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Review Article

Review of Emamectin Benzoate Poisoning

Chi-Syuan Pan, Chun-Hung Chen*, Han-Wei Mu, Kai-Wei Yang

Division of Toxicology, Department of Emergency Medicine, China Medical University Hospital, Taichung City, Taiwan

Emamectin Benzoate, a potent pesticide extensively used in agriculture, has raised concerns due to its potential for severe poisoning. While its safety in mammals is attributed to limited blood-brain barrier penetration and reduced affinity for specific channels, Emamectin Benzoate Poisoning can unexpectedly manifest with severe symptoms. Predominantly resulting from intentional ingestion, clinical presentations involve central nervous system depression, respiratory distress, gastrointestinal symptoms, and sore throat. Formulation solvents enhance toxicity, leading to corrosive injuries and metabolic imbalances. Skin contact induces irritation. Diagnosis relies on clinical evaluation, lacking specific laboratory data. Treatment lacks a designated antidote; hence, decontamination and cautious symptomatic management play pivotal roles. Severe cases require vigilant monitoring, with intensive care unit admission calling for altered consciousness and respiratory distress.

Keywords: *avermectin, Emamectin Benzoate, poisoning*

Introduction

Emamectin Benzoate, a novel pesticide registered in the United States (U.S.) and Japan since 1997, is primarily designed for the control of insects and mites, particularly in cole crops. This semisynthetic avermectin derivative, belonging to the 16-membered macrocyclic lactones, has widespread application in agriculture for pest management.[1]

Avermectin, from which Emamectin Benzoate is derived, is produced through the fermentation of Streptomyces avermitilis.[2] Analogous compounds such as abamectin, ivermectin, selamectin, and doramectin have also been employed as pesticides. The safety of avermectin compounds for mammals, including humans, stems from their limited ability to cross the blood-brain barrier, the absence of glutamate-gated chloride channels in mammals, and the reduced affinity of avermectins for other ligand-gated chloride channels in mammals.[3] However, Emamectin Benzoate Poisoning can present with severe symptoms, surpassing initial expectations, leading to manifestations such as altered consciousness, inhalation pneumonia, and gastrointestinal (GI) symptoms. The formulations of Emamectin Benzoate exhibited moderate toxicity, with an oral LD50 value ranging from 122 to 168 mg/kg in rats.[4]

The objective of our study is to review the clinical evidence on the presentation and treatment of Emamectin Benzoate poisoning.

Methods

Identification of Studies

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to identify relevant studies. We searched for "Emamectin Benzoate Poisoning" and "Emamectin Poisoning" in the following databases: PubMed, Embase, Google Scholar, Cochrane Library, Ovid Library, Scopus, and the World Health Organi-

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*Corresponding author: Chun-Hung Chen, MD, Division of Toxicology, Department of Emergency Medicine, China Medical University Hospital, No. 2, Yude Rd., North Dist., Taichung City 404327, Taiwan.
E-mail: drumbeater1978@gmail.com

zation International Clinical Trials Registry Platform (ICTRP). From these databases, we retrieved a total of ninety-five papers.

Inclusion Criteria

Studies focusing on human poisoning related to Emamectin Benzoate.

Exclusion Criteria

Studies not related to Emamectin Benzoate, concurrent poisoning with other pesticides, or lacking full articles.

Results

Selection of Studies

After applying the exclusion criteria, we selected seven papers for review. These included five case reports, one review article, and one retrospective case series study.[5-11] The PRISMA Flow Diagram (Fig. 1) was utilized.[12] We excluded fifty duplicate records, twenty-nine papers unrelated to human poisoning, six reports that were unable to be retrieved, and three reports involving other pesticide concurrent poisonings.

We calculated the percentages of symptoms, presentations, treatment modalities, and prognosis observed in these poisoning case reports.[6-10] The data

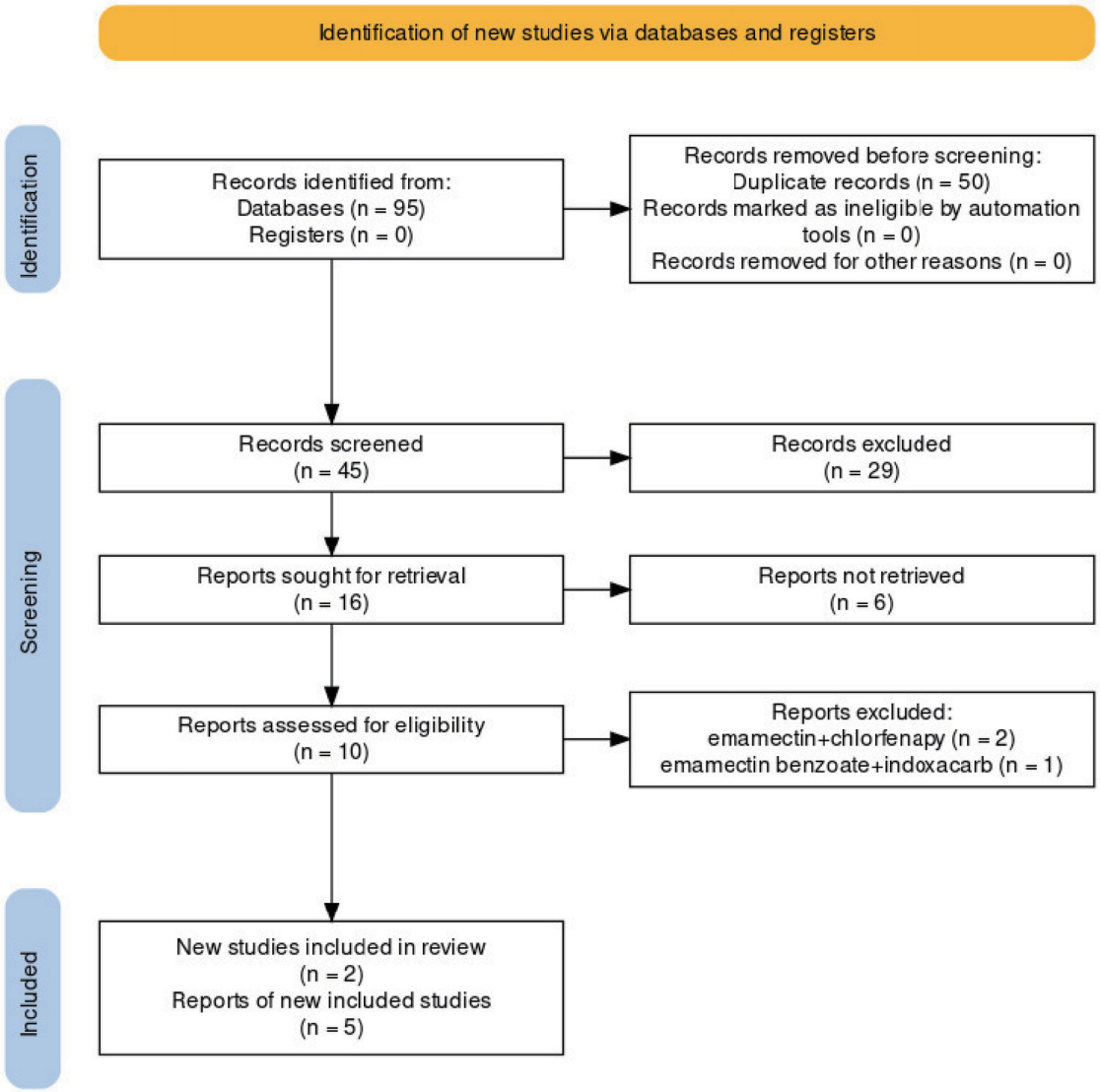

Fig. 1. Preferred Reporting Items for Systematic Reviews and the 2020 guidelines for meta-analyses (PRISMA) flowchart.

from the review of macrocyclic lactones[5] and a retrospective multicenter study that included patients with emamectin benzoate poisoning and abamectin poisoning[11] were not utilized because they did not differentiate detailed patient information between the two types of poisoning, particularly lacking detailed information on Emamectin Benzoate poisoning. Acute human toxicity of emamectin by Wang et al.[13] was excluded due to the unavailability of the full text.

We also searched for "avermectin poisoning" in PubMed, Embase, and Google Scholar. However, most of the articles focused on Abamectin, so we excluded duplicate records.

Cause

Most cases of Emamectin Benzoate poisoning result from ingestion, with intentional ingestion being most common in emergency department settings. Skin exposure and inhalation of Emamectin Benzoate are fewer common routes of exposure.

The mechanism of Emamectin Benzoate poisoning centers on its impact on the nervous system, acting as an agonist for gamma-aminobutyric acid (GABA) receptors and glutamate-gated chloride ion channels. Glutamate, an excitatory neurotransmitter, facilitates the influx of chloride ions upon binding to its receptor. Emamectin Benzoate modulates these channels, leading to an increased influx of chloride ions and hyperpolarization of the neuronal membrane. Additionally, Emamectin Benzoate functions as a chloride channel agonist. The combined effects of GABA receptor agonism and modulation of glutamate-gated chloride ion channels disrupt the normal functioning of the nervous system in target organisms. This disruption results in paralysis and death in insects or mites by hindering their ability to feed and move. Mammalian GABA receptors and glutamate-gated chloride ion channels exhibit lower sensitivity to Emamectin Benzoate, thereby reducing the risk of toxicity in humans and other mammals.[1] However, large amounts of macrocyclic lactones or mutations of P-glycoprotein may permit the crossing of the blood-brain barrier, potentially causing neurotoxicity.[14]

Clinical Presentation

Symptoms of human poisoning induced by Emamectin Benzoate include GI symptoms, respiratory distress, and neurological manifestations[6-11,13], especially in instances of high exposure (Table 1). The clinical presentation of Emamectin and abamectin poisoning exhibit similarities.[5] The case reports included five cases, with four documenting central nervous system (CNS) depression (80%), three reporting respiratory distress (60%), three indicating GI symptoms (60%), three noting aspiration pneumonia (60%), two mentioning metabolic acidosis (40%), and two describing seizures (40%) (Table 2).[6-10] In accordance with a retrospective case series study on intentional avermectin ingestion by Wu et al.[11], CNS depression was the most common symptom, followed by dyspnea and GI symptoms. Additionally, two-thirds of patients presented with aspiration pneumonia, with the majority of these cases exhibiting altered consciousness.

The presence of solvents not only enhances the toxicity of Emamectin Benzoate but also contributes to adverse effects in patients. Yen and Lin[6] noted that corrosive injuries and GI erosions may be linked to solvents, such as 2,6-bis(1,1-dimethylethyl)-4-methylphenol, while CNS depression and aspiration pneumonia were associated with the solvent 1-hexanol. Emamectin Benzoate 2.15% EC, when combined with methanol as a solvent, may lead to metabolic acidosis, even though the occurrence of Emamectin Benzoate

Table 1. The poison of Emamectin Benzoate

The Clinical Symptoms of Emamectin Benzoate Intoxication	
Signs	Clinical presentations
CNS depression	Dizziness, headache, seizures
GI symptoms	Nausea, vomiting, diarrhea, abdominal pain
Respiratory distress	Dyspnea, cough, throat irritation, aspiration pneumonia
Caustic injury	Sore throat, GI erosions
Skin irritation	Irritation, redness, itching, rash

CNS: central nervous system; GI: gastrointestinal.

Table 2. Five cases of Emamectin Benzoate poisoning from prior case reports

Case	Age/Sex	Past history	Amount/ Substance	Presentation/complications	Consciouness (GCS)	Management	Outcome	Coingestion
1	67/M	Previous healthly	100 mL 2.15% Emamectin Benzoate dilute with 400 mL of tap water	Nausea, vomiting, cramping abdominal discomfort mild confused/ aspiration pneumonia	E3M5V4	Gastric lavage and activated charcoal. Antibiotic	Recovered within 1week and discharged	No
2	40/M	Chronic alcoholic	500 gm Emamectin Benzoate 5% (water soluble granule)	Dyspnea and tachycardia seizure on 2nd day, severe metabolic acidosis, and shock on 3rd day/ aspiration pneumonia and cardiac arrest	E2V2M2	Gastric lavage and endotracheal intubation. IV fluids and diuretics. Flumazenil and Lipid emulsion. Hemodialysis, norepinephrine.	Death	Alcohol
3	75/M	Major depressive disorder	100 mL of 2.15% Emamectin Benzoate without dilution.	Epigastric burning sensation mildly tachypnea metabolic acidosis and shock/ pulseless ventricular tachycardia	Alert, oriented to time and place	Gastric lavage and activated charcoal. IV fluids and diuretics. Norepinephrine, continuous renal replacement therapy (CRRT).	Death	Alcohol
4	6/F (weight 20 kg)	Previous healthly	5 gm Emamectin Benzoate 5% (soluble granules)	Nausea, vomiting, and abdominal pain	Awake and alert mildly confused and irritable E3V4M6	Gastric lavage, activated charcoal, and coconut oil. Pantoprazole	Recovered within 3 days and discharged	No
5	57/F	Epilepsy treated with phenytoin	50 mL Emamectin Benzoate	Seizure, stupor/aspiration pneumonia	Stupor	Gastric lavage and activated charcoal. Antibiotic, naloxone, ice packing. Methylprednisolone, hemoperfusion.	Recovered within 1 week and discharged	No

GCS: Glasgow Coma Scale; IV: intravenous.

poisoning concurrently with methanol poisoning is less than 10%.[11] Sore throat emerged as the predominant symptom in our unpublished dataset of ten cases. Awareness should be increased regarding the potential for caustic injury from Emamectin Benzoate, which can lead to swelling of the epiglottis and respiratory distress. A comprehensive review of published cases involving Emamectin Benzoate poisoning revealed drowsiness, dyspnea, and GI symptoms (including sore throat) as the most frequently reported manifestations.

Contact with Emamectin Benzoate can also result in skin irritation, characterized by redness, itching, or rash.[15]

Diagnosis

Clinical diagnosis of Emamectin Benzoate poisoning relies on a thorough assessment in the absence of specific laboratory data. Physicians confirm the diagnosis based on the patient's history of Emamectin Benzoate exposure. Poisoning patients may exhibit symptoms such as GI distress, respiratory issues, and potential neurological manifestations. The differential diagnosis should encompass other pesticide poisonings or instances of combined drug exposure. Emamectin Benzoate 2.15% EC, appearing as a brown clear liquid, may be incorrectly identified as synthetic pyrethroids, organophosphorus pesticides, or Glyphosate isopropylamine.

Laboratory data for Emamectin Benzoate poisoning lacks specific plasma concentration measurements. However, in symptomatic patients, comprehensive tests including complete blood cell/differential count (CBC/DC), renal function, electrolytes, blood gas analysis, osmolarity gap, and liver enzymes should be considered.

Treatment

There is no specific antidote for Emamectin Benzoate poisoning. Supportive care is advised for Emamectin Benzoate poisoning. Decontamination through gastric lavage or activated charcoal may be considered, as avermectins can be excreted in the feces.[5] In all five case reports, gastric lavage was performed, and active charcoal was administered in 80% of cases.[6-10] However, no clear benefit was observed for gastric lavage or activated charcoal. A retrospective study of intentional avermectin poisoning found that while most patients were treated with gastric lavage and almost half with activated charcoal, these interventions did not influence outcomes.[11] Precautions should be taken for Emamectin Benzoate poisoning to prevent aspiration pneumonia in patients with CNS depression. The potential for corrosive injury caused by Emamectin Benzoate ingestion should also be considered. In our unpublished data, most patients suffered from caustic injury after ingesting Emamectin Benzoate, and decontamination by gastric lavage or activated charcoal was administered without complication. Intubation to protect the airway should be considered for Emamectin Benzoate poisoning if a patient presents with respiratory distress. In 20% of the cases, intubation was performed to protect the airway.[6-10] In a retrospective case series study of avermectin poisoning, 27% of patients required intubation.[11] The use of benzodiazepines or barbiturates, which enhance GABA activity, should be avoided in Emamectin Benzoate poisoning patients.[6]

Lipid Emulsion

Limited data exists on the use of lipid emulsion therapy for Emamectin Benzoate poisoning. A case report documented the use of lipid emulsion in Emamectin Benzoate poisoning, but the patient succumbed.[7]

Flumazenil

There is no evidence supporting the administration of Flumazenil in Emamectin Benzoate patients. Although Flumazenil acts as a selective GABA receptor antagonist[16], no clinical improvement has been observed in avermectin poisoning patients. A case report of Emamectin Benzoate using Flumazenil resulted in the patient's death.[7]

Hemodialysis and Hemoperfusion

Currently, there is no evidence supporting the use of hemodialysis or hemoperfusion in Emamectin Benzoate poisoning. The high protein binding and volume distribution may limit the effectiveness of hemodialysis. However, in cases where Emamectin Benzoate solvent, such as methanol, induces metabolic acidosis, hemodialysis may be beneficial. Limited data includes a case report using hemoperfusion for Emamectin Benzoate poisoning, while in ivermectin poisoning, single-pass lipid dialysis was utilized.[10,17] Two dogs revealed that plasma ivermectin could be removed by single-pass lipid dialysis.[18]

Disposition

Patients with severe conditions, characterized by altered consciousness, metabolic acidosis, and respiratory distress, should be closely monitored and may necessitate admission to the intensive care unit.[11,13] Sixty percent of the case reports involved admission to the intensive care unit.[6-10] Emamectin Benzoate poisoning patients displaying symptoms require admission to the ward. Asymptomatic patients with Emamectin Benzoate poisoning should undergo observation and may be discharged after a few hours if they remain asymptomatic, after receiving health education regarding CNS depression, dyspnea, and sore throat.

Prognosis

Emamectin Benzoate poisoning is associated with non-highly toxic characteristics. However, Emamectin Benzoate can sometimes lead to moderate to severe complications. Severe toxicity is often characterized by consciousness disturbance and dyspnea.[11,13] In a study involving 69 patients who ingested Emamectin, the mortality rate was 4.3%.[13] Another retrospective case series study of 64 patients most of whom experienced intentional poisoning with Emamectin Benzoate, reported a mortality rate of 6.67%. Respiratory failure and shock were observed in 31% of cases.[11] Among five cases of Emamectin Benzoate poisoning, two cases (40%) resulted in fatalities due to severe metabolic acidosis and asphyxia by vomitus.[6-10] The average mortality rate across these studies was 6.7%.[6-11,13]

Discussion

Based on the referenced articles[5-11], the typical clinical presentation includes CNS depression, respiratory distress, and GI symptoms. Patients may also present with aspiration pneumonia, metabolic acidosis, and seizures. Treatment primarily consists of supportive care to prevent complications. The more severe complications, such as aspiration pneumonia, metabolic acidosis, seizures, and death, were more commonly reported in the case reports[6-10] than in the case series study.[11] This difference may be related to selection bias, as severe and distinct cases are more likely to be reported in a case report. In Table 2, two mortality cases were associated with co-ingestion with alcohol. One individual died due to severe metabolic acidosis and shock, while another succumbed to severe metabolic acidosis, shock, and asphyxia caused by vomitus.[7,8] Alcohol consumption may worsen alterations in consciousness and metabolic acidosis in patients with Emamectin Benzoate poisoning. However, there was no significant difference in alcohol use among patients with severe outcomes in the case series study.[11] In this study, deceased patients presented with symptoms such as drowsiness, hypotension, metabolic acidosis, aspiration pneumonia, and respiratory failure. In theory, gastric lavage and activated charcoal can aid in eliminating Emamectin Benzoate.[5,6] However, their benefit in treating patients with Emamectin Benzoate poisoning is controversial.[11] In most of our case summaries (five cases from case reports),[6-10] gastric lavage and activated charcoal were used for treatment, yet the mortality rate remained high. Further evidence is needed for Emamectin Benzoate poisoning to confirm whether these methods are beneficial.

Two death cases respectively involved a large amount of 500 gm of Emamectin Benzoate and 100 mL of 2.15% Emamectin Benzoate, administered without dilution, as the study revealed severe toxicity associated with a large amount of Emamectin injected[7,8] respectively with large amount of 500 gm Emamectin Benzoate and 100 mL of 2.15% Emamectin Benzoate without dilution like the study revealed severe toxicity associated with a large amount of Emamectin injected.[13] However, in the retrospective case series study, the estimated ingested amount of Emamectin Benzoate was not found to be associated with severity. The study noted a potential recall bias that could have affected the accuracy of the estimation.[11]

In conclusion, Emamectin Benzoate is not considered a highly toxic pesticide, it can still lead to serious effects such as corrosive injury, metabolic acidosis, aspiration pneumonia, altered consciousness, and respiratory failure. The toxicity of Emamectin Benzoate, such as corrosive injury, may be associated with and enhanced by its solvent. Treatment primarily involves supportive care and prevent complications such as aspiration pneumonia and respiratory failure.

Limitation

Publication bias could limit the availability of case reports. The study is limited by the small number of cases of Emamectin Benzoate poisoning, with only five case reports containing original data, suggesting potential selection bias. Additionally, there is one retrospective study involving sixty patients and one

unpublished study involving eleven patients, both lacking original data and a control group. Furthermore, there are no randomized controlled trials available to compare treatment outcomes.

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