CAPSULES

Indication Treatment of malignant hyperthermia crisis (adjunctive therapy).

Dantrolene sodium is indicated, along with appropriate supportive measures, to reverse the symptoms of the malignant hyperthermic crisis syndrome occurring during or following surgery or anesthesia. It is indicated for administration prior to surgery or anesthesia to prevent or attenuate the symptoms of the malignant hyperthermic crisis syndrome in patients known or suspected to be at risk for this complication. It is also used to relieve the symptoms of neuroleptic malignant syndrome, which are similar to those caused by malignant hyperthermia.

Strengths available 25, 50 and 100 mg.

Dosage and administration

Adults—Prophylaxis: *Oral*, 4 to 8 mg per kg of body weight daily in 3 to 4 divided doses for 1 to 2 days prior to surgery. The last dose should be

given 3 to 4 hours prior to scheduled surgery with a minimum of water.

Therapeutic: *Oral*, (as a follow-up to intravenous therapy) 4 to 8 mg per kg of body weight daily in 4 divided doses for 1 to 3 days.

Warning

1. It should not be used in nursing mothers.
2. It should be discontinued if a patient develops symptoms of hepatitis during therapy. If hepatic function test abnormalities without symptoms of overt hepatitis occur, the medication should probably be discontinued.
3. It should be discontinued if severe diarrhea recurs when therapy is resumed.
4. It should be used with caution in patients with cardiac, hepatic or pulmonary function impairment, pre-existing myopathy or neuromuscular disease predisposing to respiratory insufficiency.
5. It may cause diarrhea, respiratory depression, dizziness or lightheadedness, drowsiness, general feeling of discomfort or illness, muscle weakness, nausea or vomiting, unusual tiredness, abdominal or stomach cramps or discomfort.
6. Concurrent use of central nervous system (CNS) depression-producing medications with dantrolene may result in increased CNS depressant effects.
7. Concomitant administration of intravenous dantrolene sodium with calcium channel blockers may cause ventricular fibrillation and cardiovascular collapse associated with severe hypokalemia.
8. Risk-benefit should be considered if it is to be used in hepatitis, cirrhosis patients or pregnancy.

Patient monitoring The following are recommended:

1. Blood cell counts and renal function determinations, at periodic intervals during chronic therapy.
2. Hepatic function determinations, including serum alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), total bilirubin, and gammaglutamyl transpeptidase (GGTP), to detect baseline values and to identify

pre-existing hepatic dysfunction or disease, before initiation and at periodic intervals during chronic therapy.

Packaging and storage Dantrolene Sodium Capsules shall be kept in well-closed containers, protected from light and stored at a temperature not exceeding 30° .

DANTROLENE SODIUM FOR INJECTION

Indication Treatment of malignant hyperthermia crisis (adjunctive therapy).

Dantrolene sodium is indicated, along with appropriate supportive measures, to reverse the symptoms of the malignant hyperthermic crisis syndrome occurring during or following surgery or anesthesia. It is indicated for administration prior to surgery or anesthesia to prevent or attenuate the symptoms of the malignant hyperthermic crisis syndrome in patients known or suspected to be at risk for this complication. It is also used to relieve the symptoms of neuroleptic malignant syndrome, which are similar to those caused by malignant hyperthermia.

Strength available 20 mg.

Dosage and administration

Prophylaxis: *Intravenous infusion*, 2.5 mg per kg of body weight, administered over a 1-hour period prior to anesthesia.

Therapeutic: *Intravenous*, by continuous rapid push, at least 1 mg per kg of body weight, initially, with administration being continued until the symptoms subside or until the maximum cumulative dose of 10 mg per kg of body weight has been reached. Administration may be repeated if symptoms recur.

For intravenous administration, dissolve 20 mg of dantrolene sodium with 60 ml of sterile water for injection without a bacteriostatic agent and shake until the solution is clear. The solution will contain 0.33 mg per ml.

Warning; Patient monitoring See under *Dantrolene Sodium Capsules*, p. 30.

Additional information

1. It is incompatible with acidic solutions, including 5 per cent dextrose injection and 0.9 per cent sodium chloride injection. Acidic solutions should not be used for reconstituting the medication.
2. Extravasation of the intravenous solution into surrounding tissues should be avoided because of the high pH of the solution.

Packaging and storage Dantrolene Sodium for Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light and stored at a temperature not exceeding 30°.

Stability Reconstituted solutions should be protected from temperature below 15° or above 30° and from direct light; use within 6 hours.

DEFEROXAMINE MESYLATE FOR INJECTION

Indication Antidote to iron and aluminium poisoning (chelating agent).

Deferoxamine facilitates the removal of iron from the body in severe, acute iron poisoning. It is used as an adjunct to, not a substitute for, standard treatment measures. In chronic iron toxicity, it is indicated for promotion of iron excretion in patients who have an iron overload secondary to multiple transfusions associated with some chronic anemias, such as thalassemia, and in secondary hemochromatosis. Deferoxamine, administered intravenously or intraperitoneally, is used to treat aluminium-induced encephalopathy, osteomalacia, and aluminium overload in children and adults with chronic renal failure, but only those who are maintained with hemodialysis or continuous ambulatory peritoneal dialysis. It is also used to diagnose aluminium toxicity in patients with end-stage renal disease.

Strengths available 500 mg and 2 g.

Dosage and administration

Adults and children over 3 years of age—

Acute iron toxicity: *Intramuscular*, initially, 90 mg per kg of body weight, followed by 45 mg per kg of body weight, up to a maximum of 1 g per dose, every 4 to 12 hours; not to exceed 6 g per day. *Intravenous infusion*, 15 mg per kg of body weight per hour, up to a total of 90 mg per kg of body weight every 8 hours; not to exceed 6 g per day. The intravenous infusion rate should not exceed 15 mg per kg of body weight per hour.

Chronic iron toxicity: *Intramuscular*, 500 mg to 1 g a day. *Intravenous infusion*, in addition to intramuscular administration, 2 g infused at a rate not to exceed 15 mg per kg of body weight per hour. This is administered at the same time each unit of blood is transfused, but through a separate line. *Subcutaneous*, 1 to 2 g (20 to 40 mg per kg of body weight) a day administered over a period of 8 to 24 hours by means of a portable, continuous mini-infusion pump.

Aluminium toxicity: Dosage must be individualized; theoretically, 100 mg of deferoxamine can bind 4.1 mg of aluminium. [**Note**: In hemodialysis or hemofiltration patients with moderate aluminium toxicity and no concomitant iron toxicity, 1 g of deferoxamine once a week has been given by slow intravenous infusion during the last 2 hours of every third dialysis session. In peritoneal dialysis patients, 1 to 1.5 g of deferoxamine have been given in the dialysis fluid once or twice a week. However, it can also be given by slow intravenous infusion or by the intramuscular or subcutaneous route.]

Diagnosis of aluminium toxicity: *Intravenous infusion*, 1 g infused at a rate not to exceed 15 mg per kg of body weight per hour, preferably administered during the post-dialysis period, although administration during the last two hours of dialysis is acceptable.

The maximum total dose should not exceed 6 g in 24 hours.

Children up to 3 years of age—

Acute iron toxicity: *Intravenous infusion*, 15 mg per kg of body weight per hour.

Chronic iron toxicity: *Subcutaneous*, 10 mg per kg of body weight a day.

Diagnosis of aluminium toxicity: *Intravenous infusion*, 15 to 20 mg per kg of body weight, infused at a rate not to exceed 15 mg per kg of

body weight per hour; preferably administered during the post-dialysis period, although administration during the last two hours of dialysis is acceptable.

For intramuscular or subcutaneous: Add 5 ml of sterile water for injection to each 500-mg vial. The powder should be completely dissolved before administration.

For intravenous infusion: Add 5 ml of sterile water for injection to each 500-mg vial. The resulting solution should be further diluted in either 0.9 per cent sodium chloride injection, dextrose injection, or lactated Ringer's injection before infusion. Reconstituted solutions should be used within the time period specified by the manufacturer.

Contra-indication It is contra-indicated in patients with severe renal disease, except those on dialysis.

Warning

1. Deferoxamine therapy should be avoided in pregnant women, especially during the first trimester, or nursing women.
2. It should not be used in patients younger than 3 years of age with relatively small degrees of iron overload.
3. It should be used with caution in patients with impaired renal function, pyelonephritis and in children under 3 years of age.
4. Caution should be exercised when it is to be used concurrently with ascorbic acid in older patients with iron overload. Although small doses of ascorbic acid improve the chelating action and increase iron excretion, it may cause adult respiratory distress syndrome.
5. Rapid intravenous injection may cause flushing, urticaria, hypotension, and shock. Prolonged administration may cause allergic-type reactions, visual and auditory neurotoxicity.
6. Iron overload increases susceptibility of patients to *Yersinia enterocolitica*; this susceptibility may be enhanced by deferoxamine therapy.
7. It may exacerbate aluminium-related encephalopathy and precipitate seizures. Prophylactic treatment with anti-epileptics such as clonazepam has been suggested for patients judged to be at risk.

Patient monitoring The following are recommended:

1. Serum ferritin or serum iron concentrations, to adjust dose of deferoxamine in relation to iron burden, periodically. Serum iron concentrations more than 500 µg per dl indicate severe toxicity.
2. Iron excretion (urinary, 24-hour), for dosage adjustment and to determine duration of therapy, periodically.
3. Total iron-binding capacity (TIBC), before and after administration of deferoxamine. TIBC should not be relied upon as an indicator of acute iron overdose because it cannot provide information on the saturation of iron-binding proteins, and it may be falsely elevated.
4. Visual acuity tests, slit-lamp eye examinations, funduscopy, and audiometry, periodically during long-term deferoxamine therapy.
5. Serum aluminium concentrations, before and after administration of deferoxamine. A rise in serum aluminium concentration of more than 150 µg per litre, measured 18 to 48 hours after the baseline measurement, indicates aluminium toxicity.

Additional information

1. The deferoxamine-iron complex excreted by the kidney may colour the urine reddish brown.
2. A 100-mg quantity of deferoxamine mesylate can bind 8.5 mg of iron or 4.1 mg of aluminium.
3. The oral dose of 150 to 250 mg of ascorbic acid per day should be given when adequate concentrations of deferoxamine have been achieved, usually an hour or two after the deferoxamine infusion has been initiated.

Packaging and storage Deferoxamine Mesylate for Injection shall be kept in Containers for Sterile Solids as described under "Parenteral Preparations" (Appendix 1.16).

Stability Reconstituted solutions of Deferoxamine Mesylate for Injection are stable for 24 hours at a temperature not exceeding 25° when stored under sterile conditions and protected from light.

DIGOXIN - SPECIFIC ANTIBODIES (Fab FRAGMENT) FOR INJECTION

[Digoxin Immune Fab (Ovine)]

Indication Antidote to digitalis glycoside toxicity.

Digoxin immune Fab (ovine) is indicated for treatment of potentially life-threatening digoxin or digitoxin overdose (i.e., with severe arrhythmias or hyperkalemia).

Not to be used for milder cases of digitalis toxicity.

Strength available 38 mg.

Dosage and administration

After reconstitution, digoxin immune Fab (ovine) is administered by intravenous infusion, through a 0.22-µm membrane filter, over 30 minutes. If cardiac arrest is imminent, give as a bolus injection.

Dosage for acute ingestion of unknown amount—

Adults and children: *Intravenous*, 760 mg of digoxin immune Fab (ovine) may be administered, which will be adequate to treat most life-threatening ingestions.

Dosage for acute ingestion of known amount—

Adults and children: *Intravenous*, in an amount equimolar to the amount of digoxin or digitoxin in the patient's body [total body load (TBL)]. A dose of 38 mg of digoxin immune Fab (ovine) binds approximately 0.5 mg of digoxin or digitoxin.

Dosage may be determined by calculating from one of the following formulas or using Table 1, 2 or 3 for approximate dose

1. Based on dose of digoxin or digitoxin ingested.

For digoxin tablets, oral solution, or intramuscular injection:

$$\text{Dose (mg)} = \frac{\text{Dose ingested (mg)} \times 0.8}{0.5} \times 38$$

For digitoxin tablets, digoxin capsules, or intravenous injection of digoxin or digitoxin:

$$\text{Dose (mg)} = \frac{\text{Dose ingested (mg)}}{0.5} \times 38$$

2. Based on steady-state serum digoxin or digitoxin concentration (SDC)

For digoxin:

$$\text{Dose (mg)} = \frac{\text{SDC (ng/ml)} \times \text{body weight (kg)}}{100} \times 38$$

For digitoxin:

$$\text{Dose (mg)} = \frac{\text{SDC (ng/ml)} \times \text{body weight (kg)}}{1000} \times 38$$

Table 1 Approximate dose of digoxin immune Fab (ovine) when amount of digoxin ingested is known.

Number of digoxin Tablets or capsules ingested[1]	Dose of digoxin immune Fab (ovine)	
	mg	Number of 38-mg vials
25	380	10
50	760	20
75	1140	30
100	1520	40
150	2280	60
200	3040	80

[1]0.25-mg tablets with 80 per cent bioavailability, or 0.2-mg capsules.

Table 2 Approximate adult dose (number of 38-mg vials) of digoxin immune Fab (ovine) when serum digoxin concentration (SDC) is known.

SDC (ng/ml)	Number of 38-mg vials				
	Body weight				
	40 kg	60 kg	70 kg	80 kg	100 kg
1	0.5	0.5	1	1	1
2	1	1	2	2	2
4	2	3	3	3	4
8	3	5	6	7	8
12	5	7	9	10	12
16	7	10	11	13	16
20	8	12	14	16	20

Table 3 Approximate children dose (mg) of digoxin immune Fab (ovine) when serum digoxin concentration (SDC) is known.

SDC (ng/ml)	Dose of digoxin immune Fab (ovine) (mg)				
	Body weight				
	1kg	3 kg	5 kg	10 kg	20 kg
1	0.4	1	2	4	8
2	1	2	4	8	15
4	1.5	5	8	15	30
8	3	9	15	30	61
12	5	14	23	46	91
16	6	18	30	61	122
20	8	23	38	76	152

(Onset: reduction of free active serum digoxin or digitoxin, less than 1 minute; improvement in signs and symptoms of digitalis toxicity, 15 to 30 minutes after administration.)

For intravenous administration: dissolve 38 mg of digoxin immune Fab (ovine) with 4 ml of Sterile Water for Injection and mix gently, to produce a solution containing 9.5 mg per ml. The resulting solution may be further diluted with 0.9 per cent w/v sodium chloride injection to a convenient volume for administration by intravenous infusion.

Warning

1. It should be used with caution in patients with renal function impairment.
2. Skin-testing for allergy to digoxin immune Fab (ovine) may be performed prior to administration in high-risk patients (i.e., those previously treated with the Fab antibody or with known allergy, especially to sheep proteins). Either of the following methods may be used:

2.1 Intradermal test: Dilute 0.1 ml of the reconstituted solution (containing 9.5 mg of the Fab antibody per ml) in 9.9 ml of 0.9 per cent sodium chloride injection to produce 10 ml of a solution containing 95 μg (0.095 mg) per ml; then inject 0.1 ml (9.5 μg or 0.0095 mg) intradermally. After 20 minutes, inspect the injection site for presence of an urticarial wheal surrounded by a zone of erythema.

2.2 Scratch test: Dilute 0.1 ml of the reconstituted solution (containing 9.5 mg of the Fab antibody per ml) in 9.9 ml of 0.9 per cent sodium chloride injection to produce 10 ml of a solution containing 95 μg (0.095 mg) per ml; then place 1 drop of the solution on the skin and make a 1/4-inch scratch through the drop with a sterile needle. After 20 minutes, inspect the site for presence of an urticarial wheal surrounded by a zone of erythema. If a positive skin test occurs, use of digoxin immune Fab (ovine) should be avoided unless absolutely necessary.

3. It may cause allergic or febrile reactions.
4. Low cardiac output including congestive heart failure, hypokalemia, rapid ventricular response in patients with atrial fibrillation may occur as a result of withdrawal of the inotropic effects of digitalis.

Patient monitoring The following are recommended:

1. Body temperature and electrocardiogram (ECG), during treatment.
2. Serum concentrations of potassium, to detect hypokalemia, at frequent intervals during treatment.

Additional information

1. Equipment and medications necessary for cardiopulmonary resuscitation should be immediately available during administration of digoxin immune Fab (ovine).
2. In patients who respond poorly to withdrawal of digoxin's inotropic effect, other intravenous inotropes such as dopamine or dobutamine or cardiac load-reducing agents may be used. Caution is necessary in use of catecholamines because of the risk of aggravation of digitalis toxicity-associated arrhythmias.
3. Redigitalization of the patient, if necessary, should be delayed until elimination of digoxin immune Fab (ovine) from the body is complete, usually after several days but may be up to a week or longer in patients with renal function impairment.

Packaging and storage Digoxin-Specific Antibodies (Fab Fragment) for Injection shall be kept in Containers for Sterile Solids as described under "Parenteral Preparations" (Appendix 1.16).

Stability Reconstituted solutions should be used immediately but may be stored between 2° and 8° for up to 4 hours.

DIMERCAPROL INJECTION
(British Anti-Lewisite; BAL)

Indication Antidote to arsenic, gold and mercury poisoning, and antidote to lead poisoning (adjunctive therapy).

Dimercaprol is indicated as a chelating agent in arsenic, gold, and mercury (soluble inorganic compounds) poisoning following

ingestion, inhalation, or absorption through the skin of these metals or their salts, or following overdose of therapeutic agents containing the metals.

It is also indicated for treatment of acute and chronic lead poisoning when administered in conjunction with edetate sodium calcium (calcium EDTA). When administered promptly, dimercaprol complements edetate sodium calcium by more rapidly removing lead from red blood cells and the central nervous system (CNS) than does edetate sodium calcium alone, and by assisting in mobilization of lead from skeletal stores. This combination is less toxic than edetate sodium calcium alone because lower doses of each can be used. The rate of lead excretion is doubled when the combination is used, thus decreasing the mortality rate and the likelihood of permanent neurologic deficits from lead poisoning.

Not to be used in the treatment of arsine gas, iron, cadmium, selenium, silver, uranium, and organic (short-chain alkyl) mercury poisoning.

Strength available 50 mg per ml in oil.

Dosage and administration

Adults—

Arsenic or gold toxicity—

Severe: *Intramuscular* (deep), 3 mg per kg of body weight every 4 hours on the first day, 2 to 3 mg per kg of body weight every 4 hours on the second day, 3 mg per kg of body weight every 6 hours on the third day, and 3 mg per kg of body weight twice a day for 10 days or until recovery.

Mild: *Intramuscular* (deep), 2.5 mg per kg of body weight every 6 hours for 2 days, every 12 hours on the third day, and once a day on each of the following 10 days or until recovery.

Mercury toxicity: *Intramuscular* (deep), 3 to 5 mg per kg of body weight every 4 hours for 2 days, then 2.5 to 3 mg per kg of body weight every 6 hours for 2 days, then 2.5 to 3 mg per kg of body weight every 12 hours for 7 days.

Lead toxicity—

Severe (encephalopathy): *Intramuscular*, 4 mg per kg of body

weight for the first dose, repeated at 4-hour intervals in conjunction with calcium EDTA injection (IV or IM, at a separate site, 30 to 50 mg per kg of body weight or 1 to 1.5 g per m^2 of body surface area per day in 2 divided doses 12 hours apart for 3 to 5 days). This treatment is maintained for 2 to 7 days. If the blood lead concentration after this first course of therapy exceeds 100 µg per dl, treatment may be resumed for an additional 5 days, following an interval of at least 2 days without treatment.

Mild: *Intramuscular*, 4 mg per kg of body weight for the first dose, the dose then being reduced to 3 mg per kg of body weight and administered at 4-hour intervals in conjunction with calcium EDTA injection, which is administered at a separate site. Dimercaprol may be discontinued after 72 hours, with calcium EDTA injection being continued for an additional 48 to 72 hours at reduced dosage.

Each single dose should not exceed 5 mg per kg of body weight.

Children—

Lead toxicity—

Symptomatic children—Acute (with or without encephalopathy): *Intramuscular* (deep), 75 mg per m^2 of body surface area every 4 hours (up to 450 mg per m^2 of body surface area per 24 hours). After 4 hours, calcium EDTA injection, 1.5 g per m^2 of body surface area per 24 hours, should be administered on a 4-hour schedule, intravenously or intramuscularly at a separate site. This treatment is maintained for 5 days. If the blood lead concentration after this first course of therapy exceeds 70 µg per dl, treatment may be resumed for an additional 5 days, following an interval of at least 2 days without treatment. The cycle may be repeated, depending on the clinical response.

Asymptomatic children—*Intramuscular* (deep), 50 mg per m^2 of body surface area every 4 hours. After 4 hours, calcium EDTA injection, 1 g per m^2 of body surface area per 24 hours, should be administered on a 4-hour schedule simultaneously intravenously or intramuscularly at a separate site. This treatment is maintained for 5 days. Dimercaprol may be discontinued after 3 days if blood lead concentrations are less than 50 µg per dl. If the blood lead concentration after this first course of therapy exceeds 70 µg per dl, treatment may be resumed for an additional 5 days, following an interval of at least 2 days without treatment. Calcium EDTA injection should be continued for

5 more days. The cycle may be repeated depending on the clinical response. (Onset: 30 minutes. Duration: about 4 hours.)

Contra-indication It is contra-indicated in patients with impaired hepatic function, except those with postarsenical jaundice.

Warning

1. It should not be administered in conjunction with medicinal iron.
2. It should be used with caution in patients with hypertension, impaired renal function, or glucose-6-phosphate dehydrogenase deficiency.
3. It consistently causes hypertension accompanied by tachycardia, proportional to the dose. Other transitory adverse effects include fever and polymorphonuclear leukocyte reduction, especially in children, gastro-intestinal disturbances, abnormal sensation of the skin, headache, conjunctivitis, abdominal pain, and nephrotoxicity.

Precaution Chelation therapy can increase absorption of lead from gastro-intestinal tract. Such therapy should only be administered to children who reside in environments that are free of lead both during and after therapy.

Patient monitoring The following are recommended:

1. Blood urea nitrogen (BUN) and serum concentrations of alkaline phosphatase, calcium, creatinine, electrolyte and phosphorus, to detect evidence of renal function impairment. Hemodialysis may be necessary.
2. Blood pressure and heart rate, periodically during therapy.
3. Fluid balance, for determination of dehydration or impending renal insufficiency. Parenteral fluids should be administered, at least during the first 2 or 3 days of dimercaprol therapy, to replace oral feedings that may not be tolerated or to minimize nausea and vomiting caused by either dimercaprol or the toxic agent or both.
4. Heavy metal concentration in blood and 24-hour urine excretion, to determine dosage and duration of therapy. Chelation therapy is recommended if urine arsenic levels are consistently above 200 μg per litre.

5. Hemoglobin, periodically in mercury toxicity.
6. Urinary pH, periodically. Maintenance of an alkaline pH decreases the risk of nephrotoxicity, which may occur because of dissociation of the dimercaprol-metal complex in an acidic urine.
7. Polymorphonuclear leukocyte count especially in children.

Packaging and storage Dimercaprol Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I or Type III glass, protected from light, and stored at a temperature not exceeding 25°.

DIPHENHYDRAMINE HYDROCHLORIDE INJECTION

Indication Antidyskinetic, to relief parkinsonism induced by antipsychotics (e.g., phenothiazines, butyrophenones and risperidone), antiemetics (e.g., metoclopramide and prochloperazine), reserpine or α-methyldopa.

Diphenhydramine is an antidyskinetic. It is indicated for the symptomatic treatment of parkinsonism and drug-induced extrapyramidal reactions in elderly patients unable to tolerate more potent antidyskinetic medications, for mild cases of parkinsonism in other age groups and, in combination with centrally acting anticholinergic agents, for other cases of parkinsonism.

Strengths available 10 and 50 mg per ml.

Dosage and administration

Adults: *Intramuscular* or *intravenous*, 10 to 50 mg.

The maximum total dose should not exceed 100 mg per dose or 400 mg daily.

Children: *Intramuscular*, 1.25 mg per kg of body weight or 37.5 mg per m^2 of body surface area, 4 times a day, not to exceed 300 mg per day. (Onset: intramuscular, 20 to 30 minutes. Duration: 6 to 8 hours.)

Contra-indication It is contra-indicated in nursing women, newborn or premature infants.

Warning

1. Hypersensitivity reactions to diphenhydramine hydrochloride, including anaphylactic shock, are more likely to occur following parenteral administration than oral administration.
2. It should be used with caution in patients with cardiovascular diseases, hyperthyroidism, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, prostatic hypertrophy, bladder neck obstruction, asthma, or in those receiving ototoxic antibiotics.
3. It may cause dry mouth and gastro-intestinal upset, palpitations, hypotension, blurred vision, central nervous system (CNS) depression or stimulation, urinary frequency, and/or dysuria.
4. Concurrent use of diphenhydramine hydrochloride with CNS depressants (e.g., alcohol, barbiturates, narcotics, anesthetics), or monoamine oxidase inhibitors or tricyclic antidepressants will potentiate the effects of each other. Dosage adjustments are necessary.
5. Infants and children are more susceptible to anticholinergic side effects of diphenhydramine hydrochloride, such as CNS excitation and an increased tendency toward convulsion; thus, overdosage may cause hallucination, convulsion and death. In older children, a paradoxical reaction characterized by hyperexcitability may occur.
6. In elderly patients, diphenhydramine hydrochloride is more likely to cause dizziness, sedation, syncope, toxic confusional states, hypotension, and extrapyramidal signs. Dosage reduction may be required.

Precaution Patients who become drowsy and dizzy when taking diphenhydramine hydrochloride should be cautioned against engaging in activities requiring alertness and skill, such as driving a car or operating hazardous machinery or appliances.

Additional information Intramuscular injections should be administered deeply into the muscle. Intravenous injections should be administered slowly, preferably with the patient in a recumbent position.

Subcutaneous or perivascular injection should be avoided.

Packaging and storage Diphenhydramine Hydrochloride Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light, and stored at a temperature not exceeding 30°.

EDETATE SODIUM CALCIUM INJECTION
(Calcium Disodium Edetate Injection)

Indication Antidote to lead poisoning.

Edetate sodium calcium is indicated for the treatment of acute and chronic lead poisoning (plumbism) and lead encephalopathy. Dimercaprol complements edetate sodium calcium by rapidly removing lead from red blood cells and by assisting in mobilizing lead from skeletal stores. When the combination is used, the rate of lead excretion is doubled, thus decreasing the mortality rate and likelihood of permanent neurologic deficits from lead poisoning. Edetate sodium calcium may be used as a sole therapy when blood lead levels fall between 45 and 69 μg per dl, unless serious symptoms such as encephalopathy are present. Clinical signs and symptoms suggesting lead poisoning that should be treated with the dimercaprol, edetate sodium calcium combination include the following:

- The patient is symptomatic (with or without encephalopathy).
- Blood lead concentrations are greater than or equal to 70 μg per dl.

Not to be used in the treatment of arsenic, gold, or mercury poisoning.

Strength available 200 mg per ml.

Dosage and administration

Adults: *Intravenous* or *intramuscular*, 30 to 50 mg per kg of body weight (1 to 1.5 g per m^2 of body surface area) per day in 2 divided doses 12 hours apart for 3 to 5 days, in conjunction with dimercaprol (4 mg per kg of body weight for the first dose, repeated at 4-hour interval).

Patients with blood lead levels between 45 and 69 μg per dl may be treated with edetate sodium calcium alone using the same dosage given above for use with dimercaprol. A second course of treatment may be administered for up to 5 additional days after at least a 2-day drug-free interval (preferably 2 weeks).

When serum creatinine is 2 mg per dl or less, the dosage is 1 g a day for 5 days. If the serum creatinine is 2 to 3 mg per dl, the dosage is 500 mg a day.

For intravenous administration, the dilution must be infused slowly over a period of at least 2 hours for symptomatic patients and 1 hour for asymptomatic patients.

The maximum total dose should not exceed 2 g a day.

Children: For blood lead levels greater than 70 μg per dl or serious symptoms, *intravenous* or *intramuscular*, 1.5 g per m^2 of body surface area per day, administered on a 4-hour schedule for 5 days, in conjunction with dimercaprol (75 mg per m^2 of body surface area every 4 hours).

Children with blood lead levels between 45 and 69 μg per dl may be treated with edetate sodium calcium alone, using a dose of 1 g per m^2 of body surface area per day for 5 days. In cases of lead encephalopathy, children may require repeated courses of therapy if blood lead levels are greater than 45 μg per dl.

A second course of treatment may be administered after a drug-free interval of at least 2 days.

For intravenous administration, dilute 5 ml of edetate sodium calcium injection with 250 to 500 ml of 0.9 per cent sodium chloride injection or 5 per cent dextrose injection.

Contra-indication It is contra-indicated in patients with severe renal disease and hepatitis.

Warning

1. Fatal lower nephron necrosis may result; if anuria occurs during therapy or is present before therapy, urine flow should be restored before starting edetate sodium calcium therapy.

2. Reduced glomerular filtration may delay the excretion of the chelate and increase the risk of nephrotoxicity.

3. Systemic febrile reaction or histamine-like reaction possibly occurs 4 to 8 hours after intravenous infusion; low blood pressure, nausea or vomiting, renal damage or renal tubular necrosis, thrombophlebitis may also occur.

Precaution Chelation therapy can increase absorption of lead from gastro-intestinal tract. Such therapy should only be administered to children who reside in environments that are free of lead both during and after therapy.

Patient monitoring The following are recommended:

1. Blood urea nitrogen (BUN), calcium, creatinine, phosphorus concentrations, and urine output, for evidence of renal function impairment, prior to treatment and on the first, third, and fifth day of each course of therapy.
2. Daily routine urinalysis, during each course of therapy. Since severe, acute lead poisoning and edetate sodium calcium may both produce the same signs of renal damage, urinalyses should be performed to determine if proteinuria or hematuria is improving or if evidence of renal tubular injury is worsening. Edetate sodium calcium must be discontinued immediately if large renal epithelial cells or increasing numbers of red blood cells are present in urinary sediment, or if there is evidence of increased proteinuria.
3. Electrocardiogram, to detect irregularities of cardiac rhythm, especially if edetate sodium calcium is given intravenously, periodically.

Additional information

1. Because the intramuscular route is painful and there may be poor blood flow to muscle, the intravenous route is recommended for children.
2. In cases of lead encephalopathy, fluid restriction may necessitate giving edetate sodium calcium intramuscularly.
3. When acutely ill patients are dehydrated from vomiting and/or diarrhea, urine flow must be established before administering the first dose of edetate sodium calcium. Once the flow is established, intravenous fluids must be restricted to basal water and electrolyte requirements.

4. Edetate sodium calcium injection is physically incompatible with 10 per cent dextrose injection, 10 per cent invert sugar, 10 per cent invert sugar in sodium chloride injection, lactated Ringer's injection, Ringer's injection, one-sixth molar sodium lactate injection, and injectable preparations of amphotericin B and hydralazine hydrochloride.

Packaging and storage Edetate Sodium Calcium Injection shall be kept in single-dose containers, preferably of Type I glass.

ETHANOL INJECTION

Indication Antidote to methanol or ethylene glycol poisoning.

Strengths available 5 and 10 per cent in a 5 per cent w/v solution of dextrose.

Dosage and administration

Loading dose, *intravenous* slowly, 750 mg per kg of body weight.

Maintenance dose, *intravenous infusion*, 100 to 150 mg per kg of body weight per hour, increase to 175 to 200 mg per kg of body weight per hour in chronic alcoholics, or during hemodialysis.

See Table 1.

Table 1 Ethanol dosing (Adults and Children)

Dose per kg of body weight	5 per cent solution	10 per cent solution
Loading	15 ml	7.5 ml
Maintenance	2 to 4 ml per hour	1 to 2 ml per hour
Maintenance during hemodialysis	4 to 7 ml per hour	2 to 3.5 ml per hour

Warning

1. It should be used with caution in patients who are receiving CNS depressants or drugs causing disulfiram-like reaction including disulfiram, chlorpropamide, metronidazole, etc.
2. It may cause postural hypotension, palpitations, inebriation, sedation, coma, hypoglycemia, nausea, vomiting, gastritis, and local phlebitis.

Patient monitoring The following are recommended:

1. Respiration rate and blood pressure.
2. Blood glucose, to detect hypoglycemia, throughout the treatment interval.

Additional information Patients receiving ethanol by infusion or mouth, may become obtunded and inebriated. They may pose health hazards to themselves and others and should be cared for in a carefully monitored environment.

Packaging and storage Ethanol Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light and stored at a temperature not exceeding 30°.

FLUMAZENIL INJECTION

Indication Antidote to benzodiazepine overdose.

Flumazenil is indicated for partial or complete reversal of post-procedure residual sedation resulting from use of benzodiazepines for induction and/or maintenance of anesthesia, conscious sedation, or deep sedation, and for the management of benzodiazepine overdose.

The benefits of reversing post-procedure residual sedation are more apparent in patients who are heavily sedated at the time of administration than in patients who are only mildly or moderately sedated. Flumazenil facilitates patient management most significantly during the first hour following administration. After 1 hour, significant

spontaneous recovery is also apparent in patients who have not received the medication.

Not to be used in patients receiving a benzodiazepine for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus) and in patients who are showing sign of serious cyclic antidepressant overdose.

Strength available 0.1 mg per ml.

Dosage and administration

Adults—

Reversal of benzodiazepine-induced sedation: *Intravenous*, initially, 0.2 mg administered over 15 seconds. If the desired response has not been obtained after 45 seconds to 1 minute, additional 0.2-mg doses may be administered over 15 seconds at one-minute intervals, up to a maximum cumulative dose of 1 mg. Most patients require 0.6 mg to 1 mg.

If resedation occurs, additional flumazenil may be administered at a rate of 0.2 mg per minute, up to a total cumulative dose of 1 mg. This dose may be repeated at twenty-minute intervals, up to a maximum of 3 mg in an one-hour period.

Treatment of benzodiazepine overdose: *Intravenous*, initially, 0.2 mg administered over 30 seconds. If the desired response has not been obtained after 30 seconds to 1 minute, 0.3 mg may be administered over 30 seconds. If necessary, additional doses of 0.5 mg may be administered over 30 seconds at one-minute intervals, up to a maximum cumulative dose of 3 mg. Most patients respond to a cumulative dose of 1 to 3 mg. If no response is obtained after a cumulative dose of 5 mg, it can be assumed that a benzodiazepine was not responsible for the overdose and that further administration of flumazenil is not likely to be helpful.

If resedation occurs, additional doses of up to a total of 1 mg of flumazenil may be administered at a rate of 0.5 mg per minute. This dose may be repeated at twenty-minute intervals, up to a maximum of 3 mg in a one-hour period. Alternatively, flumazenil may be administered as an intravenous infusion at a rate adjusted to provide the

desired level of arousal, generally 0.1 to 0.4 mg per hour.

For patients who may be tolerant to or dependent on benzodiazepines, a slower rate of administration (0.1 mg per minute) and lower total doses may be required to minimize the risk of adverse effects.

To prevent resedation after initial reversal, up to 1 mg of flumazenil may be administered intravenously at a rate of 0.2 mg per minute 30 minutes and possibly 60 minutes later.

Children: Dosage has not been established. However, the medication is being administered intravenously to pediatric patients in doses ranging from 0.01 mg per kg of body weight (for reversing sedation) to 0.1 mg per kg of body weight (for life-threatening overdose), up to a maximum cumulative dose of 1 mg. Some investigators have also administered flumazenil by intravenous infusion at a rate of 0.005 to 0.01 mg per kg of body weight per hour.

(Onset: approximately 1 to 2 minutes. Duration: dependent on the doses and concentration of the benzodiazepine being antagonized and of flumazenil)

For intravenous infusion: It may be diluted with 5 per cent w/v dextrose injection, 0.9 per cent w/v sodium chloride injection, 0.45 per cent w/v sodium chloride and 2.5 per cent w/v dextrose injection, or lactated Ringer's injection.

Warning

1. It should be used with caution in patients with anxiety or panic disorder, cardiac disease (especially with increased left ventricular end-diastolic pressure), drug abuse or history of drug abuse (especially benzodiazepine abuse or chronic use), severe head injury, hepatic function impairment, and seizure disorders (especially if treated with benzodiazepines).
2. Caution should be exercised when it is to be used in a mixed overdose with seizurogenic medication (especially tricyclic or tetracyclic antidepressants) and a benzodiazepine since seizure may increase.
3. It may cause agitation, headache, emotional lability, hypertension, convulsions, blurred vision or other vision disturbances, dizziness, nausea, vomiting, fatigue, flushing or hot flushes, sweating, hearing disturbances, and pain or thrombophlebitis at injection site.

4. To minimize injection pain, it should be injected into a large vein through a freely flowing intravenous infusion. Extravasation may result in local irritation.

Patient monitoring The following are recommended:

1. Electrocardiogram (ECG), to detect QRS prolongation (a possible sign of tricyclic or tetracyclic antidepressant toxicity), prior to flumazenil administration. It is essential when mixed overdosage with a cyclic antidepressant is suspected.
2. Oxygenation (determined via pulse oximetry), monitoring for an adequate period of time, depending on the dose and duration of action of the benzodiazepine being antagonized. It is essential following flumazenil administration because benzodiazepine-induced hypoventilation may not be completely antagonized or may recur.
3. Patient alertness, at least 1 to 2 hours following flumazenil administration. More prolonged monitoring may be needed, depending on the dose and the duration of action of the benzodiazepine being antagonized and whether other CNS depressants have been or are being given.
4. Vital signs, blood pressure, heart rate, and respiratory rate. Supplemental treatment can be instituted as required.

Additional information

1. No adjustment of initial dosage is required for patients with significant hepatic function impairment, but a reduction in the size and/or frequency of subsequent doses is recommended.
2. Flumazenil administration is not a substitute for interventions such as establishing an airway, assisting ventilation, and supporting circulation.
3. Preparation for managing seizures should be made prior to flumazenil administration, especially when flumazenil is used to reverse long-term or high-dose use of a benzodiazepine for sedation in critical care patients or to treat a mixed overdose in which a potentially seizurogenic medication may have been ingested.

Stability Infusion solutions prepared with 5 per cent w/v dextrose

injection, 0.9 per cent w/v sodium chloride injection, or 0.45 per cent w/v sodium chloride and 2.5 per cent w/v dextrose injection are stable for up to 24 hours at room temperature. Flumazenil injections that have been drawn into a syringe or mixed with intravenous infusion solutions should be discarded after 24 hours.

Packaging and storage Flumazenil Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light and stored at a temperature not exceeding 30°.

FULLER'S EARTH ORAL POWDER

Indication Antidote to paraquat poisoning (adsorbent).

Dosage and administration

Oral, 200 to 500 ml of a 30 per cent w/v suspension administered via a gastric tube every 2 hours for 3 doses, in association with 5 per cent w/v magnesium sulfate or mannitol to promote diarrhea and empty the gut.

Packaging and storage Fuller's Earth Oral Powder shall be kept in well-closed containers.

IPECACUANHA SYRUP
(Ipecac Syrup)

Indication Induction of emesis.

Ipecac Syrup is indicated as an emetic for early on-scene management of drug overdose and in some cases of oral poisonings, immediately after ingestion, in the home or at industrial on-site health care facilities without access to activated charcoal or the capacity to perform gastric lavage.

Not to be used in the treatment of poisoning caused by strychnine, corrosive substances (e.g. alkalis or strong acids), and petroleum distillates (e.g. kerosene, gasolene, coal oil, fuel oil, paint thinner, and cleaning fluid).

Dosage and administration

In prescribing Ipecac Syrup, Pediatric Ipecac Emetic Mixture (Ipecac Liquid Extract 70 ml, Hydrochloric Acid 2.5 ml, Glycerol 100 ml, Syrup sufficient to produce 1000 ml) or freshly prepared Ipecac Elixir (Ipecac Tincture 70 ml, Glycerol 10 ml, Syrup sufficient to produce 100 ml) may be used.

Adults: *Oral*, 15 to 30 ml, followed immediately by one full glass (240 ml) of water.

Children: *Oral*, 15 ml, preceded or followed by one-half to one full glass (120 to 240 ml) of water.

Infants 6 months of age and over: *Oral*, 5 to 10 ml, preceded or followed by one-half to one full glass (120 to 240 ml) of water. (Onset: 20 to 30 minutes. Duration: 20 to 25 minutes.)

If emesis does not occur, doses may be repeated after 25 to 30 minutes. No more than 2 doses of ipecac syrup should be taken since ipecac can be cardiotoxic. If emesis does not occur after the second dose, gastric lavage should be performed.

Contra-indication It is contra-indicated in semiconscious, unconscious, shock and convulsing persons.

Warning

1. It should be used with caution in patients with cardiac diseases.
2. It may cause mild CNS depression, diarrhea, gastro-intestinal upset, and cardiac toxicity.
3. Concurrent ingestion with carbonated beverages or milk products should be avoided.
4. When both ipecac and activated charcoal are to be used in the treatment of oral poisoning, it is recommended that the charcoal be administered only after vomiting has been induced and completed.

5. For infants 6 months of age and over, professional advice on proper positioning to avoid aspiration of vomitus is important.

Additional information

1. To increase the emetic action, ipecac should be administered with adequate amounts of water.
2. Ipecac Fluidextract and Ipecac Tincture have been replaced by Ipecac Syrup, the preferred dosage form. Ipecac Fluidextract is 14 times more concentrated than Ipecac Syrup, and is not recommended for use because of its high potency and toxicity.

Packaging and storage Ipecacuanha Syrup shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

LEUCOVORIN CALCIUM CAPSULES or TABLETS

Indication Antidote to folic acid antagonists.

Leucovorin is indicated as an antidote to the toxic effects of folic acid antagonists such as methotrexate, pyrimethamine, or trimethoprim. It is also indicated as a rescue after high-dose methotrexate therapy in osteosarcoma and as a part of chemotherapeutic treatment programs in the management of several forms of cancer.

Strengths available Capsules: 15 mg (base).
Tablets: 5, 15, and 25 mg (base).

Dosage and administration

Antidote to methotrexate: *Oral*, 10 mg per m^2 of body surface area every 6 hours until methotrexate blood concentrations fall to less than 5×10^{-8} M.

Antidote to pyrimethamine or trimethoprim—

Prevention: *Oral*, 0.4 mg to 5 mg with each dose of the folic acid antagonist.

Treatment: *Oral*, 5 to 15 mg per day. (Onset: 20 to 30 minutes. Duration: 3 to 6 hours.)

For doses higher than 25 mg, Leucovorin Calcium for Injection or Injection should be used because oral absorption is saturable at doses above 25 mg.

Contra-indication It is contra-indicated in patients with pernicious anemia or other megaloblastic anemias where vitamin B_{12} is deficient.

Warning

1. It may cause allergic reactions and seizures.
2. Caution should be exercised when it is to be used concomitantly with anticonvulsants (barbiturate, hydantoin or primidone) and fluorouracil.

Patient monitoring For patients receiving high-dose methotrexate, the following are recommended:

1. Creatinine clearance, prior to initiation of high-dose methotrexate with leucovorin rescue therapy or if serum creatinine concentrations increase by 50 per cent or more.
2. Serum creatinine, to detect developing renal function impairment and predict methotrexate toxicity, prior to and every 24 hours after each methotrexate dose, until plasma or serum methotrexate concentrations are less than 5×10^{-8} M. An increase of greater than 50 per cent over the pretreatment concentration at 24 hours is associated with severe renal toxicity.
3. Urine pH, to ensure that pH remains greater than 7 so as to minimize the risk of methotrexate nephropathy from precipitation of methotrexate or metabolites in urine, prior to each dose of high-dose methotrexate therapy and about every 6 hours throughout leucovorin rescue, until plasma or serum methotrexate concentrations are less than 5×10^{-8} M.
4. Plasma or serum concentrations of methotrexate, to determine dose and duration of leucovorin treatment needed to maintain rescue, every 12 to 24 hours after high-dose methotrexate administration.

Additional information

1. The first dose of leucovorin should be administered within the first 24 to 42 hours of starting a high-dose methotrexate infusion (within 1 hour of an overdose), in a dosage to produce blood concentrations equal to or greater than methotrexate blood concentrations (leucovorin in a dose of 15 mg produces peak plasma concentrations of approximately 1×10^{-6} M).

2. Administration of leucovorin should be consecutive to rather than simultaneous with methotrexate administration so as not to interfere with methotrexate's antineoplastic effects.

3. A larger dose and/or longer duration of leucovorin treatment may be required in patients with aciduria, ascites, dehydration, gastro-intestinal obstruction, renal function impairment, or pleural or peritoneal effusions because excretion of methotrexate is slowed and the length of time for plasma methotrexate concentrations to decrease to nontoxic levels ($<5\times10^{-8}$ M) is increased. It is recommended that duration of leucovorin administration in these patients be based on determination of plasma methotrexate concentrations.

Packaging and storage Leucovorin Calcium Capsules and Leucovorin Calcium Tablets shall be kept in well-closed containers, protected from light and stored at a temperature not exceeding 30°.

LEUCOVORIN CALCIUM FOR INJECTION or INJECTION

Indication Antidote to folic acid antagonists.

Leucovorin is indicated as an antidote to the toxic effects of folic acid antagonists such as methotrexate, pyrimethamine, or trimethoprim. It is also indicated as a rescue after high-dose methotrexate therapy in osteosarcoma and as a part of chemotherapeutic treatment programs in the management of several forms of cancer.

Strengths available For injection: 50, 100, and 350 mg (base).
Injection: 3, 5 and 10 mg (base) per ml.

Dosage and administration

Antidote to methotrexate (inadvertent overdose): *Intramuscular* or *intravenous*, 10 mg per m^2 of body surface area every 6 hours until methotrexate blood concentrations fall to less than 5×10^{-8} M.

If, at 24 hours following methotrexate administration, the serum creatinine is increased by 50 per cent or greater over baseline or serum methotrexate is greater than 5×10^{-6} M, the dose of leucovorin should be 100 mg per m^2 of body surface area every 3 hours intravenously until methotrexate concentrations are reduced to appropriate levels.

Antidote to pyrimethamine or trimethoprim—

Prevention: *Intramuscular*, 0.4 mg to 5 mg with each dose of the folic acid antagonist.

Treatment: *Intramuscular*, 5 to 15 mg per day. (Onset: Intramuscular, 10 to 20 minutes; intravenous, less than 5 minutes. Duration: 3 to 6 hours.)

Preparation of Leucovorin Calcium for Injection: Add 5 or 10 ml of bacteriostatic water for injection (preserved with benzyl alcohol) to the vial containing 50 or 100 mg, respectively, producing a solution containing 10 mg per ml. If doses greater than 10 mg per m^2 of body surface area are to be used, sterile water for injection (i.e. without benzyl alcohol) should be used for reconstitution and the resulting solution used immediately.

Contra-indication; Patient monitoring See under *Leucovorin Calcium Capsules* or *Tablets*, p. 57.

Warning

1. It should not be administered intrathecally for the treatment of accidental overdoses of intrathecally administered folic acid antagonists.

2. For leucovorin calcium for injection, use of diluents containing benzyl alcohol is not recommended for preparation of medications for use in neonates. A fatal toxic syndrome consisting of metabolic acidosis, CNS depression, respiratory problems, renal failure, hypotension, and possibly seizures and intracranial hemorrhages has been associated with this use.

3. Leucovorin calcium for injection is incompatible with fluorouracil; precipitation will occur if these agents are combined in the same infusion solution.

See also under *Leucovorin Calcium Capsules* or *Tablets*, p. 57.

Additional information Because of its calcium content, leucovorin calcium for injection should be administered by intravenous injection slowly, at a rate that does not exceed 160 mg of leucovorin per minute.

See also under *Leucovorin Calcium Capsules* or *Tablets*, p. 57.

Packaging and storage Leucovorin Calcium for Injection shall be kept in Containers for Sterile Solids as described under "Parenteral Preparations" (Appendix 1.16), protected from light and stored at a temperature not exceeding 25°.

Leucovorin Calcium Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass containers and stored at a temperature between 2° and 8°.

Stability When leucovorin calcium for injection is reconstituted as directed, resultant solutions should be used immediately when reconstituted with sterile water for injection or within 7 days when reconstituted with bacteriostatic water for injection containing benzyl alcohol. The solution that has been admixed with 10 per cent dextrose injection, 10 per cent dextrose and 0.9 per cent sodium chloride injection, Ringer's injection, or lactated Ringer's injection is stable for 24 hours when stored at a temperature not exceeding 25°, protected from light.

Intravenous solutions containing leucovorin calcium in lactated Ringer's injection, Ringer's injection, 0.9 per cent sodium chloride injection are stable for up to 24 hours at a temperature not exceeding 25°. When diluted in 5 per cent dextrose injection, intravenous solutions containing leucovorin calcium are stable for 12 hours at a temperature not exceeding 25°. When diluted in 10 per cent dextrose in 0.9 per cent sodium chloride injection, solutions are stable for 6 hours at a temperature not exceeding 25°.

MESNA INJECTION

Indication Hemorrhagic cystitis prophylactic.

Mesna is indicated to reduce the incidence of ifosfamide-induced or cyclophosphamide-induced hemorrhagic cystitis.

Not to be used in preventing hematuria due to other pathologic conditions such as thrombocytopenia, and does not affect other toxicities of oxazaphosphorines.

Strength available 100 mg per ml.

Dosage and administration

Adults—

Prophylaxis of ifosfamide-induced hemorrhagic cystitis: *Intravenous*, rapid, in a dosage equal to 20 per cent of the ifosfamide dosage (w/w) at the time of ifosfamide administration and four and eight hours after each dose of ifosfamide (i.e., the total daily dose of mesna is equal to 60 per cent of the total daily dose of ifosfamide) each day that ifosfamide is administered. If the dose of ifosfamide is adjusted, the dose of mesna should be adjusted accordingly.

For intravenous administration, admix with 5 per cent dextrose injection, 5 per cent dextrose and sodium chloride injection, 0.9 per cent sodium chloride injection, or lactated Ringer's injection to produce a solution containing 20 mg per ml.

Warning

1. It should be used with caution in patients sensitive to other thiol compounds.
2. It may cause allergic reactions, diarrhea, nausea or vomiting, and unpleasant taste.

Patient monitoring The following is recommended:

Examination of urine for microscopic hematuria, prior to administration of each dose of ifosfamide or cyclophosphamide and mesna.

Additional information

1. Mesna injection is incompatible with cisplatin injection.
2. If hematuria develops when mesna is given with ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of ifosfamide therapy may be initiated.

Packaging and storage Mesna Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass containers, and stored at a temperature not exceeding 30°.

Stability Diluted solutions of mesna are chemically and physically stable for 24 hours when stored at a temperature not exceeding 25°.

DL-METHIONINE TABLETS
(Racemethionine Tablets)

Indication Antidote to paracetamol overdose.

DL-Methionine is used in the treatment of paracetamol overdose to protect against hepatotoxicity. However, oral *N*-acetylcysteine is considered the treatment of choice for paracetamol overdose. Use of racemethionine should be limited to emergency situations in which *N*-acetylcysteine is not available.

Strength available 500 mg.

Dosage and administration

Oral, 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol.

Warning

1. It should be used with caution in patients with metabolic acidosis, and severe or history of hepatic function impairment.
2. It may cause drowsiness, nausea and vomiting.

3. Concurrent use of DL-methionine with levodopa may decrease the therapeutic effects of levodopa.

Patient monitoring The following are recommended:

1. Plasma concentration of paracetamol, to determine the need for antidotal therapy, not less than 4 hours following ingestion of paracetamol overdose.
2. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and prothrombin time, daily for 3 or 4 consecutive days if plasma paracetamol concentrations indicate potential hepatotoxicity.
3. Blood urea nitrogen (BUN) and serum creatinine, to detect the development of renal failure. However, BUN may not be elevated if the liver is unable to produce urea by-products.
4. Complete blood counts, to detect thrombocytopenia, daily for 3 or 4 days.
5. Blood glucose, to detect hypoglycemia, daily for 3 or 4 days.
6. Urine toxicology screen, to detect other potentially toxic medications.

Additional information DL-Methionine must be administered as soon as possible (within 8 to 12 hours) after ingestion of an overdose is suspected, without waiting for the results of plasma paracetamol concentrations or other laboratory tests.

Packaging and storage DL-Methionine Tablets shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

METHYLENE BLUE INJECTION

Indication Antimethemoglobinemia.

Methylene blue is indicated in the treatment of acquired and idiopathic methemoglobinemia, in which the patient has a methemoglobin concentration level greater than 30 per cent or in which there are clinical signs of hypoxemia.

Strength available 10 mg per ml.

Dosage and administration

Intravenous, 1 to 2 mg per kg of body weight or 25 to 50 mg per m^2 of body surface area, administered over 5 minutes. The dose may be repeated after 1 hour if needed.

Treatment of prolonged or continuous methemoglobin formation: Continuous *intravenous infusion* at a rate of 0.1 to 0.15 mg per kg of body weight per hour, following an initial dose of 1 to 2 mg per kg of body weight.

The maximum total dose should not exceed 7 mg per kg of body weight.

For continuous intravenous infusion, methylene blue should be admixed with a compatible solution, such as 0.9 per cent sodium chloride injection, to a final concentration of 0.05 per cent.

Contra-indication It is contra-indicated in patients with severe renal insufficiency.

Warning

1. It should not be administered subcutaneously or intrathecally.
2. It should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency, and infants up to 4 months of age.
3. It may cause gastro-intestinal upsets, headache and dizziness.
4. Extravasation may result in tissue necrosis.

Patient monitoring The following are recommended:

1. Complete blood counts and reticulocyte counts, to assure that hemolysis has not occurred, following methylene blue therapy.
2. Methemoglobin concentrations, to assess the effectiveness of therapy, 1 to 2 hours following administration of methylene blue.

Additional information

1. Intra-amniotic injection may cause hemolytic anemia, hyperbilirubinemia, methemoglobinemia, or deep blue staining of newborn.

2. It turns the urine and sometimes the stool and skin blue-green.
3. If no response after 2 doses, do not repeat dosing; consider glucose-6-phosphate dehydrogenase or methemoglobin reductase deficiency.

Packaging and storage Methylene Blue Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass.

NALOXONE HYDROCHLORIDE INJECTION

Indication Antidote to opioid (narcotic) toxicity.

Naloxone is considered the drug of choice to reverse respiratory depression caused by opioid drugs, including those with mixed agonist-antagonist activity such as buprenorphine (although the effects of buprenorphine are especially resistant to reversal by naloxone), butorphanol, nalbuphine, and pentazocine, and other effects due to known or suspected opioid overdose, including sedation, coma, excitation, or convulsions. It is also indicated in neonates to reverse respiratory depression caused by opioid given to the mothers during labor and delivery.

Naloxone will not increase respiratory depression caused by nonopioid medications or disease processes and may therefore be used when the cause is unknown. A satisfactory response to naloxone confirms the diagnosis of opioid toxicity.

Not to be used in the management of acute toxicity caused by levopropoxyphene.

Strengths available 0.02 and 0.4 mg per ml.

Dosage and administration

Adults—

Opioid (narcotic) toxicity: *Intravenous* (preferred in emergencies), *intramuscular*, or *subcutaneous*, 0.4 to 2 mg as a single dose. The intravenous dose may be repeated at 2- to 3-minute intervals as needed.

If the patient is suspected of being physically dependent on an opioid medication and is not in immediate danger, the dose may be reduced to 0.1 to 0.2 mg. This dose may be repeated at 2- to 3-minute intervals as needed.

Additional single doses of naloxone may be administered intravenously as needed. However, longer-lasting effects may be obtained if supplemental doses are administered via the intramuscular route. Also, initial treatment may be followed by continuous intravenous infusion of naloxone, with adjustment of the infusion rate according to the response of the patient.

Opioid (narcotic)-induced respiratory depression: *Intravenous*, 0.1 to 0.2 mg every 2 to 3 minutes until adequate ventilation and alertness without significant pain are obtained. If necessary, the dose may be repeated at 1- or 2-hour intervals.

The dose should be titrated to avoid interference with control of postoperative pain; initial doses as low as 0.5 μg per kg of body weight have been recommended.

Children—

Opioid (narcotic) toxicity: *Intravenous* (preferred in emergencies), *intramuscular*, or *subcutaneous*, 0.01 mg per kg of body weight. If this dose does not result in improvement in the condition of the patient, an additional 0.1 mg per kg of body weight may be given.

Doses higher than those listed above have been used to treat opioid toxicity. For infants and children up to 5 years of age and weighing less than 20 kg, an initial dose of 0.1 mg per kg of body weight is recommended. For children 5 years of age and older or weighing more than 20 kg, an initial dose of 2 mg is recommended.

Opioid (narcotic)-induced respiratory depression: *Intravenous*, 0.005 to 0.01 mg every 2 to 3 minutes until adequate ventilation and alertness without significant pain are obtained. If necessary, the dose may be repeated at 1- or 2-hour intervals.

Neonates—

Neonatal opioid (narcotic)-induced respiratory depression: *Intravenous* via the umbilical vein (preferred), *intramuscular*, or *subcutaneous*, 0.01 mg per kg of body weight. The intravenous dose may be repeated at 2- to 3-minute intervals until the desired response is obtained.

(Onset: Intravenous, 1 or 2 minutes; Intramuscular, 2 to 5 minutes. Duration: dose- and route-dependent.)

For continuous intravenous infusion, add 2 mg of naloxone hydrochloride to 500 ml of 0.9 per cent sodium chloride injection or 5 per cent dextrose injection to prepare a solution containing 0.004 mg per ml.

Warning

1. It should be used with caution in patients with cardiovascular disease, pulmonary disease and current opioid dependence or addiction.
2. It may cause convulsions, cardiac arrhythmia, hypotension, hypertension, pulmonary edema, violent behavior, increased sweating, nausea or vomiting, nervousness, restlessness, excitement, irritability, and trembling.
3. Concomitant administration of naloxone with opioid agonist analgesics (alfentanil, fentanyl, remifentanil, and sufentanil) and opioid agonist-antagonist analgesics (butorphanol, nalbuphine or pentazocine) may reverse the analgesic and side effects of these opioid analgesics and may precipitate withdrawal symptoms in physically dependent patients.

Additional information

1. When naloxone is used to antagonize the effects of buprenorphine, butorphanol, nalbuphine, or pentazocine, larger doses may be needed than are required to antagonize the effects of most opioids having only agonist activity.
2. Use of naloxone should be supplemented by other resuscitative procedures, such as administration of oxygen and/or vasopressors, artificial respiration, mechanical ventilation, and/or cardiac massage.
3. When naloxone is used to treat opioid toxicity, continued monitoring of the patient is necessary after naloxone is administered. If the duration of action of the opioid exceeds that of naloxone, re-emergence of opioid toxicity following initial reversal is likely.
4. Lack of significant improvement of CNS depression and/or respiratory depression following administration of an adequate dose (10 mg) of naloxone usually indicates that the condition is either due to a nonopioid CNS depressant not affected by the antagonist or to disease processes.

5. Buprenorphine-induced respiratory depression is especially resistant to reversal by naloxone; therefore, the reversal may be incomplete. If an incomplete response occurs, mechanical respiration is recommended.

6. When naloxone is administered to a patient known or suspected to be physically dependent on an opioid analgesic, the dose should be carefully titrated. Withdrawal symptoms may occur within a few minutes and may last up to 2 hours. The duration and severity of the withdrawal syndrome depend upon the dose of the antagonist, the specific opioid involved, and the degree to which dependence has developed. However, naloxone does not precipitate withdrawal symptoms in buprenorphine-dependent individuals.

Packaging and storage Naloxone Hydrochloride Injection shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

Stability Following dilution in 5 per cent dextrose or 0.9 per cent sodium chloride injection to a concentration of 0.004 mg/ml, naloxone hydrochloride solutions are apparently stable for 24 hours; after 24 hours, any unused solution should be discarded. Naloxone Hydrochloride Injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions or any solution having an alkaline pH.

PENICILLAMINE CAPSULES

Indication Antidote to heavy metals (chelating agent).

Penicillamine is a heavy metal antagonist that chelates copper, iron, mercury, lead, and probably other heavy metals as well as cystine*. It is less effective than other chelating agents (calcium EDTA or dimercaprol) for the treatment of severe lead poisoning. It is used as adjunctive treatment following initial therapy with another chelating agent. It may

* See Additional information 2.

also be used as a sole therapy in the treatment of asymptomatic patients with moderately elevated blood concentrations of lead.

[**Note**: Oral Succimer Capsules (DMSA) is preferable for lead or mercury poisoning.]

Penicillamine is also indicated in the treatment of Wilson's disease which causes tissue damage due to deposition of excessive copper in various tissues.

Strengths available 125 and 250 mg.

Dosage and administration

Antidote to heavy metals—

Adults: *Oral*, 500 mg to 1.5 g per day for 1 to 2 months.

Children: *Oral*, 30 to 40 mg per kg of body weight or 600 to 750 mg per m^2 of body surface area per day for 1 to 6 months.

Geriatric: *Oral*, initially 125 mg per day. Dosage may be increased, if necessary and tolerated, by adding 125 mg per day at 2- to 3-month intervals, up to a maximum of 750 mg per day.

Chelating agent—

Adults and children: *Oral*, 250 mg 4 times a day.

Infants over 6 months of age and young children: *Oral*, 250 mg as a single dose administered in fruit juice.

Wilson's disease (Doses titrated to maintain urinary copper excretion more than 1 mg per day.)—

Adults: *Oral*, 250 mg 4 times a day.

Children: *Oral*, 250 mg 2 or 3 times a day.

Infants up to 6 months: *Oral*, 250 mg once daily.

Contra-indication It is contra-indicated in patients with systemic lupus erythematosus or a history of penicillamine-induced agranulocytosis, aplastic anemia, or severe thrombocytopenia and in pregnant women.

Warning

1. Penicillamine should not be used in patients who are receiving

concurrently gold therapy, immunosuppressive drugs (except glucocorticoids), phenylbutazone, antimalarial or cytotoxic drugs or other drugs capable of causing similar serious hematological or renal adverse effects.

2. It should be used with caution in patients with renal insufficiency, in those hypersensitive to penicillin, and in nursing women.

3. It may cause fatal agranulocytosis, bone marrow suppression, gastro-intestinal disturbances, cutaneous allergic reactions, nephrotoxicity, increased skin friability, myasthenia gravis, and oral ulcerations.

Patient monitoring The following are recommended:

1. White and differential blood cell counts, hemoglobin determinations, direct platelet counts, and urinalyses (especially for protein and cells), at least every 2 weeks during the first 6 months of therapy, then monthly thereafter during therapy.

2. Hepatic function determinations, to detect intrahepatic cholestasis and toxic hepatitis, every 6 months during the first 18 months of therapy.

3. Urinary and blood metal concentrations, to assess the need for continued therapy and dosage adjustment, weekly.

Additional information

1. During the therapy, a low-copper diet of less than 2 mg daily should be maintained. Distilled or demineralized water should be used if the patient's drinking water contains more than 100 µg of copper per litre.

2. Penicillamine combines chemically with cystine (cysteine-cysteine disulfide) to form penicillamine-cysteine disulfide, which is more soluble than cystine and readily excreted. As a result, urinary cystine concentrations are lowered and the formation of cystine calculi is prevented. With prolonged treatment, existing cystine calculi may be gradually dissolved.

Packaging and storage Penicillamine Capsules shall be kept in tightly closed containers.

PRALIDOXIME CHLORIDE FOR INJECTION
(2-Pyridine Aldoxime Methyl Chloride; 2-PAM Chloride)

Indication Antidote to organophosphate pesticides, organophosphate chemicals and cholinesterase inhibitors.

Pralidoxime, used in conjunction with atropine, reverses nicotinic effects, such as muscle weakness and fasciculation, respiratory depression, and central nervous system (CNS) effects, associated with toxic exposure to organophosphate anticholinesterase pesticides and chemicals and with cholinesterase inhibitor overdose. Atropine, by antagonizing the action of cholinesterase inhibitors at muscarinic receptor sites, reverses muscarinic effects, such as tracheobronchial and salivary secretion, bronchoconstriction, bradycardia, and, to a moderate extent, CNS effects. Atropine does not reverse nicotinic effects. Pralidoxime should also be used in poisonings in which the patient presents with symptoms typical of acetylcholinesterase inhibition, although the source of the poisoning is not known, or in which the patient suffers from mixed organophosphate-carbamate pesticide poisoning.

Not to be used in the treatment of poisoning caused by carbamate, phosphorus, inorganic phosphates, or organophosphates not having anticholinesterase activity.

Strength available 1 g.

Dosage and administration

Adults: *Intravenous infusion*, 1 to 2 g in 100 ml of 0.9 per cent sodium chloride injection, for 15 to 30 minutes. If this is not practicable or if pulmonary edema is present, give slowly intravenously as a 5 per cent w/v solution in sterile water for injection over not less than 5 minutes. A second dose may be needed after about 1 hour if muscle weakness is not relieved.

Adjunct therapy: Prior to or concomitantly with Pralidoxime, atropine, 2 to 4 mg intravenously (absence of cyanosis) or

intramuscularly (presence of cyanosis), repeated every 5 to 10 minutes until signs of atropine toxicity appear. Maintain atropinization for at least 48 hours.

Children: 20 to 40 mg per kg of body weight per dose, given as above.

Warning

1. In high doses, pralidoxime may inhibit acetylcholinesterase and cause neuromuscular blockade.
2. It may cause blurred or double vision, dizziness, hyperventilation, impaired accommodation, increased blood pressure, laryngospasm, muscle rigidity or weakness, pain at injection site following intramuscular administration, or tachycardia.
3. It should be used with caution in patients receiving xanthines, such as aminophylline, caffeine, and theophylline or in those with myasthenia gravis or renal function impairment.

Patient monitoring The following are recommended:

1. True cholinesterase and pseudocholinesterase activities, to confirm diagnosis and to assess the degree of exposure to organophosphate poisoning, prior to therapy.
2. Electrocardiogram, to detect arrhythmias, especially in patients with pulmonary edema or patients who are severely poisoned or unconscious.
3. Urinary paranitrophenol, to confirm diagnosis and monitor clinical progress of parathion toxicity.

Packaging and storage Pralidoxime Chloride for Injection shall be kept in single-dose containers, preferably of Type I glass, protected from light and stored at a temperature not exceeding 25°.

PROTAMINE SULFATE INJECTION

Indication Antidote to heparin and low molecular weight heparins, e.g. enoxaparin.

Protamine is indicated in the treatment of severe heparin overdose resulting in hemorrhage; it is also used to neutralize the hemorrhagic effects following overdose of the low molecular weight heparins, enoxaparin. Transfusion of whole blood or fresh frozen plasma may also be required to replace lost volume if hemorrhaging has been severe; this may dilute, but will not neutralize the effects of heparin. Protamine is also indicated for administration following cardiac or arterial surgery or dialysis procedures when required to neutralize the effects of heparin administered during extracorporeal circulation.

Not to be used in treating minor heparin overdose that may respond to withdrawal of heparin, or in treating hemorrhage not caused by heparin.

Strength available 10 mg per ml.

Dosage and administration

Intravenous, 1 mg of protamine sulfate for approximately every 100 units of heparin or 1 mg of enoxaparin to be neutralized, or as determined by blood coagulation test results, administered at a rate of 5 mg per minute, not to exceed 50 mg in any 10-minute period. (Onset: 30 seconds to 1 minute. Duration: 2 hours.)

Since protamine has anticoagulant activity of its own, it is not advisable to administer more than 100 mg of protamine sulfate over a 2-hour period of time (the duration of action of protamine), unless blood coagulation tests indicate a larger requirement.

Warning

1. It may cause systemic hypertension, nausea, vomiting, and lassitude.
2. Too rapid administration of protamine sulfate may cause severe hypotension, anaphylactoid-like reactions, bradycardia, dyspnea, transitory flushing, a feeling of warmth, and hypertension.
3. Anaphylactic or anaphylactoid reaction or bleeding may be caused by protamine overdose or by a rebound of heparin activity.

Patient monitoring The following are recommended:

1. Patient's blood volume, to assure that it is adequate, prior to therapy.
2. Blood coagulation tests, to evaluate protamine efficacy and to determine optimum dosage of protamine, especially when neutralizing large doses of heparin given during cardiac or arterial surgery.
3. Blood titration tests with protamine, to establish protamine dosage, especially when large doses of heparin have been administered.
4. Activated clotting time (ACT), activated partial thromboplastin time (APTT), thrombin time (TT), and/or direct titration of a sample of the patient's blood with protamine, to monitor protamine therapy, at least 5 to 15 minutes following initial administration of protamine and repeated as necessary.

Additional information

1. APTT and TT may not be useful in monitoring protamine therapy after administration of enoxaparin because enoxaparin, in therapeutic doses, does not alter the value of these tests.
2. Protamine sulfate solutions are incompatible with certain antibiotics, including several of the cephalosporins and penicillins. It is recommended that no other medications be mixed with protamine sulfate unless they are known to be compatible.

Packaging and storage Protamine Sulfate Injection shall be kept in single-dose containers, preferably of Type I glass, and stored between 2° and 8°.

Stability It is potentially physically and/or chemically incompatible with some anti-infective agents, including some cephalosporins and penicillins.

PRUSSIAN BLUE FOR ORAL SUSPENSION
(Potassium Ferric Hexacyanoferrate(II)
for Oral Suspension)

Indication Antidote to thallium and radio-cesium poisoning (chelating agent).

The insoluble form of prussian blue is used for the treatment of acute and chronic thallium poisoning. It may also be used for the treatment of radio-cesium contamination. Radio-cesium's biological half-life may be as long as 150 days in humans. Administration of prussian blue has been shown to reduce the half-life of radio-cesium by one-third in some patients.

Dosage and administration

Acute thallium toxicity: *Oral*, 3 g administered immediately, followed by either 3 to 20 g a day in evenly divided doses or 250 mg per kg of body weight a day in 4 divided doses. The dosage may be given for 2 to 3 weeks or until the 24-hour urinary thallium excretion is less than 0.5 mg.

Chronic thallium toxicity: *Oral*, 3 to 20 g a day in evenly divided doses or 250 mg per kg of body weight a day in 4 divided doses. The dosage may be given for 2 to 3 weeks or until the 24-hour urinary thallium excretion is less than 0.5 mg.

Radio-cesium toxicity: *Oral*, 500 mg six times a day at 2-hour intervals for several days to 3 weeks.

The maximum total dose should not exceed 20 g a day.

For patients who cannot be administered the drug orally, 1 g of prussian blue per 10 ml of 15 per cent mannitol solution may be given via duodenal or nasogastric tube.

Warning

1. Risk-benefit should be considered if it is to be used in patients with constipation and paralytic ileus.
2. It may cause constipation, and dark feces.
3. Administration of systemic chelating agents including soluble or colloidal form of prussian blue is not recommended in thallium

poisoning because these agents may cause an increase in the uptake of thallium into the brain.

Patient monitoring The following is recommended:

Serum or urine concentrations of thallium, to assess the extent of thallium exposure and to guide treatment.

Additional information Prussian blue may be mixed with a cathartic, such as 15 per cent mannitol solution or sorbitol, to prevent or lessen constipation.

Packaging and storage Prussian Blue for Oral Suspension shall be kept in single-dose or in multiple-dose containers, preferably of Type I glass.

PYRIDOXINE HYDROCHLORIDE INJECTION

Indication Antidote to cycloserine and isoniazid poisoning.

Strength available 100 mg per ml.

Dosage and administration

Cycloserine poisoning: *Intramuscular* or *intravenous*, 300 mg or more per day.

Isoniazid poisoning (10 g or more): An amount of pyridoxine equal to the amount of isoniazid ingested. *Intravenous*, 4 g followed by 1 g intramuscularly every 30 minutes.

Warning

1. Burning and stinging at the injection site may occur following intramuscular or subcutaneous injection.
2. Intravenous injection of large doses may cause seizure.

Packaging and storage Pyridoxine Hydrochloride Injection shall be kept in single-dose containers, preferably of Type I glass, protected from light.

SODIUM NITRITE INJECTION

Indication Antidote to cyanide poisoning.

Strength available 300 mg per 10 ml (3 per cent w/v solution).

Dosage and administration

Sodium nitrite is used in conjunction with sodium thiosulfate in the treatment of cyanide poisoning.

Adults: *Intravenous*, 300 mg (10 ml) administered at a rate of 75 to 150 mg (2.5 to 5 ml) per minute, followed by sodium thiosulfate injection (25 per cent w/v solution) in a dose of 12.5 g (50 ml).

Children: *Intravenous*, 6 mg (0.2 ml) per kg of body weight or approximately 180 to 240 mg (6 to 8 ml) per m^2 of body surface area administered at a rate of 75 to 150 mg (2.5 to 5 ml) per minute, followed by sodium thiosulfate injection (25 per cent w/v solution) in a dose of 412.5 mg per kg of body weight or 7 g per m^2 of body surface area, at a rate of 0.625 to 1.25 g (2.5 to 5 ml) per minute. The maximum total dose should not exceed 300 mg (10 ml).

If signs of cyanide toxicity are still present 2 hours following administration of sodium nitrite and sodium thiosulfate, administration of both may be repeated at one-half the original dose.

Contra-indication It is contra-indicated in patients with acquired or congenital methemoglobinemia.

Warning It may cause nausea and vomiting, headache, cyanosis, dyspnea, hypotension, and tachycardia.

Patient monitoring The following are recommended:

1. Arterial blood gas, to correct severe metabolic acidosis, frequently during administration of 100 per cent oxygen.
2. Blood pressure, to guide the rate of administration of sodium nitrite. Rapid administration may result in excessive vasodilation and hypotension.

3. Methemoglobin concentrations, to ensure that the methemoglobin concentration does not exceed 40 per cent in adults or 30 per cent in children, periodically during administration.

Additional information Sodium nitrite solutions are unstable and should be used immediately.

Packaging and storage Sodium Nitrite Injection shall be kept in single-dose containers, preferably of Type I glass, protected from light.

SODIUM POLYSTYRENE SULFONATE POWDER

Indication Antihyperkalemic.

Sodium polystyrene sulfonate is indicated in the treatment of hyperkalemia associated with oliguria or anuria due to acute renal failure.

Dosage and administration

Oral, 15 g one to four times a day, up to 40 g four times a day. (Onset: hours to days.)

To improve palatability, it may be mixed with food or a beverage, with the sorbitol given in addition. Alternate vehicles for mixing include warm water, 1 per cent w/v methylcellulose, or 5 to 10 per cent w/v dextrose in water.

Rectal, 25 to 100 g as needed, administered as a retention enema or inserted into rectum in a dialysis bag to facilitate recovery. Sodium polystyrene sulfonate is less effective with rectal administration than by the oral route.

For rectal administration, sodium polystyrene sulfonate is suspended in 100 to 200 ml of an aqueous vehicle (for example, 25 per cent sorbitol, 1 per cent methylcellulose or 10 per cent dextrose). Care should be taken that paste is not too thick because it will be less effective.

Warning

1. With large doses, constipation, loss of appetite, nausea or vomiting may occur.
2. Sodium polystyrene sulfonate may bind with magnesium or calcium found in nonsystemic antacids and laxatives, preventing neutralization of bicarbonate ions and leading to systemic alkalosis that may be severe; concurrent use is not recommended.

Patient monitoring The following are recommended:

1. Serum bicarbonate concentrations, once a week during chronic therapy, especially if patient is also receiving antacids or laxatives.
2. Serum calcium or magnesium concentrations, in patients receiving sodium polystyrene sulfonate for longer than 3 days.
3. Serum potassium concentration, to monitor effectiveness of treatment, at least once a day or as necessary.

Additional information Treatment with sodium polystyrene sulfonate may be discontinued when the serum potassium concentrations have been reduced to 4 to 5 mEq (mmol) per litre.

Packaging and storage Sodium Polystyrene Sulfonate Powder shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

Stability Sodium Polystyrene Sulfonate Powder should not be heated because changes in the exchange properties of the resin may occur. The extemporaneous suspensions of the resin should be freshly prepared and should not be stored for more than 24 hours.

SODIUM THIOSULFATE INJECTION

Indication Antidote to cyanide poisoning.

Sodium thiosulfate, in conjunction with sodium nitrite, is indicated for use as an antidote in the treatment of cyanide poisoning. Sodium

thiosulfate may be used to prevent cyanide toxicity caused by rapid infusion of sodium nitroprusside.

Cyanide poisoning is rapidly fatal either by inhalation or ingestion. Blood cyanide concentrations often are not available for several hours. Therefore, therapy should be instituted immediately based upon reasonable suspicion of cyanide toxicity.

Strength available 12.5 g per 50 ml (25 per cent w/v solution).

Dosage and administration

Sodium thiosulfate is used in conjunction with sodium nitrite in the treatment of cyanide poisoning.

Adults—Cyanide toxicity: *Intravenous*, 12.5 g (50 ml) administered at a rate of 0.625 to 1.25 g (2.5 to 5 ml) per minute, **after receiving** sodium nitrite (3 per cent w/v solution) in a dose of 300 mg (10 ml).

Cyanide toxicity, sodium nitroprusside-induced: *Intravenous*, administered concurrently with sodium nitroprusside at 5 to 10 times the rate of sodium nitroprusside.

Children—Cyanide toxicity: *Intravenous*, 412.5 mg per kg of body weight or 7 g per m^2 of body surface area, administered at a rate of 0.625 to 1.25 g (2.5 to 5 ml) per minute, **after receiving** sodium nitrite 180 to 240 mg (6 to 8 ml) per m^2 of body surface area [approximately 6 mg (0.2 ml) per kg of body weight] at a rate of 75 to 150 mg (2.5 to 5 ml) per minute. The maximum total dose of sodium nitrite injection (3 per cent w/v solution) should not exceed 300 mg (10 ml).

The maximum total dose of sodium thiosulfate injection should not exceed 12.5 g (50 ml).

If signs of cyanide toxicity are still present 2 hours following administration of sodium nitrite and sodium thiosulfate, administration of both may be repeated at one-half the original dose.

Warning

1. Risk-benefit should be considered if it is to be used in patients with cirrhosis, congestive heart failure, renal function impairment or toxemia of pregnancy.

2. It may cause thiocyanate toxicity at serum thiocyanate concentration above 10 mg per 100 ml, including arthralgia, blurred vision, hyperreflexia, muscle cramps, nausea, vomiting, psychotic behaviour or tinnitus.

3. Rapid administration may cause hypotension.

4. Edematous sodium-retaining conditions, especially hypertension, may be exacerbated.

Patient monitoring The following is recommended:

Blood pressure and methemoglobin concentrations, monitored closely.

Packaging and storage Sodium Thiosulfate Injection shall be kept in single-dose containers, preferably of Type I glass.

SUCCIMER CAPSULES

(Meso-2,3-dimercaptosuccinic Acid; DMSA)

Indication Antidote to lead.

Succimer is indicated for the treatment of lead poisoning in children with blood lead concentrations above 45 μg per dl.

Strength available 100 mg.

Dosage and administration

Children: *Oral*, 10 mg per kg of body weight or 350 mg per m^2 of body surface area every 8 hours for 5 days, then 10 mg per kg of body weight every 12 hours for the next 14 days for a total of 19 days therapy. Treatment may be repeated after a drug-free interval of 2 weeks, unless blood lead concentrations indicate the need for immediate retreatment.

Warning

1. Gastro-intestinal disturbances, specifically loss of appetite,

diarrhea, loose stools, nausea and vomiting, unpleasant odour to urine, sweat, and feces may occur.

2. As succimer heavy metal chelates are excreted in urine, renal function impairment may delay or decrease excretion.

Patient monitoring The following are recommended:

1. Alkaline phosphatase, blood urea nitrogen (BUN) concentrations, complete blood count (CBC) with differential, serum creatinine and hepatic transaminases concentrations and platelet counts determinations, before therapy and weekly during therapy.

2. Lead concentration in blood, to ascertain dosage and duration of therapy, after therapy. Weekly monitoring for a rebound of blood lead concentration is suggested until the patient is stable.

Additional information Adequate urine flow must be established before and during succimer chelation therapy.

Packaging and storage Succimer Capsules shall be kept in well-closed containers and stored at a temperature not exceeding 30°.

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ประกาศกระทรวงสาธารณสุข

เรื่อง ระบุตำรายา พ.ศ. 2547

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อาศัยอำนาจตามความในมาตรา 76(1) แห่งพระราชบัญญัติยา พ.ศ. 2510 ซึ่งแก้ไขเพิ่มเติมโดยพระราชบัญญัติยา (ฉบับที่ 3) พ.ศ. 2522 รัฐมนตรีว่าการกระทรวงสาธารณสุข โดยคำแนะนำของคณะกรรมการยาออกประกาศไว้ดังต่อไปนี้

ข้อ 1 ให้ยกเลิก

1.1 ประกาศกระทรวงสาธารณสุข เรื่อง ระบุตำรายา พ.ศ. 2544

1.2 ประกาศกระทรวงสาธารณสุข เรื่อง ระบุตำรายา (ฉบับที่ 2) พ.ศ. 2544

ข้อ 2 ให้ตำรายาต่อไปนี้เป็นตำรายาแผนปัจจุบัน

2.1 ตำรายาของประเทศไทย เล่มที่ 1 ภาค 1 และภาค 2 และฉบับเพิ่มเติม (Thai Pharmacopoeia Volume I Part 1, Part 2 and Supplement) ซึ่งจัดพิมพ์โดยกระทรวงสาธารณสุข

2.2 ตำรายาของประเทศไทย เล่มที่ 2 ภาค 1 ภาค 2 และภาค 3 และฉบับเพิ่มเติม (Thai Pharmacopoeia Volume II Part 1, Part 2, Part 3 and Supplements) ซึ่งจัดพิมพ์โดยกระทรวงสาธารณสุข

2.3 ตำรามาตรฐานยาสมุนไพรไทย เล่มที่ 1 และฉบับเพิ่มเติม (Thai Herbal Pharmacopoeia Volume I and Supplements)

2.4 ตำรามาตรฐานยาสมุนไพรไทย เล่มที่ 2 และฉบับเพิ่มเติม (Thai Herbal Pharmacopoeia Volume II and Supplements)

2.5 ตำราอินเตอร์แนชนาลฟาร์มาโคเปีย ฉบับพิมพ์ ครั้งที่ 3 และฉบับเพิ่มเติม (Third Edition of the International Pharmacopoeia and Supplements)

2.6 ตำราฟาร์มาโคเปียของสหรัฐอเมริกา ฉบับแก้ไข ครั้งที่ 22 (ค.ศ. 1990) และฉบับเพิ่มเติมตำราแนชนาลฟอร์มูลารี่ ฉบับที่ 17 (ค.ศ. 1990) และฉบับเพิ่มเติม (The United States Pharmacopoeia Twenty Second Revision 1990 and Supplement, The National Formulary, Seventeenth Edition (1990) and Supplements)

2.7 ตำราฟาร์มาโคเปียของสหรัฐอเมริกา ฉบับแก้ไข ครั้งที่ 23 (ค.ศ. 1995) และฉบับเพิ่มเติมตำราแนชนาลฟอร์มูลารี่ ฉบับที่ 18 (ค.ศ. 1995) และฉบับเพิ่มเติม (The United States Pharmacopoeia Twenty Third Revision 1995 and Supplements, The National Formulary, Eighteenth Edition (1995) and Supplements)

2.8 ตำราบริติชฟาร์มาโคเปีย ฉบับ ค.ศ. 1988 เล่มที่ 1 และเล่มที่ 2 และฉบับเพิ่มเติม (British Pharmacopoeia 1988 Volume I, Volume II and Addenda)

2.9 ตำราบริติชฟาร์มาโคเปีย ฉบับ ค.ศ. 1993 เล่มที่ 1 และเล่มที่ 2 และฉบับเพิ่มเติม (British Pharmacopoeia 1993 Volume I, Volume II and Addenda)

2.10 ตำราบริติชฟาร์มาโคเปีย (สัตวแพทยศาสตร์) ฉบับ ค.ศ. 1998 และฉบับเพิ่มเติม (British Pharmacopoeia (Veterinary) 1998 and Supplements)

ข้อ 3 ให้ตำรายาต่อไปนี้เป็นตำรายาแผนโบราณ

3.1 ตำราเวชศึกษาของพระยาพิศณุประสาทเวช

3.2 ตำราแพทย์ศาสตร์สงเคราะห์ เล่ม 1 เล่ม 2 และเล่ม 3

3.3 ตำราแพทย์ศาสตร์สงเคราะห์ ฉบับหลวง เล่ม 1 และเล่ม 2

3.4 ตำราคัมภีร์แพทย์แผนโบราณของขุนโสภิตบรรณลักษณ์ เล่ม 1 เล่ม 2 และเล่ม 3

3.5 ตำรามาตรฐานยาสมุนไพรไทย เล่มที่ 1 และฉบับเพิ่มเติม (Thai Herbal Pharmacopoeia Volume I and Supplements)

3.6 ตำรามาตรฐานยาสมุนไพรไทย เล่มที่ 2 และฉบับเพิ่มเติม (Thai Herbal Pharmacopoeia Volume II and Supplements)

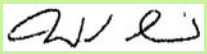
ข้อ 4 ประกาศฉบับนี้ให้ใช้บังคับตั้งแต่วันถัดจากวันประกาศในราชกิจจานุเบกษาเป็นต้นไป

ประกาศ ณ วันที่ 30 กันยายน พ.ศ. 2547

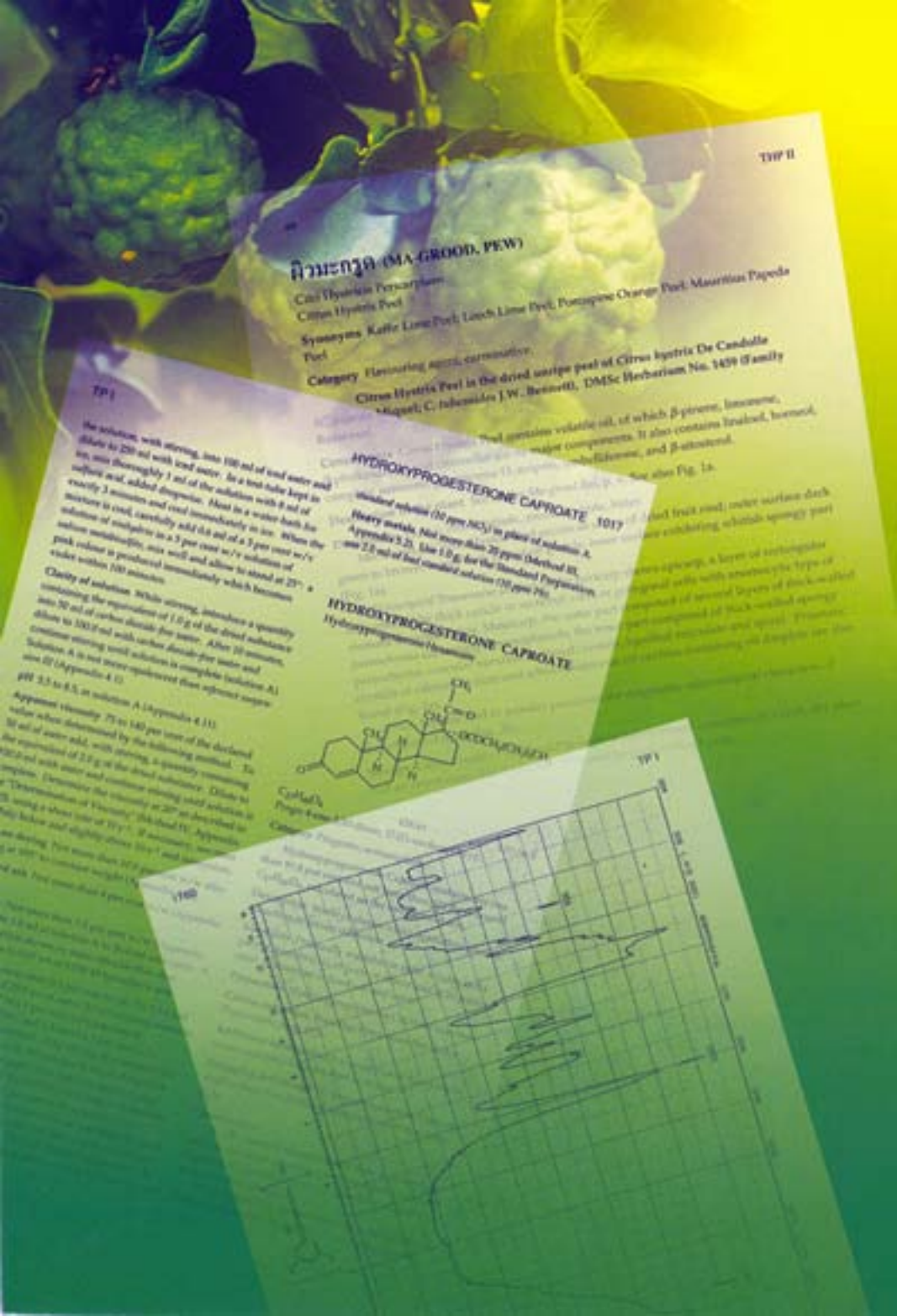
สุดารัตน์ เกยุราพันธ์
(สุดารัตน์ เกยุราพันธ์)
รัฐมนตรีว่าการกระทรวงสาธารณสุข

(คัดจากราชกิจจานุเบกษา ฉบับประกาศทั่วไป เล่ม 121 ตอนพิเศษ 121 ง วันที่ 27 ตุลาคม 2547)

สำเนาถูกต้อง



(นางสาวนันทรัตน์ ราชนานนท์)
เภสัชกร 7 วช.



มะกรูด (MA-GROOD, PEW)

Citrus Hystrix Perscarpium
Citrus Hystrix Peel

Synonyms Kaffir Lime Peel; Leech Lime Peel; Porcupine Orange Peel; Mauritius Papeda Peel

Category Flavouring agent; carminative.

**Citrus Hystrix Peel is the dried unripe peel of *Citrus hystrix* De Candolle (Nagel; C. Schneider J.W. Bennett), DMSc Herbarium No. 1459 (Family

TYP II

TYP I

HYDROXYPROGESTERONE CAPROATE 1017

HYDROXYPROGESTERONE CAPROATE

TYP I