

Avermectins (Lexi-Tox)

CAS Registration

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Use

Avermectins are macrocyclic lactone antihelminthic agents used for the systemic treatment of human and veterinary helminth and arthropod infections, as well as topically for the treatment of external parasites. Agriculturally, avermectins are used against insects and mites.

Most recently, ivermectin has demonstrated *in vitro* activity against SARS-CoV-2, the causative pathogen of coronavirus disease 2019 (COVID-19) (Caly 2020); the US Food and Drug Administration has warned against the use of products intended for animal use in humans (FDA 2020).

Clinical Presentation

Ingestion: Mild toxicity is characterized by gastrointestinal irritation (eg, abdominal pain, nausea, vomiting, diarrhea), CNS depression (eg, dizziness, drowsiness, headache and weakness), and mydriasis; symptoms may persist for ≤ 2 days (Chung 1999; Wimmersberger 2018). Patients with severe toxicity may develop coma, paralysis, weakness, headache, joint and muscle pain, hypotension, mild hypothermia, aspiration pneumonia, respiratory failure, and shock (Chung 1999; Hall 1985; Makenga 2019; Soyuncu 2007; Yang 2012; Yen 2004); onset of symptoms may occur within 3 hours of ingestion (Chung 1999).

Note: Clinicians should be aware that some avermectin products may be contained within solvents (eg, hexanol, propylene glycol) that can contribute to the toxicity and clinical presentation (Yang 2012).

Injection: Signs and symptoms of toxicity are similar to those seen following ingestion. Specific symptoms described following parenteral administration of avermectins have included

nausea, abdominal pain, pallor, and transient irritation, pain, and numbness at the site of injection (Chung 1999; Hall 1985).

Ocular: Ocular exposures may result in irritation (Hall 1985).

Comprehensive listing by system (listed alphabetically):

Cardiovascular: Hypotension, tachycardia

Dermatologic: Pallor, urticaria

Endocrine & metabolic: Metabolic acidosis (Chung 1999)

Gastrointestinal: Abdominal pain, cholelithiasis (Guzzo 2002), diarrhea, gastric erosion, gastritis (superficial), nausea, salivation, vomiting

Hematologic & oncologic: Prolonged prothrombin time (Homedia 1988)

Hepatic: Increased gamma-glutamyl transferase (Guzzo 2002), increased serum alanine aminotransferase (Guzzo 2002)

Local: Irritation, pain, numbness

Nervous system: Agitation, altered mental status, anxiety, ataxia, coma, confusion, delirium, dizziness, drowsiness, drug-induced psychosis (Mohapatra 2015), hyperactive deep tendon reflex, hypothermia, headache, lethargy, myoclonus, numbness, paresthesia, polyneuropathy (Sung 2009), restlessness, seizure, somnolence

Neuromuscular & skeletal: Asthenia, tremor

Ophthalmic: Blurred vision, mydriasis, nystagmus (Wenjie 2016), visual disturbance (ie, black spots, flashing lights)

Respiratory: Aspiration pneumonia (Chung 1999; Yen 2004), dyspnea, respiratory failure (Sung 2009)

Mechanism of Toxicity

The mechanism by which exposure to avermectins result in acute toxicity is thought to be an extension of their pharmacological properties. Avermectins bind with vertebrate and invertebrate g-aminobutyric acid (GABA) receptors and invertebrate glutamate-gated chloride ion channels (Chung 1999). This leads to increased permeability of cell membranes to chloride ions and then hyperpolarization of the nerve and/or muscle cells (Chung 1999). At high doses, avermectins may cross the blood brain barrier to produce GABA-mimetic toxic effects (Yang 2012).

Diagnosis

Diagnosis should be made based upon patient history, physical examination, laboratory findings, and clinical suspicion. Quantitative tests to determine serum avermectin concentrations are not widely available and would not be beneficial in the management of these patients.

Patients who present with symptoms of toxicity secondary to an avermectin agent should undergo evaluation of serum electrolytes, liver function as well as monitoring of hemodynamic and respiratory status.

Note: Intoxication secondary to an avermectin product contained within solvents (eg, hexanol, propylene glycol, etc) should prompt the clinician to include laboratory tests to evaluate other possible intoxicants (Yang 2012).

Laboratory Testing/Diagnostic Procedures

- Electrolyte Panel, Serum or Plasma
- Liver Function Panel, Serum or Plasma

Treatment: Stabilization

Initially, evaluate and correct immediate life-threatening complications (eg, airway, breathing, and circulation). The most serious complications include hypotension, respiratory failure, and coma (Yang 2012). Treatment is supportive and dependent on symptoms.

The following agents are **not** recommended for use in patients with avermectin intoxication:

- GABAergic drugs (eg, benzodiazepines, barbiturates): Because avermectins produce GABA-mimetic effects at large doses, GABAergic drugs (eg, benzodiazepines, barbiturates) should be avoided in patients with acute toxicity (Karunatilake 2012).

Treatment: Decontamination

Ingestion: If the patient presents within 1 hour of ingestion, consider the following decontamination procedure(s):

- Gastric lavage: In rare situations when gastric lavage is deemed appropriate, it is most effective if initiated within 1 hour of the ingestion; however, gastric lavage has not been proven to be beneficial and is not routinely recommended due to the risk of complications and the lack of demonstrated efficacy. Use is contraindicated in a patient with an unprotected airway, in a patient in whom its use increases the risk and severity of aspiration, and in a patient who is at risk of hemorrhage or gastrointestinal perforation due to pathology (Benson 2013; Vale 2004).
- Single-dose activated charcoal: Use may be considered in a patient who presents within 1 hour of the ingestion (Chyka 2005). Use is contraindicated in a patient who has a diminished level of consciousness, unless the airway is protected.

Activated charcoal in water: Single dose: Oral or NG:

Infants <1 year: 10 to 25 g; **Note:** Although dosing by body weight is reported in children (0.5 to 1 g/kg) and published in many resources, there are no data or scientific rationale to support this recommendation (Chyka 2005).

Infants and Children 1 to 12 years: 25 to 50 g

Adolescents and Adults: 25 to 100 g

Based on experimental and clinical studies, the following decontamination procedures have **not** been shown to be beneficial:

- Ipecac (AACT 2004; AAP 2003; Höjer 2013)
- Cathartics (AACT 2004)

Ocular: Irrigate with copious amounts of tap water or normal saline for at least 15 minutes; remove contact lenses if easily removable without causing additional trauma to the eye.

Treatment: Antidote(s)

No specific antidote exists.

Treatment: Pharmacologic Supportive Therapy

Treatment is supportive and dependent on symptoms.

Hypotension: Initial intervention should include fluid resuscitation. Refractory hypotension may require treatment with vasopressors (eg, dopamine, norepinephrine).

Hemodynamic compromise unresponsive to conventional treatment:

Fat emulsion (off-label use): Lipid emulsion therapy has been reported to be successful in the management of animals poisoned with avermectins, which may signal a potential benefit in humans (Becker 2017; Levine 2016; Saqib 2015). Because avermectins are lipophilic (Saqib 2015), it is thought that exogenous lipids act to draw tissue-bound drugs from cellular receptors into the expanded lipid phase. This effect is also known as the "lipid sink" effect. Clinicians should be aware that fat emulsion administration is experimental in this patient population (Gosselin 2016).

Indication for use: Hemodynamic instability unresponsive to conventional resuscitation

Mechanism of action: Exogenous lipids provide an alternative source of binding lipid-soluble agents. It has been suggested that improved cardiac fatty acid utilization, as well as changes in calcium and sodium channels, may contribute to improved hemodynamics (Walter 2018).

Dosage:

Note: Administration of large volumes of intravenous lipid emulsion may result in adverse effects; doses greater than the recommended amount should be used with caution, if at all.

Serious hemodynamic or other instability secondary to highly lipid soluble substances (off-label use): Note: Continue chest compressions during administration (lipid must circulate): 20%: IV: 1.5 **mL/kg** (maximum: 100 **mL**; ASRA [Neal 2018]) administered over 1 to 3 minutes, followed immediately by an infusion of 0.25 **mL/kg/minute** (maximum: 200 to 250 **mL**; ASRA [Neal 2018]) (recommended infusion durations vary; see below); may repeat the bolus as necessary for persistent cardiovascular collapse or if instability reemerges (ACMT 2017; AHA [Lavonas 2015]; ASRA [Neal 2018]). Some suggest dosing based on lean body weight (AHA [Lavonas 2015]; ASRA [Neal 2018]). Suggested maximum dose: 10 to 12 **mL/kg** over 30 to 60 minutes (AHA [Lavonas 2015]; ASRA [Neal 2018]).

After administration of the initial bolus and continuous infusion, recommendations regarding the continuous infusion vary significantly:

American College of Medical Toxicology: If after the bolus and continuing the infusion for 3 minutes, the patient demonstrates a significant response, the infusion rate may be reduced to 0.025 **mL/kg/minute** (ie, one-tenth the initial rate). If instability reemerges, the infusion rate may be increased back to 0.25 **mL/kg/minute** **or** the bolus may be repeated (ACMT 2017).

American Heart Association recommendations: Continue infusion for 30 to 60 minutes (AHA [Lavonas 2015]).

American Society of Regional Anesthesia and Pain Medicine: Continue infusion for at least 10 minutes after hemodynamic stability has been restored. Consider rebolus or increase the infusion rate to 0.5 **mL/kg/minute** if hemodynamic instability persists or recurs (ASRA [Neal 2018]).

Treatment: Nonpharmacologic Supportive Therapy

Due to the pharmacokinetic parameters of avermectins (eg, highly protein bound, large volume of distribution, excretion via feces), enhanced elimination techniques such as forced diuresis, hemodialysis, or hemoperfusion are **unlikely** to be beneficial (Yang 2012).

Patient Disposition

Initial evaluation: The following individuals need to be evaluated in an emergency department (ED):

- Patients who expose themselves to an avermectin with the intent of self-harm or intentional abuse
- Victims of abuse or neglect who were exposed to an avermectin with malicious intent
- Patients experiencing signs and symptoms of overdose (eg, nausea, vomiting, diarrhea, CNS depression)

Emergency department monitoring

- The ideal duration of ED monitoring has not been clearly established; some experts recommend a minimum of 6 hours of ED observation for asymptomatic patients who present to the ED soon after ingestion of ivermectin based on the expected time to peak serum concentrations.
- All patients should undergo monitoring of vital signs and mental status; symptomatic patients should undergo evaluation of serum electrolytes, liver function, and monitoring of hemodynamic and respiratory status.

Criteria for emergency department discharge

- Patients who remain asymptomatic or experience a complete resolution of symptoms may be considered for discharge.

Criteria for hospital admission

- Patients who exhibit signs and symptoms of overdose (eg, nausea, vomiting, CNS depression, hypotension, respiratory depression) should be considered for hospital admission for treatment and monitoring.
- Patients may require critical care capabilities based upon the severity of their illness.

Pharmacodynamics/Kinetics

Note: The following data is based on therapeutic doses (except where noted); parameters may change in overdose.

Ivermectin

Distribution: V_d : 3.1 to 3.5 L/kg (healthy males); high concentration in the liver and adipose tissue; does not readily cross the blood-brain barrier (González Canga 2008)

Protein binding: ~93% primarily to albumin (González Canga 2008)

Metabolism: Hepatic via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor)

Half-life, elimination: Systemic: 18 hours; Topical (cream): ~6.5 days

Time to peak, serum: Systemic: ~4 hours; Topical (cream): ~10 hours post application

Excretion: Feces; urine (<1%)

Moxidectin

Distribution: V_d : 2,421 ± 1,658 L

Protein binding: Unknown

Metabolism: Minimal

Half-life, elimination: 23.3 days (559 hours)

Time to peak: 4 hours

Excretion: Feces: 2% (as unchanged drug)

Complications of Exposure

Polyneuropathy: Sensorimotor polyneuropathy and combined axonopathy and myelinopathy have been documented at 1 month postingestion following a high dose avermectin ingestion (200 mL of avermectin 14.5%) (Sung 2009).

Additional Information

Optimal care decisions are made based upon specific patient details. Consider consultation with a poison control center. To reach poison control centers in the United States and its territories, call 1-800-222-1222. Attention should be paid to veterinary products containing avermectins. A large number of those patients may become symptomatic and require hospitalization (Wylie 2019).

Index Terms

Abamectin; Doramectin; Emamectin; Eprinomectin; Ivermectin; Macrocyclic lactones; Milbemectin; Milbemycins; Moxidectin; Selamectin

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