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Pharmacotherapeutics in Critical Care



Editors
Srinivas Samavedam
Ganshyam Jagathkar

JAYPEE

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CHAPTER 2.9

Toxicology/Envenomation

Srinivas Samavedam, Nandha Kishore Jampala

ANTIDOTES, BINDING AGENTS AND CHELATION THERAPY IN THE INTENSIVE CARE UNIT

Srinivas Samavedam

INTRODUCTION

Antidotes are therapeutic agents that counteract the toxic effects of poisons by modifying toxin kinetics or interfering with their biological effects. They may reduce toxin absorption, bind and neutralize the poison, inhibit conversion to toxic metabolites, block receptors, or reverse end-organ effects. Chelating agents are a specific class of antidotes that form stable, nontoxic complexes with metals or metal ions, facilitating their mobilization from tissues and subsequent renal or biliary excretion. Binding agents act by physically sequestering toxins in the circulation or gastrointestinal tract, thereby reducing the free or biologically active fraction of the poison. This group includes nonspecific adsorbents such as activated charcoal as well as specific binders such as immunotherapy (e.g., digoxin-specific Fab fragments). Together, antidotes, chelators, and binding agents play a targeted yet adjunctive role in toxicological emergencies, complementing definitive supportive care and organ support.[1]

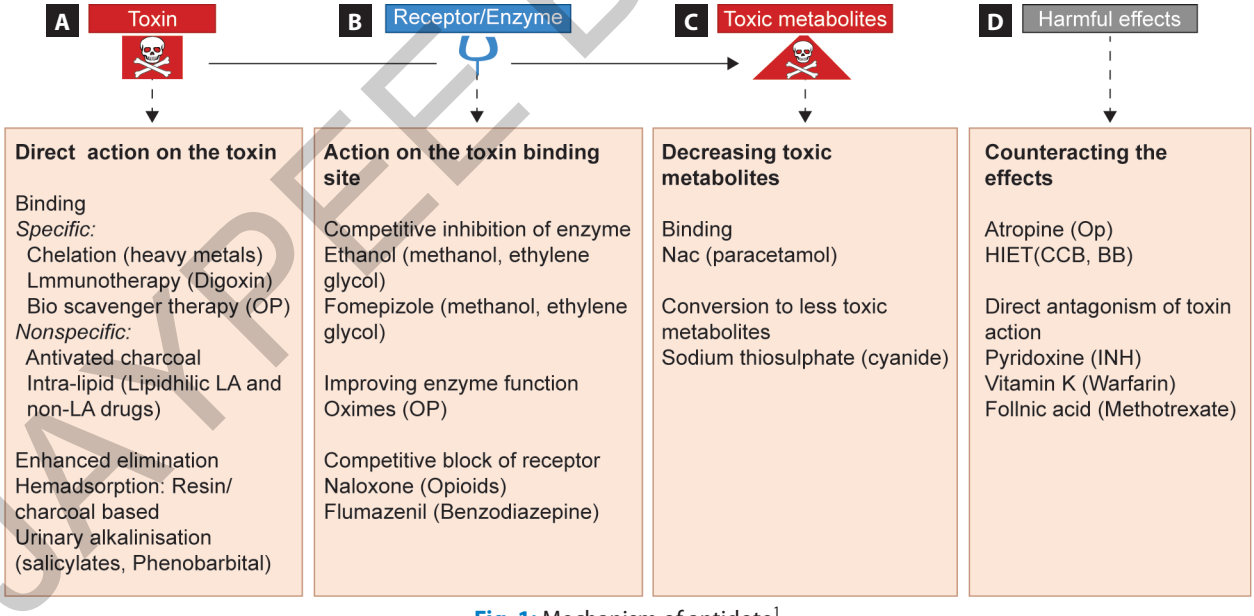

Fig. 1: Mechanism of antidote[1]

ACTIVATED CHARCOAL

Pharmacological Class

Antidote—binding agent

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Pharmaceutical Composition

Activated charcoal, available as oral tablets containing 500 mg per unit.

Mechanism of Action

Activated charcoal exerts its effect through adsorption, binding a wide range of ingested drugs and toxins to its large surface area within the gastrointestinal tract, thereby reducing systemic absorption.

When administered as multidose activated charcoal (MDAC), it enhances elimination of certain drugs by interrupting enterohepatic and enteroenteric circulation. This is particularly effective for substances with prolonged absorption or significant enterohepatic circulation, such as carbamazepine, dapsone, quinine, phenobarbital, and theophylline.

Pharmacokinetics

Activated charcoal is not absorbed from the gastrointestinal tract. It remains confined to the intestinal lumen, passes through the gut unchanged, and is completely eliminated in the feces.

Routes of Administration

Oral

Indications

Activated charcoal is indicated in selected cases of acute poisoning when there is a high risk of severe systemic toxicity, no specific antidote is available, or ingestion involves modified-release or extended-release formulations.

Multidose activated charcoal is specifically indicated in overdoses involving carbamazepine, dapsone, quinine, phenobarbital, and theophylline.

Contraindications

Contraindications include altered mental status with absent protective airway reflexes, uncooperative patients, known or suspected intestinal obstruction, gastrointestinal hemorrhage, or gastrointestinal perforation.[2] Activated charcoal is contraindicated in poisonings involving hydrocarbons, corrosive acids or alkalis, and iron.

Dosage and Administration

Activated charcoal is most effective when administered within 1 hour of toxin ingestion.

- *Single-dose activated charcoal:* 1 g/kg orally or via nasogastric tube, up to a maximum of 50 g
- *MDAC:* Initial dose of 50 g orally or via nasogastric tube, followed by 25–50 g every 4 hours

Adverse Effects

Adverse effects include nausea, vomiting, risk of pulmonary aspiration, bezoar formation, constipation, and, rarely, intestinal obstruction.

ANTIDIGOXIN FAB FRAGMENTS

Pharmacological Class

Toxin-binding agent (immunotherapy)

Pharmaceutical Composition

Purified, lyophilized Fab fragments derived from ovine immunoglobulin G (IgG) antibodies specific to digoxin, supplied at a concentration equivalent to 40 mg per vial after reconstitution.[3]

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Mechanism of Action

Antidigoxin Fab fragments bind free digoxin molecules with high affinity, forming antibody–toxin complexes that redistribute digoxin from intracellular to extracellular compartments. These complexes are pharmacologically inactive and are subsequently eliminated through renal excretion, thereby rapidly reducing the biologically active fraction of circulating digoxin.

Pharmacokinetics

The apparent volume of distribution is approximately 0.4 L/kg, with a biphasic or triphasic distribution pattern. In patients with normal renal function, the elimination half-life ranges from 19 to 30 hours, which may increase more than tenfold (>100 hours) in the presence of renal failure.

Route of Administration

Intravenous

Indications

Antidigoxin Fab fragments are indicated in patients with acute or chronic digoxin toxicity associated with:

- Life-threatening ventricular or severe supraventricular arrhythmias
- Symptomatic bradyarrhythmias unresponsive to conventional therapy
- Hyperkalemia (serum potassium >6 mmol/L)
- Hemodynamic instability with elevated serum digoxin concentrations (>2 ng/mL or >2.6 nmol/L)

Owing to structural similarities among cardiac glycosides (cardenolides), antidigoxin Fab fragments are also effective in neutralizing other glycosides, including lanatoside C, proscillaridin, scilliroside, and toxins found in *Nerium oleander*, as well as certain toad and crab venoms.

Contraindications

Known hypersensitivity to sheep-derived immunoglobulins.

Dosage and Administration

Each 40 mg vial of antidigoxin Fab fragments binds approximately 0.5 mg of digoxin. Serum digoxin concentrations measured at least 6 hours after the last digoxin dose provide an accurate estimate of total body digoxin burden:

- *Acute digoxin toxicity:* 80 mg administered intravenously over a minimum of 30 minutes; a repeat dose may be given after 60 minutes if clinical response is inadequate or toxicity recurs.
- *Chronic digoxin toxicity:* 40 mg administered intravenously over at least 30 minutes, with a repeat dose after 60 minutes if required.
- *Nondigoxin cardiac glycoside poisoning (e.g., yellow oleander):* Higher cumulative doses, up to 800 mg, may be necessary due to greater toxin load and binding requirements.

Preparation and Dilution

The lyophilized powder should be reconstituted with sterile isotonic saline solution. Following reconstitution, the preparation should be administered immediately or stored under refrigeration and used within 4 hours.

Adverse Effects

Adverse effects are generally mild and include hypersensitivity reactions. Rapid neutralization of digoxin may precipitate atrial fibrillation, worsening left ventricular function, and hypokalemia due to the abrupt reversal of digoxin-mediated potassium shifts.

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ANTISNAKE VENOM

Pharmacological Class

Antidote (immunotherapy)

Pharmaceutical Composition

Antisnake venom (ASV) used in India is a refined and concentrated equine-derived immunoglobulin preparation intended for intravenous administration. It contains $F(ab')_2$ fragments obtained from the plasma of healthy horses hyperimmunized against the venoms of the following medically important snakes:

- Indian cobra (*Naja naja*)
- Common krait (*Bungarus caeruleus*)
- Russell's viper (*Daboia russelii*)
- Saw-scaled viper (*Echis carinatus*)

The formulation also contains cresol as an antimicrobial preservative.

Mechanism of Action

Antisnake venom consists of specific antibodies that bind circulating venom toxins to form high-molecular-weight venom–antivenom immunocomplexes. These complexes sequester toxins within the central circulation, thereby limiting their distribution to peripheral tissues and target organs.

The $F(ab')_2$ fragments facilitate the formation of multivalent immunocomplexes, which are subsequently cleared by phagocytic cells of the reticuloendothelial system. Antivenom can neutralize toxins present in the plasma, interstitial fluid, and, to a limited extent, toxins already bound to tissue targets. Consequently, its therapeutic effects extend to both free and tissue-associated venom components.

Pharmacokinetics

$F(ab')_2$ fragments have a relatively low molecular weight and a large volume of distribution. Following intravenous administration, antivenom demonstrates a biphasic decline in plasma concentration, characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. Clearance of venom–antivenom complexes is primarily mediated by the mononuclear phagocyte system.

Route of Administration

Intravenous

Indications

Management of clinically significant local and systemic envenomation following snakebite.

Contraindications

There are no absolute contraindications to the use of ASV in life-threatening envenomation.

Dosage and Administration

Neurotoxic envenomation:

- *Initial dose:* 10 vials administered as an intravenous infusion over 30 minutes
- If there is no clinical improvement within the first hour, a second dose of 10 vials may be administered.
- *Maximum recommended dose:* 20 vials

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Vasculotoxic envenomation: Two-dosing strategies are commonly used—low-dose continuous infusion and high-dose intermittent bolus therapy. Evidence suggests that low-dose infusion is as effective as high-dose bolus therapy while conserving antivenom resources.

- *Low-dose infusion regimen*
  - Russell's viper: 10 vials stat infusion over 30 minutes
  - Saw-scaled viper: 6 vials stat infusion over 30 minutes
  - Followed by 2 vials every 6 hours diluted in 100 mL normal saline, continued until clotting parameters normalize or for a maximum of 3 days, whichever occurs earlier.
- *High-dose intermittent bolus regimen*
  - 10 vials administered stat as an intravenous infusion over 30 minutes
  - Followed by 6 vials every 6 hours as bolus therapy until clotting time normalizes and/or local swelling subsides

If a cumulative dose of 30 vials has been administered, further antivenom therapy should be carefully reconsidered, particularly in the absence of ongoing systemic bleeding or clear evidence of active envenomation.[4]

Preparation and Dilution

Antisnake venom supplied in lyophilized form should be reconstituted with 10 mL of sterile distilled water or normal saline. Reconstitution should be performed by gentle swirling and not by vigorous shaking. The solution should not be used if it appears turbid or opaque. Routine test dosing is not recommended.

Adverse Effects

Adverse reactions may include urticaria, anaphylaxis, nausea, vomiting, abdominal pain, diarrhea, chills, fever, and delayed serum sickness.

ATROPINE

Pharmacological Class

Antimuscarinic (anticholinergic) agent

Pharmaceutical Composition

Atropine sulfate is available in injectable formulations with variable concentrations, commonly 0.6 mg/mL and 1 mg/mL.

Mechanism of Action

Atropine acts as a competitive antagonist at muscarinic acetylcholine receptors (M1–M5), thereby reversing the effects of excessive cholinergic stimulation at parasympathetic effector sites.

Pharmacokinetics

Atropine exhibits rapid systemic distribution with an apparent volume of distribution of approximately 1.6 ± 0.4 L/kg.[5] The elimination half-life (β phase) is approximately 3.0 ± 0.9 hours. Following intravenous administration, peak plasma concentrations are achieved immediately, while intramuscular and subcutaneous routes result in a time to peak concentration of approximately 30 minutes.

Atropine undergoes stereoselective hepatic metabolism, with preferential biotransformation of the biologically active levoenantiomer. The inactive dextroenantiomer is excreted unchanged in the urine. Identified urinary metabolites include tropine, noratropine, atropine-*N*-oxide, and tropic acid.

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Routes of Administration

Intravenous administration is preferred in acute intoxication in intensive care settings. Intramuscular administration is recommended in prehospital or field settings. Subcutaneous, oral, and ophthalmic routes are also available for nontoxicological indications.

Indications

Management of organophosphorus and carbamate poisoning.

Contraindications

There are no absolute contraindications to atropine use in life-threatening cholinergic toxicity.

Dosage and Administration

Multiple dosing strategies have been described; however, a titrated dosing approach is recommended in acute poisoning. An initial adult loading dose of 1.8–3 mg of atropine is administered intravenously. Subsequent doses are doubled every 3–5 minutes until clinical atropinization is achieved.

Therapeutic endpoints of atropinization include:

- Clear lung fields on auscultation
- Heart rate >80 beats per minute
- Resolution of miosis
- Dry axillae
- Systolic blood pressure >80 mm Hg

Following initial atropinization, a continuous atropine infusion should be initiated at 10–20% of the total effective bolus dose per hour, with ongoing titration based on clinical response.

Adverse Effects

Adverse effects may include hypersensitivity reactions, delirium, urinary retention, constipation, and paralytic ileus.

CALCIUM DISODIUM EDTA (CALCIUM EDETATE)

Pharmacological Class

Chelating agent

Pharmaceutical Composition

Calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$) is available as a 200 mg/mL injectable ampoule.

Mechanism of Action

Calcium disodium EDTA chelates divalent and trivalent metal ions, particularly lead, by forming stable, water-soluble complexes. These metal–chelator complexes are biologically inert and are eliminated primarily through renal excretion.[6]

Pharmacokinetics

Calcium disodium EDTA is poorly absorbed following oral administration and therefore must be given parenterally. The apparent volume of distribution is approximately 0.19 L/kg. In individuals with normal renal function, the serum elimination half-life is approximately 2 hours. The drug is excreted unchanged in the urine, predominantly via glomerular filtration.

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Routes of Administration

Intravenous infusion or deep intramuscular injection

Indications

Management of severe lead poisoning

Contraindications and Precautions

Calcium disodium EDTA should be used with caution in patients with underlying renal impairment due to the risk of nephrotoxicity.

Dosage and Administration

- *Intravenous route:* A total daily dose of 2–4 g of $CaNa_2EDTA$ diluted to a concentration of 2–4 mg/mL in 0.9% normal saline or 5% dextrose, administered as a continuous intravenous infusion over 24 hours. Therapy should not exceed 5 consecutive days to minimize the risk of renal toxicity.
- *Intramuscular route:* A total daily dose of 2–4 g is administered as deep intramuscular injections in divided doses at 8–12-hours intervals.

Adverse Effects

Adverse effects include elevations in serum creatinine, mild and reversible increases in hepatic transaminases, and depletion of essential trace elements, particularly zinc.

CYPROHEPTADINE

Pharmacological Class

First-generation antihistamine

Pharmaceutical Formulation

Cyproheptadine hydrochloride, available as 4 mg oral tablets

Mechanism of Action

Cyproheptadine is a nonselective antihistamine with additional potent antagonistic activity at 5-HT2A serotonin receptors. This serotonergic receptor blockade forms the pharmacological basis for its use in the treatment of serotonin syndrome, where it mitigates the effects of excessive serotonergic activity.

Pharmacokinetics

Cyproheptadine is well absorbed following oral administration and exhibits a high volume of distribution. Hepatic metabolism occurs predominantly via hydroxylation, *N*-demethylation, oxidation, and subsequent glucuronidation. Approximately, two-thirds of the administered drug is excreted through the kidneys, with the remainder eliminated via fecal routes.

Route of Administration

Oral

Indications

Management of acute serotonin syndrome.

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Contraindications

Cyproheptadine is contraindicated in patients with known hypersensitivity to the drug, pyloroduodenal obstruction, or angle-closure glaucoma. Its use is also contraindicated during lactation.

Dosage and Administration

An initial oral dose of 12 mg is recommended, followed by 2 mg every 2 hours until clinical improvement or resolution of serotonergic toxicity is achieved. Maintenance therapy may be continued with 8 mg administered every 6 hours, based on clinical response.[7]

Adverse Effects

Reported adverse effects include hypersensitivity reactions, dizziness, sedation, and anticholinergic effects such as dry mouth and urinary retention, precipitation of glaucoma, thrombocytopenia, and cholestatic liver injury.

DEFEROXAMINE

Pharmacological Class

Chelating agent

Pharmaceutical Composition

Deferoxamine mesylate is supplied as a lyophilized powder containing 500 mg per vial.

Mechanism of Action

Deferoxamine selectively chelates ferric (Fe^{3+}) ions to form a highly stable, water-soluble iron–deferoxamine complex known as ferrioxamine. This complex is readily excreted in the urine, often resulting in a characteristic orange-pink to red discoloration.

Deferoxamine primarily binds circulating nontransferrin-bound iron and progressively mobilizes iron from intracellular storage forms such as ferritin and hemosiderin. It does not chelate iron bound to heme-containing proteins or enzymatic systems. Approximately, 100 mg of deferoxamine is capable of binding about 8.5 mg of elemental iron.[8]

Pharmacokinetics

Oral absorption of deferoxamine is poor, necessitating parenteral administration. The apparent volume of distribution ranges from 0.6 to 1.33 L/kg. The elimination half-life is approximately 3–6 hours, with predominant renal excretion of ferrioxamine complexes.

Routes of Administration

Intravenous, intramuscular, and subcutaneous.

Indications

- Acute and chronic iron poisoning
- Aluminum toxicity, particularly in patients with chronic kidney disease

Contraindications

- Known hypersensitivity to deferoxamine
- Severe renal impairment

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Dosage and Administration

- *Acute iron toxicity:*
  - *Hemodynamically stable patients:* An initial dose of 1,000 mg administered intramuscularly, followed by 500 mg every 4 hours for two additional doses. Thereafter, 500 mg may be administered intramuscularly every 4–12 hours based on clinical response. The total dose should not exceed 6,000 mg in 24 hours.
  - *Hemodynamically unstable patients:* An initial intravenous dose of 1,000 mg administered at a rate not exceeding 15 mg/kg/h, followed by 500 mg every 4 hours for two doses at an infusion rate not exceeding 125 mg/h. Additional doses of 500 mg may be administered as slow intravenous infusions every 4–12 hours according to clinical response. Once the patient stabilizes, intravenous therapy should be discontinued and treatment transitioned to the intramuscular route. The total daily dose should not exceed 6,000 mg.
- *Chronic iron overload:* A daily dose of 1,000–2,000 mg (20–40 mg/kg/day) administered over 8–12 hours is recommended. Alternatively, doses of 40–50 mg/kg/day may be administered intravenously over 8–12 hours for 5–7 days per week, depending on clinical indication and tolerance.

Adverse Effects

Rapid or inadvertent bolus administration may result in hypotension, tachycardia, agitation, transient visual disturbances, and acute renal failure. High cumulative doses have been associated with acute respiratory distress syndrome. Other adverse effects include local injection-site reactions, anaphylaxis, gastrointestinal symptoms (diarrhea, nausea, and vomiting), thrombocytopenia, transaminitis, and an increased susceptibility to infections, particularly with *Yersinia* species and mucormycosis.

DIMERCAPROL (BRITISH ANTI-LEWISITE)

Pharmacological Class

Chelating agent

Pharmaceutical Composition

Dimercaprol is supplied as an injectable formulation in ampoules containing 3 mL of a 10% solution of 2,3-dimercapto-1-propanol dissolved in 20% benzyl benzoate in peanut oil.

Mechanism of Action

Dimercaprol exerts its chelating effect through sulfhydryl (–SH) groups that bind heavy metal ions, thereby preventing or reversing the inhibition of sulfhydryl-dependent enzymes.[9] The resulting metal–dimercaprol complexes are rendered less toxic and are subsequently eliminated from the body. Continued administration promotes sustained mobilization and excretion of metals such as arsenic, gold, and mercury.

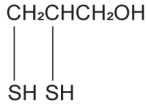

Fig. 2: Chemical structure of Dimercaprol/British Anti-Lewisite.

Pharmacokinetics

Following intramuscular administration in individuals exposed to arsenic, dimercaprol produces a rapid increase in urinary arsenic excretion, with peak elimination occurring within 2–4 hours, followed by a prompt decline. After chelation with metals including arsenic, gold, and mercury, the complexes are predominantly excreted via the kidneys, with smaller amounts eliminated through the biliary and fecal routes.

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Route of Administration

Intramuscular

Indications

- Acute intoxication with arsenic, gold, or mercury
- Acute lead poisoning, particularly lead encephalopathy, when used in combination with $CaNa_2EDTA$

Contraindications

Dimercaprol is contraindicated in patients with hepatic insufficiency.

Dosage and Administration

- *Arsenic and gold poisoning:*
  - *Mild toxicity:* Dimercaprol 2.5 mg/kg intramuscularly four times daily for the first 2 days, followed by twice-daily dosing on day 3, and then once daily for the subsequent 10 days.
  - *Severe toxicity:* Dimercaprol 3 mg/kg intramuscularly every 4 hours for the first 2 days, followed by four doses on day 3, and then twice-daily administration for the next 10 days.
- *Mercury poisoning:* An initial intramuscular dose of 5 mg/kg, followed by 2.5 mg/kg administered once or twice daily for a total duration of 10 days.
- *Acute lead encephalopathy:* Dimercaprol 4 mg/kg administered intramuscularly as an initial dose, followed by 4 mg/kg every 4 hours in combination with $CaNa_2EDTA$ for ongoing chelation therapy.

Adverse Effects

Intramuscular administration is frequently associated with tachycardia and hypertension. Other adverse effects include nausea, vomiting, headache, chest tightness, abdominal pain, and painful sterile abscesses at injection sites.

FLUMAZENIL

Pharmacological Class

Antidote (benzodiazepine receptor antagonist).

Pharmaceutical Composition

Flumazenil is supplied as an injectable solution at a concentration of 0.1 mg/mL.

Mechanism of Action

Flumazenil is a competitive antagonist at the γ-aminobutyric acid type A (GABA-A) receptor benzodiazepine-binding site. By displacing benzodiazepine agonists from the receptor, it reverses their sedative and hypnotic effects without intrinsic agonist activity.

Pharmacokinetics

Flumazenil undergoes extensive first-pass hepatic metabolism, resulting in low oral bioavailability (approximately 16%). It has a volume of distribution of approximately 1 L/kg and is approximately 50% protein-bound. Following intravenous administration, the onset of action occurs within 1–2 minutes, with peak clinical effects observed at 6–10 minutes. The drug is metabolized hepatically to inactive metabolites and has a short elimination half-life of approximately 0.8 hours.

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Route of Administration

Intravenous

Indications

Flumazenil may be considered in selected cases of isolated benzodiazepine overdose in benzodiazepine-naïve patients.

Contraindications

- *Absolute:* Known hypersensitivity to flumazenil
- *Relative:*
  - Coingestion of proconvulsant agents (e.g., tricyclic antidepressants)
  - Benzodiazepine dependence or tolerance
  - Current treatment for seizure disorders or a prior history of seizures

Dosage and Administration

The U.S. Food and Drug Administration–approved regimen for reversal of benzodiazepine-induced sedation involves an initial dose of 0.2 mg administered intravenously over 30 seconds. If the desired level of consciousness is not achieved within 1 minute, an additional 0.3 mg may be administered over 30 seconds. Subsequent doses of 0.5 mg may be given at 1-minute intervals, to a maximum cumulative dose of 3.0 mg.[10]

Given its short duration of action, patients should be closely monitored for resedation, and repeat dosing may be required.

Adverse Effects

Adverse effects include agitation, sympathetic activation, hypotension, and seizures, particularly in patients with benzodiazepine dependence or mixed-drug overdoses.[11]

FOLINIC ACID (LEUCOVORIN)

Pharmacological Class

- Water-soluble vitamin
- Antidote

Pharmaceutical Composition

Folinic acid is available as calcium folinate in the following formulations:

- Sterile, preservative-free injectable solution containing 10 mg/mL per vial
- Oral tablets containing 15 mg calcium folinate

Mechanism of Action

Folinic acid is a reduced and biologically active form of folate that does not require activation by dihydrofolate reductase. As a result, it bypasses the enzymatic blockade induced by methotrexate and restores intracellular folate pools, thereby enabling DNA and RNA synthesis. This protective mechanism, known as leucovorin rescue, selectively mitigates methotrexate toxicity in normal tissues without reversing its antineoplastic effects.[12]

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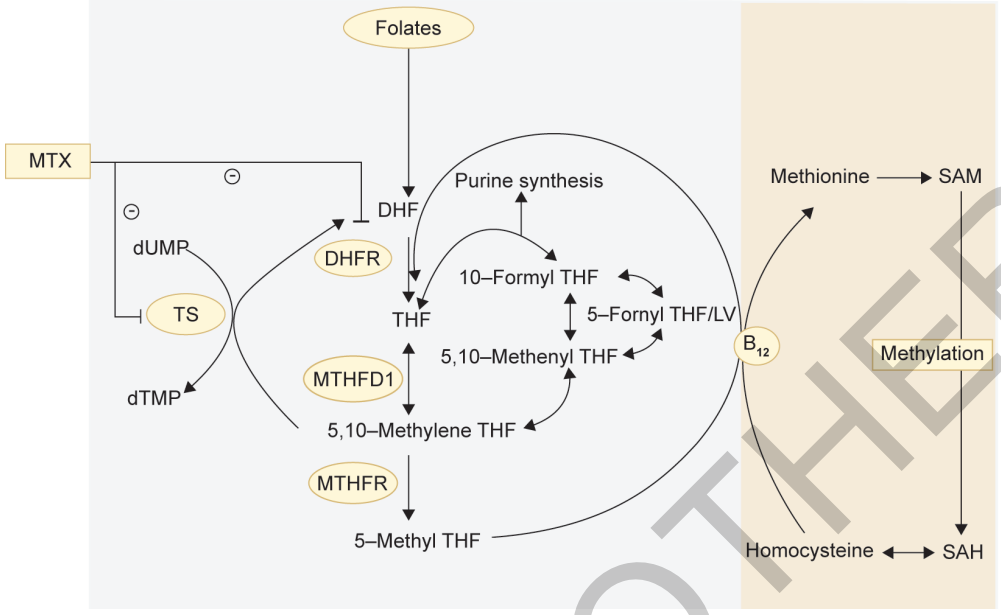

Fig. 3: Leucovorin (5-formyl THF) rescue therapy.[12]
(DHF: dihydrofolate; DHFR: dihydrofolate reductase; MTHFD1: methylenetetrahydrofolate dehydrogenase 1; MTHFR: methylenetetrahydrofolate reductase; MTX: methotrexate; LV: Leucovorin; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; THF: tetrahydrofolate; TS: thymidylate synthase)

Pharmacokinetics

Oral absorption of folinic acid is high, with approximately 97% bioavailability following a 25-mg dose; absorption decreases with doses exceeding 25 mg. Peak plasma concentrations are achieved within 1–2 hours after oral administration. Folinic acid undergoes hepatic metabolism to active metabolites, including 5-methyltetrahydrofolate and L-formyltetrahydrofolate, as well as an inactive metabolite, D-formyltetrahydrofolate. Excretion occurs predominantly via the kidneys in urine.

Routes of Administration

Oral, intramuscular, and intravenous.

Indications

Management and prevention of toxicity associated with high-dose methotrexate chemotherapy.

Contraindications

Known hypersensitivity to folinic acid or its components.

Dosage and Administration

Serum methotrexate concentrations and renal function guide leucovorin dosing.

Normal methotrexate elimination:

- *Laboratory findings:* Serum methotrexate ~10 µmol/L at 24 hours, ~1 µmol/L at 48 hours, and <0.2 µmol/L at 72 hours
- *Dose:* 15 mg orally, intramuscularly, or intravenously every 6 hours for 60 hours (10 doses), beginning 24 hours after initiation of methotrexate infusion

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Delayed late methotrexate elimination:

- *Laboratory findings:* Serum methotrexate >0.2 μmol/L at 72 hours and >0.05 μmol/L at 96 hours
- *Dose:* Continue 15 mg orally, intramuscularly, or intravenously every 6 hours until the methotrexate concentration falls below 0.05 μmol/L

Delayed early methotrexate elimination and/or acute kidney injury:

- *Laboratory findings:* Serum methotrexate ≥ 50 μmol/L at 24 hours or ≥5 μmol/L at 48 hours, or a ≥100% rise in serum creatinine at 24 hours
- *Dose:* 150 mg intravenously every 3 hours until the methotrexate concentration decreases to <1 μmol/L, followed by 15 mg intravenously every 3 hours until the concentration is <0.05 μmol/L

Intravenous leucovorin infusions should not exceed a rate of 160 mg/min due to the calcium content of the formulation.

Adverse Effects

Adverse effects are generally mild and include hypersensitivity reactions, anaphylaxis, nausea, abdominal discomfort, and sleep disturbances.

FOMEPIZOLE

Pharmacological Class

Antidote (alcohol dehydrogenase inhibitor).

Pharmaceutical Composition

Fomepizole is supplied as a sterile injectable solution containing 1 g/mL.

Mechanism of Action

Fomepizole acts as a competitive inhibitor of alcohol dehydrogenase, thereby preventing the metabolism of ethylene glycol and methanol into their respective toxic metabolites. By inhibiting the formation of glycolic acid, oxalic acid, and formic acid, fomepizole mitigates metabolic acidosis and end-organ toxicity associated with these alcohols.

Pharmacokinetics

The apparent volume of distribution ranges from 0.6 to 1.02 L/kg. Fomepizole undergoes hepatic metabolism, primarily via oxidation to 4-hydroxymethylpyrazole and subsequently to 4-carboxypyrazole. The drug demonstrates nonlinear (saturable) elimination kinetics. Its metabolites are excreted renally in the urine. Fomepizole is efficiently removed by hemodialysis, with intermittent modalities providing greater clearance than continuous renal replacement therapies.

Route of Administration

Intravenous

Indications

Fomepizole is indicated for the treatment of confirmed or suspected ethylene glycol or methanol poisoning, either as monotherapy or in conjunction with hemodialysis.

Contraindications

Known hypersensitivity to fomepizole

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Dosage and Administration

Fomepizole therapy should be initiated immediately upon suspicion of ethylene glycol or methanol ingestion, based on clinical history and/or laboratory findings such as high anion gap metabolic acidosis, elevated osmolar gap, visual disturbances, presence of oxalate crystals in urine, or a documented serum ethylene glycol or methanol concentration >20 mg/dL.[13]

The recommended dosing regimen consists of:

- A loading dose of 15 mg/kg should be administered intravenously
- Followed by 10 mg/kg every 12 hours for four doses intravenously
- Thereafter, 15 mg/kg every 12 hours intravenously

Treatment should be continued until ethylene glycol or methanol concentrations are undetectable or reduced below 20 mg/dL, the patient is asymptomatic, and acid–base status has normalized. All doses should be administered as slow intravenous infusions over 30 minutes.

Adverse Effects

Common adverse effects include headache, nausea, dizziness, increased drowsiness, and an unpleasant metallic or bitter taste.

GLUCAGON

Pharmacological Class

- Antihypoglycemic agent
- Pancreatic hormone

Pharmaceutical Composition

Glucagon hydrochloride, supplied as a lyophilized powder containing 1 mg per vial for parenteral administration.

Mechanism of Action

Glucagon increases plasma glucose concentrations by activating hepatic glucagon receptors, leading to stimulation of glycogenolysis and subsequent release of glucose from hepatic stores.

In addition, glucagon exerts potent positive inotropic and chronotropic effects on the myocardium by binding to specific cardiac glucagon receptors. These effects are mediated through increased intracellular cyclic adenosine monophosphate (cAMP) generation and occur independently of β-adrenergic receptors. This unique mechanism underlies its therapeutic role in the management of β-blocker and calcium channel blocker overdose.[14]

Pharmacokinetics

Following subcutaneous or intramuscular administration, peak plasma glucagon concentrations are typically achieved within 10–13 minutes. The apparent elimination half-life ranges from approximately 25–45 minutes. Glucagon is rapidly degraded in the liver, kidneys, and plasma.

Routes of Administration

Subcutaneous, intramuscular, and intravenous.

Indications

- Severe hypoglycemia
- Hemodynamically significant β-blocker or calcium channel blocker overdose

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Contraindications

- Pheochromocytoma
- Insulinoma or glucagonoma
- Known hypersensitivity to glucagon

Dosage and Administration

- *Severe hypoglycemia:* An initial dose of 1 mg glucagon administered subcutaneously or intramuscularly into the upper arm, thigh, or buttock. If there is no clinical response within 15 minutes, a second 1-mg dose may be administered.
- *β-blocker or calcium channel blocker overdose:* An initial intravenous bolus of 2–10 mg glucagon is administered, followed by a continuous intravenous infusion at a rate of 1–15 mg/h, titrated to hemodynamic response.

Adverse Effects

Adverse effects include nausea and vomiting, hypersensitivity reactions, and metabolic disturbances. Hypertensive crisis may occur in patients with pheochromocytoma, while paradoxical hypoglycemia may be seen in patients with insulinoma or glucagonoma. Rarely, necrolytic migratory erythema has been reported.

HIGH-DOSE INSULIN EUGLYCEMIA THERAPY

Pharmacological Class

Pancreatic hormone

Pharmaceutical Composition

Human regular insulin supplied as a sterile solution containing 40 U/mL per vial. The formulation includes *m*-cresol as a preservative and glycerin as a tonicity-modifying agent.

Mechanism of Action

High-dose insulin euglycemia therapy (HIET) mitigates cardiogenic shock through multiple complementary mechanisms:

- *Enhanced myocardial glucose utilization:* It improves myocardial energy efficiency and augments cardiac contractility, particularly in states of impaired free-fatty-acid utilization.
- *Vasodilatory effects:* Insulin increases endothelial nitric oxide synthase activity, resulting in vasodilation of systemic, coronary, and pulmonary vascular beds, thereby improving tissue perfusion.
- *Improved calcium handling:* Insulin enhances intracellular calcium signaling within cardiomyocytes, contributing to positive inotropic effects independent of β-adrenergic pathways.

These mechanisms are particularly beneficial in β-blocker and calcium channel blocker toxicity, where conventional catecholamine-based therapies may be ineffective.[15]

Pharmacokinetics

Following intravenous administration, human regular insulin has an onset of action within 10–15 minutes, with peak effects occurring at 15–30 minutes and a duration of action of approximately 30–60 minutes. Elimination occurs predominantly via renal degradation (approximately 60%), with the remaining 30–40% metabolized hepatically.

Route of Administration

Intravenous

Indications

Management of cardiogenic shock secondary to β-blocker or calcium channel blocker overdose.

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Contraindications

Persistent or refractory hypoglycemia.

Dosage and Administration

The recommended regimen for HIET includes:

- *Initial bolus:* Regular insulin 1 U/kg administered intravenously
- *Continuous infusion:* 1–2 U/kg/h intravenously, titrated according to hemodynamic response, up to a maximum of 10 U/kg/h

Concurrent intravenous dextrose infusion is mandatory to maintain blood glucose concentrations between 100 and 180 mg/dL. Potassium supplementation should be administered to maintain serum potassium levels between 3.0 and 3.5 mEq/L, with close monitoring of electrolytes.

Adverse Effects

Common adverse effects include hypoglycemia, hypokalemia, hypomagnesemia, and hypophosphatemia, necessitating vigilant glucose and electrolyte monitoring throughout therapy.

HYDROXOCOBALAMIN

Pharmacological Class

Chelating agent

Pharmaceutical Composition

Hydroxocobalamin is supplied as a lyophilized, dark red crystalline powder for injection, containing 5 g per vial.

Mechanism of Action

Hydroxocobalamin contains a cobalt atom that avidly binds cyanide ions to form cyanocobalamin, a nontoxic compound. Cyanocobalamin is subsequently eliminated via renal excretion, thereby facilitating detoxification of cyanide.

Pharmacokinetics

Following intravenous administration of a 5-g dose, mean peak plasma concentrations (C_{max}) of approximately 579 µg-equivalents/mL have been reported. The steady-state volume of distribution ranges between 21.8 and 25.6 L. The elimination half-life varies from 24 to 48 hours.[16]

Route of Administration

Intravenous

Indications

- Treatment of acute cyanide poisoning
- Refractory vasoplegia associated with intoxications

Contraindications

There are no absolute contraindications to hydroxocobalamin administration in suspected or confirmed cyanide toxicity.

Dosage and Administration

The recommended initial dose is 5 g administered intravenously over 15 minutes. Based on clinical severity and response, an additional 5 g may be administered over 15 minutes. The maximum cumulative dose is 15 g.

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Adverse Effects

Adverse reactions include hypersensitivity reactions, anaphylaxis, transient hypertension, acute kidney injury, photosensitivity, and characteristic reddish discoloration of the skin, mucous membranes, and urine. These discolorations are benign and self-limiting but may interfere with certain laboratory assays.

INTRAVENOUS LIPID EMULSION (INTRALIPID)

Pharmacological Class

- Lipid emulsion for parenteral nutrition
- Antidote

Pharmaceutical Composition

Intralipid is a sterile intravenous lipid emulsion containing 20% soybean oil, 1.2% egg yolk phospholipids as emulsifying agents, 2.25% glycerol for isotonicity, and water for injection.

Mechanism of Action

The antidotal effect of intravenous lipid emulsion in toxicity due to local anesthetics and other highly lipophilic drugs is multifactorial and incompletely understood.[17] Proposed mechanisms include:

- *Lipid sink (or lipid shuttle) effect:* The lipid emulsion sequesters lipophilic drugs from highly perfused organs such as the brain and myocardium, thereby reducing tissue drug concentrations. These drug–lipid complexes are subsequently redistributed to the liver, skeletal muscle, and adipose tissue for metabolism and storage.
- *Metabolic support and mitochondrial effects:* Provision of free fatty acids may improve myocardial energy substrate availability and attenuate mitochondrial dysfunction. Lipid emulsion may also reduce nitric oxide–mediated myocardial depression.
- *Direct cardiotonic effects:* Free fatty acids can activate voltage-gated calcium channels in cardiomyocytes, increasing intracellular calcium concentrations and partially counteracting toxin-induced myocardial depression.

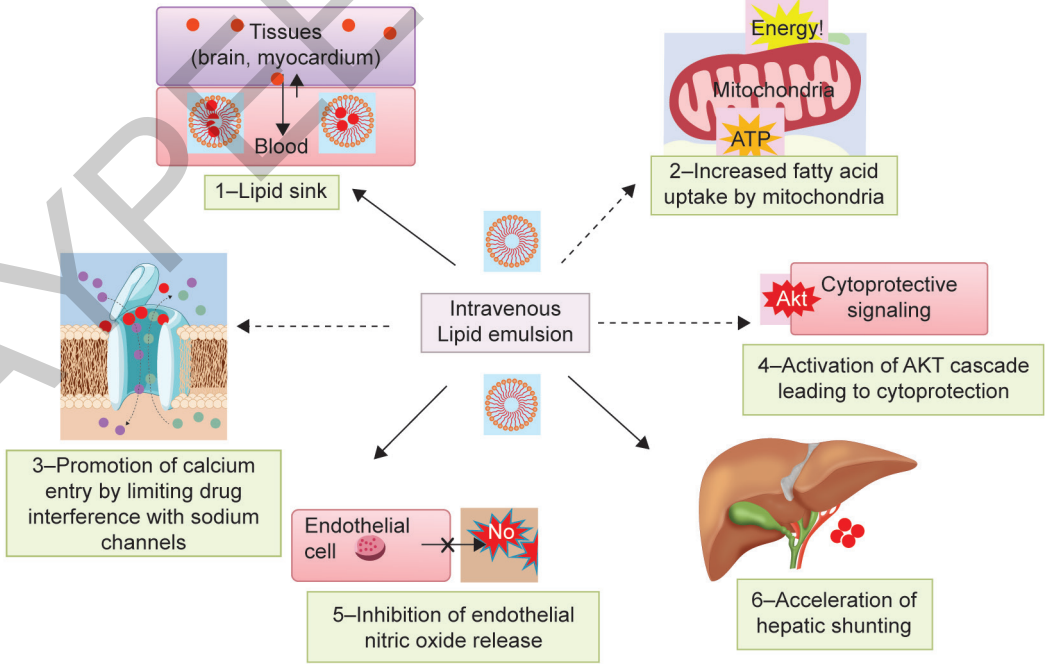

Fig. 4: Suggestive mechanism of action of Intralipid[17]

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Pharmacokinetics

Intralipid follows first-order kinetics. The reported half-life of triglycerides in the emulsion is approximately 13.7 ± 5.2 minutes, which is shorter than the elimination half-life of many local anesthetics and other lipophilic toxins. Consequently, continuous infusion following an initial bolus is recommended to maintain therapeutic lipid concentrations.

Route of Administration

Intravenous

Indications

- Local anesthetic systemic toxicity (LAST)
- Severe poisoning with highly lipid-soluble drugs causing cardiovascular or neurological compromise refractory to standard resuscitative measures

Contraindications

- Known hypersensitivity to soybean oil or egg phospholipids
- Active pancreatitis
- Severe hypertriglyceridemia

Dosage and Administration

The American College of Medical Toxicology (ACMT) recommends the following regimen using 20% intravenous lipid emulsion:

- Initial bolus: 1.5 mL/kg administered intravenously over 2–3 minutes
- Continuous infusion: 0.25 mL/kg/min following the bolus

In cases of cardiac arrest (asystole or pulseless electrical activity), the bolus may be repeated if there is an inadequate response. Unless clinically indicated, the infusion should be discontinued after 60 minutes.

Adverse Effects

Reported adverse effects include acute kidney injury, acute respiratory distress syndrome, venous thromboembolism, hypersensitivity reactions, fat embolism, pancreatitis, interference with extracorporeal circuits, and allergic reactions. Except for allergic reactions, most adverse effects appear to be dose dependent.

METHYLENE BLUE

Pharmacological Class

Antidote

Pharmaceutical Composition

Methylene blue is available as an injectable solution at a concentration of 10 mg/mL per ampoule.

Mechanism of Action

Methylene blue acts as an artificial electron carrier within the erythrocyte. In the presence of nicotinamide adenine dinucleotide phosphate (reduced form; NADPH), it is reduced to leucomethylene blue, which subsequently donates electrons to methemoglobin (Fe^{3+}), converting it back to functional hemoglobin (ferrous iron, Fe^{2+}). This process enhances the activity of the alternative nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-dependent methemoglobin reductase pathway.[18]

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