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Principles and Practice of Critical Care Toxicology



Omender Singh
Deven Juneja

Foreword
Farhad N Kapadia

JAYPEE

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CHAPTER

Antidotes

Omender Singh, Anish Gupta

INTRODUCTION

Antidotes are substances which counteract and reverse the effects of poisons and toxins. Despite advances in medical science antidotes are available for a small number of toxins and poisons. However, whenever available they can be life-saving.

Antidotes act by various mechanisms to alleviate the effects of poisons (Table 1).

N-ACETYLCYSTEINE[1]

Specific antidote for paracetamol (acetaminophen) overdose/poisoning.

Mechanism of action:

- N-acetylcysteine (NAC) is a *glutathione* (GSH) precursor which increases GSH stores
- Directly binds to N-acetyl-p-benzoquinone imine (NAPQI)
- Increases metabolism of acetaminophen by sulfation pathway
- Antioxidant effect—reduces free radical generation and injury

Dose

Acute Paracetamol Poisoning

Both oral and intravenous routes can be used with no difference in efficacy. Both protocols are United States: the Food and Drug Administration (US-FDA) approved (Box 1).

Table 1: Mechanism of action of antidotes.

Mechanism	*Examples*
Chelation Antidotes combine with the poison to form inert nontoxic complexes, thus preventing their absorption and adverse effects	Deferoxamine, D-penicillamine, sodium calcium edetate, digoxin specific antibody fragments, pralidoxime, protamine
Detoxification of poison Certain antidotes prevent conversion of the poison to its toxic metabolite and hence prevent adverse effects	Fomepizole, ethanol, N-acetyl cysteine, methylene blue, sodium thiosulfate
Compete with effective receptor sites	Oxygen, naloxone, phytomenadione
Block the receptors through which toxic effects are mediated	Oxygen, glucagon, atropine.
Increase elimination	

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Box 1: Dosage protocols of N-acetylcysteine (NAC) for acute acetaminophen poisoning.

Protocols for NAC

Oral protocol:
- Loading dose: 140 mg/kg orally
- Maintenance doses: 70 mg/kg orally every 4 hours—Total 17 doses

IV protocol: 20-hour protocols (3 bag regimen and 2 bag regimen)

Traditional 3 bag regimen:
- Loading dose of 150 mg/kg IV over 1 hour, followed by
- 50 mg/kg IV over the next 4 hours (12.5 mg/kg/h), followed by
- 100 mg/kg IV over the next 16 hours (6.25 mg/kg/h)

The dilution is in 5% dextrose

2 bag regimen:[2]
- 50 mg/kg/hour over 4 hours (total 200 mg/kg) followed by
- 6.25 mg/kg/hour for 16 hours (total 100 mg/kg over 16 hours)

12 hour protocol:
- 50 mg/kg for 2 hours followed by
- 20 mg/kg/hour for 10 hours

When to Administer N-acetylcysteine?

The maximum benefit is when NAC is administered within 8 hours of acute acetaminophen ingestion but should be administered as soon as possible. It can be administered beyond 8 hours in cases of suspected poisoning, delayed presentation and ingestion of sustained release tablets.

Duration of Therapy

- Both the NAC protocols are time and fixed dose-based therapies.
- By convention, IV N-acetylcysteine is given for at least 20–21 hours and oral NAC is given for at least 72 hours.
- Extended duration of therapy may be needed in certain situations vis-à-vis:
  - Hepatic failure
  - Massive overdose, and
  - Ingestion of extended or sustained release preparations.

In such cases, treatment is continued till patients show clinical improvement, aminotransferase levels show a declining trend, coagulation parameters show an improving trend and the serum acetaminophen level is falling or undetectable (<10 μg/mL).

Adverse Effects of N-acetylcysteine

Allergic Reactions

Seen in 10–50% cases. Most often witnessed with intravenous preparations. Patients present with rash and urticaria. Although uncommon, anaphylactoid reactions can occur and are life-threatening. Reactions are related to the rate of NAC administration and are more often seen in asthmatics and in patients with low serum acetaminophen levels. In case a reaction occurs, the drug should be stopped and an antihistaminic should be administered. H1 antihistamine such as diphenhydramine is given IV at a dose of 25–50 mg and can be repeated to a maximum of 400 mg in 24 hours. Once symptoms settle, the infusion can be restarted at half the rate for 30 minutes, followed by the normal rate of infusion in the absence of any allergic reaction. In case of severe reactions, management is as for anaphylactic shock. Airway, breathing and circulation are assessed and stabilized. Adrenaline (1 mg/mL) at a dose of 0.1 mg/kg is administered intramuscularly in the vastus lateralis muscle (lateral aspect of mid-thigh).

All patients on NAC therapy should be monitored, preferably in an intensive care unit for any adverse reactions.

Nausea and Vomiting

Oral NAC is not palatable and leads to nausea and vomiting. To counter this effect, it is usually given with juices or as a chilled solution. In case vomiting occurs within 1 hour, the dose should be repeated. In patients intolerant to oral NAC, intravenous therapy may be needed.

Special situations

Massive Overdose (>500 mg/kg or >30 g)

The intravenous dose of NAC is same as previously mentioned except that the dose of the final infusion is doubled from 100 mg/kg to 200 mg/kg and continued till hepatic transaminase levels start declining and patient shows clinical improvement.

Dialysis

N-acetylcysteine is dialyzable and serum levels are reduced with hemodialysis. There are no clear-cut guidelines but it is advisable to double to dose of NAC during HD.

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Pregnancy/Breastfeeding

N-acetylcysteine is a pregnancy category B drug. It can be administered in pregnancy at usual doses as described for adults. It is not known if acetylcysteine is excreted in breast milk. Acetylcysteine is cleared off the body in about 30 hours. Nursing mothers can resume feeding 30 hours after the last dose.

ATROPINE[3]

It is an anticholinergic agent which inhibits the action of acetylcholine on parasympathetic sites and acts as a competitive antagonist of acetylcholine at muscarinic receptors. Atropine has no action on nicotine receptors. The indications of atropine are summarized in Table 2.

We will be discussing role of atropine in organophosphates poisoning.

Indications

Organophosphate and Carbamate Poisoning (OPC)[4]

These compounds bind to the enzyme acetylcholinesterase and inhibit its activity. As a result, there is excess acetylcholine (Ach) at the neuromuscular junction leading to cholinergic toxicity. Respiratory failure is the most common cause of death in OP poisoning and is secondary to muscarinic (bronchospasm, bronchorrhea, arrhythmias, and hypotension) and nicotinic effects (weakness and paralysis).

Atropine competitively inhibits the action of acetylcholine by competing with Ach for the muscarinic effects thus alleviating the cholinergic symptoms.

There is no standard dosing regimen of atropine for OP poisoning. The commonly followed dosing protocol is mentioned in the subsequent Box 2.

Other routes of administration: Atropine can be administered by intraosseous route or via endotracheal tube.

Intraosseous administration: The dose is 1:1 with IV dose.

Table 2: Indications of atropine.

General	*Off-label*
• Bradycardia • Preanesthetic agent • Organophosphorus compounds poisoning • Nerve agent poisoning • Beta-blocker poisoning	• Rapid sequence intubation • Stress echocardiography (chronotropic effect) • Mushroom poisoning (antimuscarinic effects)

Box 2: Dosing schedule for atropine in organophosphate (OP) poisoning.

Dose of Atropine

Adults
Loading dose:
Initial dose is 1–3 mg IV (depending on the severity)
Initial bolus dose can be 5 mg IV (in severe cases)
Double the dose every 3–5 minutes till atropinization is achieved
Continue bolus doses of atropine till the

- Heart rate > 80 beats/min
- Systolic blood pressure > 80 mm Hg and
- Chest is clear of secretions

} Atropinization

Tachycardia and pupillary dilatation (mydriasis) are no longer considered appropriate markers for atropinization as they can be confounded by hypoxia, hypovolemia and sympathetic overactivity.

Maintenance dose:

- About 10–20% of the total loading dose is started as an infusion to be administered over 1 hour
- Monitor for inadequate or excessive atropine dosing. In cases with inadequate dosing the cholinergic signs and symptoms may re-emerge while in excessive dosing the patient may become confused, agitated, hyperpyrexic and develop constipation and urinary retention

In cases of atropine toxicity it is advisable to stop the infusion for about an hour and let the symptoms abate before restarting the infusion.

Children (<12 years)
Loading dose: 0.05 mg/kg IV
Maintenance dose: 10–20 % of total loading dose and is usually in the range of 0.02–0.05 mg/kg/hour
Monitoring for features of cholinergic toxicity (suboptimal dosing) or atropine toxicity (excessive dosing)

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Endotracheal tube (ETT) administration: The dose is 2–3 times the IV dose diluted with 5 mL of normal saline and administered via ET. This is followed by five positive pressure breaths.

Nerve Agent Poisoning

Atropine can be used for nerve agent poisoning. However, the total dose required is lesser as compared to that required for organophosphorus compounds and depends on the severity of clinical features.

Mild features: Dose is 0.05 mg/kg by IV, IM or IO route (maximum 2 mg/dose).

Moderate features: Dose is 0.05 mg/kg (maximum 4 mg/dose).

Repeat every 3–5 minutes with a target of decrease in bronchial secretions and bronchospasm. Pralidoxime is administered along with atropine and will be discussed elsewhere.

Severe features: Dose is 0.1 mg/kg by IM route only (maximum 6 mg/dose). Dose can be repeated and titrated as per clinical end points.

Cardiac Glycoside Poisoning

Atropine has a role in the management of symptomatic bradycardia and high-degree AV-block due to cardiac glycoside toxicity and has been used with moderate success. The dose of atropine used is as per the 2010 ALCS/PALS guidelines for symptomatic bradycardia.

Adults: A bolus of 0.5 mg IV. The dose can be repeated every 5 minutes to a maximum of 3 mg.

Children: Bolus dose 0.02 mg/kg IV (minimum 0.1 mg, maximum 0.5 mg), repeated up to maximum 0.04 mg/kg (not to exceed 3 mg).

Beta-blocker and Calcium Channel Blocker Poisoning

Atropine can be used for mild cases of β-blocker and calcium blocker induced bradycardia but is usually ineffective. The doses are similar to that mentioned for cardiac glycoside toxicity.

Pregnancy/Breastfeeding

Pregnancy category B/C. Atropine crosses the placenta. No adverse events reported in animal studies. Atropine may suppress lactation. Use with caution.

BOTULINUM ANTITOXIN-HEPTAVALENT

It is an equine-derived antitoxin which is effective against 7 *Clostridium botulinum* antitoxins namely A, B, C, D, E, F and G (hence the name heptavalent). The total volume in a vial varies from 10 mL to 20 mL. It is used for the treatment of botulism.

Botulism[5]

Dose

The dose is based on the age and weight of the patient.

For infants less than 1 year of age, 10% of a single vial is to be administered irrespective of weight.

For patients 1–17 years of age dose is calculated based on weight of patient and varies from 20% to 100% of the vial. A minimum of 20% is to be used. The following formulas are used for calculating the dose.

≤30 kg: Percentage (%) of adult dose to be administered
= Weight (kg) × 2

>30 kg: Percentage (%) of adult dose to be administered
= Weight (kg) + 30

For patients more than 17 year of age one vial is administered.

There are no dose modifications in patients with renal or liver impairment.

Administration

The frozen antitoxin is thawed in a water bath at a temperature of 37°C. The vial should be inspected for any particulate matter, impurities and discoloration. Do not shake the vial and avoid any foaming. The antitoxin is diluted with normal saline (0.9%) to a ratio of 1:10. In some cases a premixed bag may be stored but should be used within 8–10 hours.

A hypersensitivity testing should be performed before starting the infusion. An intradermal test can be performed with 0.02 mL of 1:1,000 saline diluted antitoxin. A positive test is defined as a wheal with erythema of more than 3 mm than the control test with normal saline. The test is read at 15–20 minutes.

The antitoxin is administered by a slow IV infusion via an infusion pump at a dose of 0.5 mL/min for the first 30 minutes. In case there are no reactions the infusion is doubled every 30 minutes to a maximum of 2 mL/min. Epinephrine, antihistamines and crash cart should be kept available and accessible in case of dire emergencies.

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Pediatric patients (1–17 years): Start the infusion at 0.01 mL/kg/min for the first 30 minutes. In case of no reactions, increase the rate by 0.01 mL/kg/min every 30 minutes to a maximum rate of 0.03 mL/kg/min.

Adverse Effects

The common adverse effects are headache, chills, rash, urticaria, pruritis, fever, nausea, and anaphylaxis.

Pregnancy/Breastfeeding

Not known if the toxin crosses the placenta or is excreted in breast milk. Nursing mothers may have to discontinue feeding during therapy.

BOTULINUM IMMUNO GLOBULIN (INTRAVENOUS HUMAN) (BABYBIG)[6]

It provides antibodies from immunized adults for use in infant botulism (<1 year of age) caused by toxin type A and B. The dosage schedule is discussed in Box 3.

Administration

- Preferably administer via an infusion pump with a low-volume tubing.
- Always infuse through a separate IV line.
- Do not administer if solution is turbid.
- No dose modifications in renal/hepatic impairment.

Adverse Effects

Exact frequency is not defined. All systems can be affected and are more related to infant botulism rather than the immunoglobulin.

For allergic reactions, anaphylaxis the infusion should be slowed or temporarily stopped. Keep epinephrine handy for severe acute allergic reactions.

Box 3: Dose of botulinum immunoglobulin.

- Single dose 50 mg/kg as intravenous infusion.
- Always verify dose with manufacturer's drug insert as the dose may vary with each manufactured lot.
- Start infusion at 25 mg/kg/hour for the first 15 minutes, *then*
- Increase the infusion to a maximum rate of 50 mg/kg/hour (if well tolerated).
- The infusion should be completed in about 4 hours (if no adverse reaction).

Contraindications

- Hypersensitivity or previous allergic reaction to immune globulin or any component of the formulation
- Selective IgA deficiency.

Pregnancy/Breastfeeding

Only for use in infants less than 1 year. Do not administer to pregnant and breastfeeding women.

BROMOCRIPTINE

It is an ergot alkaloid with dopamine D2 receptor agonist activity. It activates the postsynaptic dopamine receptors in the tuberoinfundibular and nigrostriatal pathways, thereby decreasing prolactin secretions and increasing coordinated motor control.

Uses

- Parkinson's disease
- Hyperprolactinemia
- Acromegaly
- Diabetes mellitus—not routine recommendation
- Neuroleptic malignant syndrome (off-label use)

Neuroleptic Malignant Syndrome[7]

- Used for moderate to severe cases. Evidence supporting its use is minimal
- Dose—2.5 mg via PO route 3–4 times per day. Maximum dose 45 mg/day
- Continue treatment till NMS is controlled. Pediatric dose is unknown
- Administer with food to alleviate gastrointestinal distress
- No renal/hepatic dose modifications.

Adverse Effects

Orthostatic hypotension and syncope are commonly seen during initiation and escalation of therapy.

Most adverse effects are seen after prolonged use. Cardiac valvular fibrosis, pleural/pericardial effusions and fibrosis (pleural, pulmonary and retroperitoneal) have been reported.

Increased risk for melanoma especially in patients with Parkinson's disease.

CNS depression, hallucinations and loss of impulse control have all been reported.

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Use with caution in tasks requiring mental activity.

Discontinuation of therapy or dose reduction may be needed in some cases.

Pregnancy/Breastfeeding

- Pregnancy risk factor category B. It crosses placenta but data has not shown to increase the risk of birth defects. Preferable to discontinue bromocriptine once pregnancy is confirmed.
- Contraindicated during breastfeeding as it is known to inhibit lactation.

ACTIVATED CHARCOAL

It is commonly known as the "universal antidote". It is the most frequently used substance for gastrointestinal decontamination. It acts by the mechanism of adsorption wherein it binds various ingested drugs and toxins and prevents their systemic absorption. However, not all drugs/toxins can be adsorbed by charcoal and hence the term universal antidote may be a misnomer. It can be administered as both single-dose activated charcoal (SDAC) and multiple-dose activated charcoal (MDAC). MDAC is helpful for adsorbing toxins/drugs with high enterohepatic circulation. The efficacy of activated charcoal depends upon the lag time between toxin ingestion and AC administration. The more the lag time the lesser is the efficacy.

Dose

Previously, the recommended dosing was a ratio of 10:1 for charcoal: poison.[8] However, in most cases the amount of poison ingested is unknown making this approach challenging and impractical.[9]

The usual dose is 1 g/kg to a maximum for 50 g for a single dose.[9]

MDAC—the initial dose is up to 50 g followed by 25–50 g every 4 hours.

Administration

- Activated charcoal is unpalatable. Use flavoring or thickening agents (e.g. chocolate syrup, concentrated fruit juice, bentonite, carboxymethyl cellulose) to increase its palatability. However, these may reduce the ability of activated charcoal to adsorb poisons.
- Always check for the presence of bowel sounds before administration.
- Intravenous antiemetics may be required to reduce the risk of vomiting.
- Shake the activated charcoal container thoroughly before administration.
- Rinse the container with a small quantity of water to ensure that the patient has received all of the activated charcoal.[10]

Indications

Used in cases of poisoning wherein:

- Severe systemic toxicity is anticipated
- No effective antidote is available
- A modified release or extended release formulation is ingested
- Absence of contraindications (such as decreased mental status, poor airway reflexes precluding to an unprotected airway, uncooperative patient, ileus or intestinal obstruction).

It is important to note that AC is not effective in cases of poisoning with hydrocarbons, caustic acids and alkali, lithium and iron.

Administration of SDAC is not mandatory and decision is clinical and based on the risk: benefit ratio.

The maximal benefit of activated charcoal is when it is administered within 1 hour of poison ingestion.

Safety

Activated charcoal is considered safe as it has no systemic absorption. Risks include pulmonary aspiration, bezoar formation and intestinal obstruction.

Contraindications

As per the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centers and Clinical Toxicologists (EAPCCT) the contraindications to the use of AC are:

- Intestinal obstruction
- Anatomically abnormal GI tract
- Risk of GI hemorrhage or perforation
- Unprotected airway (poor airway reflexes, depressed level of consciousness, Glasgow coma scale < 8).

Pregnancy and Breastfeeding

Activated charcoal has no systemic adsorption after oral administration. Hence, use during pregnancy and breastfeeding is not expected to result in significant

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fetal exposure. In general antidotes if clearly indicated should be administered to a pregnant woman and should not be withheld because of the fear of teratogenicity.[11]

CALCIUM

Calcium is mainly used in body for modulation of nerve and muscle function. It plays a role in various metabolic and chemical reactions in the body.

Indications

- Hypocalcemia
- Calcium blocker overdose/poisoning (off label use)
- Beta-blocker overdose/poisoning (off label use)
- Hydrofluoric acid exposure/burns (off label use).

Calcium Channel Blocker Poisoning (Off Label)[12]

Indications: Causing hypotension and conduction disturbances.

Shock not responding to standard therapy:

- Bolus
  - Calcium gluconate (10%): 0.6 mL/kg. Repeat as needed
  - Calcium chloride (10%): 0.2 mL/kg
- Infusion
  - Calcium gluconate (10%): 0.6–1.5 mL/kg/hour *or*
  - Calcium chloride (10%): 0.2–0.5 mL/kg/hour.

Titrate the infusion rate to achieve adequate hemodynamic response (i.e. improvement in blood pressure and cardiac contractility).

Monitor serum ionized calcium levels. Goal is to maintain ionized calcium at twice normal only in life-threatening situations. Avoid hypercalcemia. Infusions should be administered only via a central venous access.

Beta-blocker Poisoning (Off-label)

- Hypotension or conduction disturbances not responding to standard therapy
- Optimal dose has not been established.
- The bolus dose and infusion are same as mentioned above for calcium channel blocker (CCB) poisoning.

Hydrofluoric Acid Burns/Exposure

Calcium gluconate provides calcium ions which complex with free fluoride ions and thus prevent or reduce toxicity and correct fluoride-induced hypocalcemia.

Used as various formulations:

- *Topical treatment*: Calcium gluconate gel (2.5%) to be applied within 3 hours of exposure.
- *Subcutaneous dose*: 0.5 mL/cm^2 of 5–10% calcium gluconate to be infiltrated 0.5 cm away from the margin of the injured tissue. Endpoint of therapy is relief of pain. Never use calcium chloride for subcutaneous injection.
- *Intra-arterial*: To be performed only by an expert accustomed with the technique. A clinical toxicologist should be consulted prior to administration. Meticulous care needs to be taken to prevent extravasation.

Dilute 10–20 mL of 10% calcium gluconate in 50 mL of normal saline or 5% dextrose and infuse into the artery supplying the affected area. Give the infusion slowly over 4 hours.

- *Inhalation*: A 2.5% nebulization solution is used for nebulization. Mix 1.5 mL of 10% calcium gluconate solution with 4.5 mL NS.

Note: Ocular exposure is treated with saline or sterile water irrigation. Calcium is not used in the irrigation fluid for cleaning eyes.

CALCIUM DISODIUM EDTA ($CaNa_2EDTA$)[13,14]

It is a chelating agent used in the treatment of lead poisoning and cadmium poisoning (off label). The heavy metal ions displace calcium and form calcium as nonionizing soluble complexes. These complexes are readily excreted in urine.

Indications

Lead Poisoning

Adults

Therapy recommended when blood lead levels > 50 µg/dL with symptoms *or* Blood levels > 100 µg/dL with or without symptoms Repeat doses may be required but should be administered after 2–3 days depending on blood lead levels. The dosing regimens are mentioned in Table 3.

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Table 3: Dosing regimen of edetate calcium disodium ($CaNa_2EDTA$).	
Blood lead levels and symptoms	Dose
<70 µg/dL + asymptomatic	1000 m^2/day for 5 days (IV, IM)
>70 µg/dL + symptomatic	Treat with both $CaNa_2EDTA$ and dimercaprol Begin treatment with $CaNa_2EDTA$ followed by dimercaprol IM, IV: 1,000 mg/m^2/day or 25–50 mg/kg/day for 5 days; a maximum dose of 3,000 mg has been suggested
Lead encephalopathy	Dimercaprol added to treatment regimen Begin treatment with $CaNa_2EDTA$ with the second dimercaprol dose 1,500 mg/m^2/day or 50–75 mg/kg/day for 5 days (maximum dose—3,000 mg)
Lead nephropathy	Modify dosing regimen due to decrease in creatinine clearance Regimen may need to be repeated monthly till lead levels are reduced to an acceptable level Creatinine: 2–3 mg/dL: 500 mg/m^2 every 24 hours x 5 days Creatinine: 3–4 mg/dL: 500 mg/m^2 every 48 hours for 3 doses Creatinine: >4 mg/dL: 500 mg/m^2 once weekly

Administration: Both intravenous (IV) and intramuscular (IM) routes can be used but intravenous route is preferred. IM route is preferred when cerebral edema is present.

IV infusion: Administer as a diluted solution over 8–12 hours or continuously over 24 hours.

For IM injection: Divide the daily dose into 2–3 equal doses and administer by deep IM injection 8–12 hours apart. Procaine hydrochloride or lidocaine may be added to minimize pain at injection site. When dimercaprol is also used inject into a separate site.

Dose reduction in renal disease. No dose modification in hepatic disease.

Pregnancy/breastfeeding: It is a pregnancy category B drug. No well-controlled studies in pregnant women.

Chelation therapy should be initiated with blood lead levels more than or equal to 45 µg/dL. If blood levels are more than 70 µg/dL or clinical features suggest lead encephalopathy, chelation therapy should be initiated irrespective of trimester.

Nursing mothers with blood lead levels more than or equal to 40 µg/dL should avoid breastfeeding. Calcium supplementation may reduce the amount of lead in breast milk.

Cadmium poisoning (off-label): May be beneficial in some cases. Chelation is effective only up to 24–48 hours postexposure.

Therapy is for 5 days with a dose of about 75 mg/kg/day divided into 3–6 doses. Total dose for 5 days should not exceed 500 mg/kg. A repeat course may be considered based on blood cadmium levels after 2 days.

DANTROLENE

It is a skeletal muscle relaxant used for the treatment of malignant hyperthermia and neuroleptic malignant syndrome (off label). It prevents the release of calcium from the sarcoplasmic reticulum in the skeletal muscle and thus decreases myoplasmic calcium concentrations.

Malignant Hyperthermia[15]

The Malignant Hyperthermia Association of the United States (MHAUS) recommendation is followed.

Dantrolene is administered at a dose of 2.5 mg/kg by intravenous route.

Dose may be repeated every 5–15 minutes till symptoms abate or a cumulative dose of 10 mg/kg is reached.

Post-crisis Management

As per MHAUS protocol, administer 1 mg/kg every 4–6 hours (route not specified) or a continuous IV infusion of 0.25 mg/kg/hour for at least 24 hours.

Administration

Doses are administered as rapid IV push during crisis. Follow-up doses are administered over at least 1 minute.

Adverse Effects

- Dantrolene is hepatotoxic and is reported at variable drug doses.

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- Risk of hepatotoxicity is higher in women (>35 years) and elderly patients.
- Begin treatment with the lowest possible effective dose.
- Monitor liver function tests routinely.

Pregnancy/Breastfeeding

It is a pregnancy category C drug. Dantrolene crosses placenta and small amounts are also present in breast milk.

DEFEROXAMINE

It is a chelating agent that forms complexes with ferric ions to form ferrioxamine, which is excreted by the kidneys. 100 mg of deferoxamine binds to 8.5 mg of free circulating elemental iron (85 mg per 1,000 mg dose). It does not bind to iron from transferrin or hemoglobin. It reduces the cytoplasmic free iron levels and thus free iron-induced disruption of mitochondrial cell membranes and enzyme systems. Ferrioxamine produces a pink- to red- or orange-colored urine. It is the drug of choice for iron poisoning.

Iron Poisoning[16]

- Severe intoxication with serum iron more than or equal to 500 µg/dL irrespective of symptoms.
- Severe symptomatic toxicity characterized by coma, metabolic acidosis, shock, gastrointestinal bleeding and cardiovascular collapse.
- Initial dose is 5 mg/kg/hour, which is gradually titrated up to 15 mg/kg/hour if well tolerated.
- Repeat dose of 500 mg every 4 hours can be administered for a maximum of two doses.
- Subsequent doses are administered at 4–12 hour intervals to a maximum of 6 g in 24 hours.
- Optimal duration of therapy is unknown. Therapeutic endpoints include serum iron level less than 350 µg/dL and resolution of signs of toxicity.
- Intravenous route is preferred. Rarely, intramuscular route may be used but is not recommended.

Dose Modification

No dose modification in hepatic disease. Contraindicated in severe renal disease or anuric patients[17] (Table 4).

Pregnancy and Breastfeeding

It is a pregnancy category C drug. Deferoxamine is not known to cross the placenta or excreted in breast milk. Use with caution.

DIMERCAPROL

It is also called British anti-Lewisite (BAL). It is used for the treatment of arsenic, gold and mercury poisoning. It provides sulfhydryl groups which combine with heavy metals to form nontoxic soluble chelates which are excreted in urine. The dosing regimens of dimercaprol is mentioned in Box 4.

Premedication with a H_1 histamine antagonist such as diphenhydramine is recommended.

Dose Modification

No renal dose modification. It is contraindicated in hepatic dysfunction except in hepatocellular injury secondary to arsenic.

Table 4: Dose modification of deferoxamine in renal dysfunction.

Creatinine clearance	>50 mL/min	10–50 mL/min or CRRT	<10 mL/min hemodialysis Peritoneal dialysis
Dose modification	No adjustment	Give 25–50% of dose	Contraindicated

Box 4: Dosing regimens of British anti-Lewisite (BAL) in arsenic, gold and mercury poisoning.

Arsenic or gold poisoning (Mild): 2.5 mg/kg every 6 hours for 2 days, then every 12 hours for 1 day, followed by once daily for 10 days

Arsenic or gold poisoning (Severe): 3 mg/kg every 4 hours for 2 days, then every 6 hours for 1 day, followed every 12 hours for 10 days

Inorganic mercury poisoning: 5 mg/kg initially, followed by 2.5 mg/kg 1–2 times/day for 10 days

Lead poisoning[13] *(No guideline or recommendation at present)*: 3–5 mg/kg IM followed by 3–4 mg/kg along with $CaNa_2EDTA$ every 4–6 hours for 3–5 days. Lower doses (2–3 mg/kg) may be used in the absence of encephalopathy

Note: Urine alkalization stabilizes the dimercaprol-metal complex, and is recommended during chelation therapy to prevent kidney damage.

All injections are administered deep intramuscular.

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Adverse Effects

- British anti-Lewisite is nephrotoxic. Maintain alkaline urine pH.
- Use with caution in G6PD patients as it can lead to hemolysis.

Pregnancy and Breastfeeding

Pregnancy category C drug. Not known if secreted in breast milk. Use with caution and only if benefits outweigh risks.

DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS

They are purified preparations of the Fab portion of the IgG anti-digoxin antibodies which are derived from immunized sheep. They bind to free digoxin to form immune complexes which are freely excreted in urine. As the free digoxin levels decrease in blood, digoxin dissociates from the sodium-potassium ATPase channel (Na-K-ATPase) along the concentration gradient thereby alleviating toxic symptoms. Hemodialysis is an ineffective treatment modality as the digoxin-immune fragment complexes are of large molecular size.

DigiFab is one of the commercial preparations and each vial contains 40 mg of Fab fragments which binds 0.5 mg of digoxin. It lacks the Fc portion of the antibody and hence allergic reactions are uncommon. However, individuals with allergies to sheep or papaya extracts (papain), which are used to cleave the antibody, are at risk.

Fab is used for the treatment of digitalis poisoning associated with life-threatening arrhythmias (Tachyarrhythmias—VT/VF, bradyarrhythmias—heart block, symptomatic bradycardia), hemodynamic instability and hyperkalemia.

It is also used for other cardiac glycoside toxicities such as oleander, quill and toad venom.

For acute toxicity the dose is calculated by various methods depending upon the clinical scenario (Table 5).[18,19]

Chronic Digoxin Ingestion

Lower dose of digoxin-Fab is used as the total body digoxin load is lower. Usually half the normal dose is given. One way is to administer 1 vial of Fab and observe for clinical response. If no response is seen in 1 hour a second ampule is given.

Nonpharmacological Cardiac Glycoside Poisoning

The serum concentrations do not correlate well and cannot be used to calculate the dose of Fab. Dose is 10 vials of Fab initially which is repeated if clinical response is inadequate.

Administration

- Administer slowly over 30 minutes in all cases
- Administer by slow IV push in cases of cardiac arrest or in whom arrest is imminent.

FLUMAZENIL[20]

It is an antidote used for the treatment of benzodiazepine poisoning and reversal of benzodiazepine induced sedation. It is an imidazobenzodiazepine derivative and is a competitive benzodiazepine receptor antagonist. It inhibits the activity at the benzodiazepine receptor site on the GABA/benzodiazepine receptor complex. Flumazenil does not antagonize the effect of drugs

Table 5: FAB dose for acute digitalis toxicity.

Digoxin level, *or* Amount ingested unknown	Amount of Digoxin ingested known but Digoxin concentration unknown	Digoxin concentration known
Empirical treatment 10 vials of DigiFab Repeat if no clinical response	Calculate total body load (TBL) TBL for digoxin = Dose in mg x 0.8 (0.8 – refers to bioavailability of digoxin and is a constant) No. of vials = TBL/0.5 (round off to nearest whole no.)	Number of vials = (Digoxin conc. ng/mL) (Wt kg) 100 or Digitoxin (ng/mL) × Wt (kg) 1,000

(FAB: antibody fragments; conc: concentration; Wt: weight))

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affecting GABA-ergic neurons and does not reverse the effects of opioids.

Benzodiazepine Poisoning

Initial dose is 0.2 mg over 30 seconds

↓ Response (regain of consciousness) is inadequate after 30 seconds

Repeat 0.3 mg over 30 seconds after 1 minute

↓ Response inadequate

Repeat 0.5 mg over 30 seconds at 1-minute intervals

↓

Maximum cumulative dose: 3 mg (usual total dose: 1 to 3 mg)

For patients with partial response at total dose of 3 mg, additional doses up to a total dose of 5 mg may be required. If no response after a total of 5 mg consider alternative diagnosis or effect of coingestants.

Monitor for at least 2 hours for sedation, respiratory depression, benzodiazepine withdrawal, and residual effects of benzodiazepines.

Although not FDA approved, IV infusion of 0.1–1 mg/hour may be used in certain cases of re-sedation.

Always administer into a large vein with a freely running intravenous fluid.

Dose modification is not needed for the initial doses in patients with hepatic impairment. However, subsequent doses may need to be reduced or frequency decreased. No renal dose modification required.

Adverse Effect

A notable adverse effect is seizures. They are mostly seen in patients on long-term benzodiazepine for sedation or in cases with signs of tricyclic antidepressant overdose. Keep a benzodiazepine at bedside in case of seizure.

Pregnancy and Breastfeeding

Pregnancy category C drug. Avoid used during labor and delivery. Not known if secreted in breast milk. Use with caution.

FOMEPIZOLE (4-METHYLPYRAZOLE)

Fomepizole is a competitive inhibitor of the enzyme alcohol dehydrogenase which catalyzes the metabolism of ethanol, ethylene glycol, and methanol. Methanol is metabolized to formaldehyde by alcohol dehydrogenase and by a series of subsequent reactions to formic acid. Formic acid leads to metabolic acidosis and visual impairment in methanol poisoning. Similarly, ethylene glycol is metabolized to glycoaldehyde and finally oxidized to form glycolate and oxalate. These compounds lead to metabolic acidosis and kidney damage. Hence, fomepizole is used for the treatment of ethylene glycol and ethanol poisoning.

Ethylene Glycol and Methanol Poisoning[21,22]

Begin treatment immediately.

Dose

Loading dose of 15 mg/kg, followed by 10 mg/kg 12 hourly for 2 days, followed by 15 mg/kg every 12 hours, until

- Ethylene glycol or methanol concentrations are less than 20 mg/dL *or*
- Patient is asymptomatic
- Acidosis is resolved.

Dose modification in hemodialysis[23] *(Table 6)*

Dose modification in liver disease: Fomepizole is metabolized in the liver. However, no dose modification has been described in hepatic impairment.

Table 6: Dosing schedule of fomepizole in patients on hemodialysis (HD).

Before	Determine when the last dose was given If given <6 hours: No additional dose required If ≥6 hours: Administer the next dose prior to HD
During	Administer fomepizole every 4 hours *or* Loading dose of 10–20 mg/kg followed by infusion at 1–1.5 mg/kg/hour
After	Determine when the last dose was given Last dose < 1 hour prior to completion—No additional dose Last dose 1–3 hour prior to completion—Administer half the scheduled dose Last dose > 3 hour prior to completion—Administer full scheduled dose after completion Maintenance dose when dialysis is stopped is 10–15 mg/kg every 12 hours.

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Role of hemodialysis in toxic alcohol poisoning:

- In severe cases hemodialysis may be required along with antidote. Hemodialysis should be considered as an adjunct to fomepizole.
- Indications of hemodialysis are renal failure, refractory metabolic acidosis and high alcohol concentrations more than 50 mg/dL.

Administration

All IV doses should be administered by slow infusion over 30 minutes. Do not administer as a bolus injection or in undiluted form.

Adverse Effects

- Hypersensitivity to fomepizole or components is contraindication to its use.
- Nausea and headache are common adverse effects.

Pregnancy/Breastfeeding

Pregnancy category C drug. Not known whether it is secreted in breast milk.

FOLIC ACID (VITAMIN B_9)

Folic acid is used as a cofactor for various metabolic reactions in the body. It is essential for purine and pyrimidine synthesis, nucleoprotein synthesis, maturation of RBCs and production of WBCs and platelets.

It has an off-label use for methanol poisoning[22] as it increases the metabolism of formic acid to nontoxic metabolites. It is used as an adjunct and should not be used as the sole agent for treatment.

Dose

It can be administered by both IV and oral route.[24]

- *Intravenous:* 50–70 mg every 4 hours
- *Oral:* 50 mg every 3–4 hours

Continue treatment till both methanol and formic acid are undetectable.

For dialysis patients administer the dose after completion of dialysis irrespective of timing of last dose.

Administration

- Administered by oral, IV, IM, and SC routes. Oral route preferred.
- Dose less than or equal to 5 mg administered undiluted over more than or equal to 1 minute or dilute in 50 mL of NS or D_5W and infuse over 30 minutes.

Pregnancy/Breastfeeding

Folic acid crosses placenta and is present in breast milk. Requirements of folic acid increase during pregnancy and supplementation is necessary.

GLUCAGON

Glucagon is a hormone which increases cyclic AMP production by stimulating adenylate cyclase. This increases glycogenolysis and gluconeogenesis in the liver leading to an increase in blood sugar. It also induces relaxation of smooth muscles especially in the stomach and gut. Glucagon also has a positive chronotropic and inotropic effect in the heart which is mediated by glucagon receptors. This mechanism makes it a treatment option for β-blocker or CCB poisoning induced myocardial depression.[25] It is used as an adjunct in cases not responding to standard therapy.

Dose

A bolus dose of 0.05–0.15 mg/kg (5–10 mg) is given over 1 minute followed by an infusion of 3–5 mg/hour (or 0.05–0.1 mg/kg/hour). Titrate infusion to clinical response and a target mean arterial pressure (MAP) of 65 mm Hg.[12] No hepatic/renal dose adjustments.

It is contraindicated in patients with pheochromocytoma, insulinoma, and glucagonoma. No adverse effect has been reported in pregnancy and breastfeeding.

Pregnancy/Breastfeeding

No reported adverse events. Use with caution.

HIGH-DOSE INSULIN THERAPY

High-dose insulin therapy (HDIT) is used for the treatment of β-blocker and CCB toxicity refractory to standard therapy.[26]

The exact mechanism of action is unknown. Both β-blockers and CCBs interfere with fatty acid metabolism in myocytes. This leads to insulin resistance and glucose dependence for functioning in the myocardial cells. In addition, secretion of insulin from beta cells of pancreas

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