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Management and prognosis of acute Emamectin Benzoate poisoning in a human

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ABSTRACT

Emamectin Benzoate (EB) is a semi-synthetic insecticide which was primarily created to combat lepidopteron insects. EB disrupts the neurotransmitters Gamma Amino Butyric Acid (GABA) through enhancing permeability of membrane chloride ion, resulting in the loss of cell function progressing to irreversible paralysis in invertebrates.

Poisoning with EB in humans is rare; till date with just about five reported cases, two of which resulted in fatalities. Scarcity of treatment management information may cause a delay in the initiation of treatment, which is often general therapy rather than specific. By reporting this rare case of poisoning in human, the researchers wish to add value to the existing information and aid in forming a standard management of EB poisoning in humans.

Here within, we report an acute case of EB poisoning in an adult male with no history of co-morbidities, had allegedly consumed approximately 125 mL of EB 1.9 % and, presented with complaints of vomiting, profuse sweating and drowsiness. The patient was treated with gastric lavage, fluid replenishment, and other supportive as well as symptomatic measures. The prognosis of the patient was guarded and care has been taken not to administer any Central Nervous System (CNS) depressants. Fortunately, the patient was discharged from the hospital by day 4 without any sequelae.

1. Introduction

Emamectin Benzoate (EB) is a semi-synthetic insecticide that belongs to a class of avermectin family and was primarily created to combat lepidopteron insects [1]. It was first developed at Merck & Co. and was introduced to the market in 1997 in countries such as Japan [2]. EB is a derivative of Abamectin, a product derived from the natural fermentation of *Streptomyces avermitilis*, a naturally occurring soil actinomycete, and is the 4′-deoxy-4′-epi-methyl-amino benzoate salt of avermectin B1 (avermectin family of 16-membered macro cyclic lactones, an epi-amino-methyl (-NHCH3) group is substituted for a hydroxyl (-OH) group at the 4-position. The compound is a mixture of two homologs designated B1a and B1b, which differ only by one methylene (CH2) unit on the C-25 side chain, where B1a contains a sec-butyl group and B1b contains an isopropyl group [3]. It is important to note that, even though Avermectin and Ivermectin are related to each other, their action as well as uses differs greatly.

EB seems to be a cost-effective pesticide with only 6 g/acre requirement leading to its soaring popularity [3]. Several nations, including the USA, Canada, Japan, etc., widely employ EB as a pesticide in their agriculture and practices and aquaculture for treating *Lepeophtheirus salmonis* i.e., fish lice [4].

GABA receptors with high affinity are thought to be stimulated by EB, which results in increased influx of membrane chloride ions into the neuronal cells, causing damage to cell and nerve impulse. This process causes minimal damage to the crops as the insects cease feeding [2,3].

Furthermore, till date there were only five peer reviewed case reports on EB poisoning in humans. Unfortunately, due to lack of standard treatment protocol for EB poisoning, all these

reports solely relied on symptomatic management. In this report, the

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authors described the management of EB poisoning in a male adult presented with complaints of vomiting and profuse sweating and drowsiness. The patient showed no signs of altered sensorium during the course of treatment, which in certain poisoning cases indicates poor prognosis.

2. Case narration

A male patient in his early 20 s, with complaints of three episodes of vomiting, profuse sweating and drowsiness was presented to the Emergency Department (ED) of a tertiary care teaching hospital with alleged consumption of 125 mL of EB 1.9 % mixed with food. The patient was primarily treated with gastric lavage at a rural primary health care center.

On examination the patient, was afebrile, drowsy, with tenderness in the epigastric region, oriented to time and place, and without any co-morbidities. The patient weighed around 58 kgs and ingested about 125 mL of the compound EB which is approximately 47.5 mg/kg. Pulse rate was 107 beats per minute (BPM), Blood Pressure (BP) showed 130/96 mmHg, and Glasgow Coma Scale (GCS) of Eye response-4 Verbal response-5 Motor response-6 ($E_4V_5M_6$). Patient's ECG revealed normal sinus rhythm. Patient was treated symptomatically with injection pantoprazole and ondansetron STAT doses for epigastric pain and vomiting. Ryle's tube was inserted and patient was shifted to intensive care unit for further management.

Laboratory reports highlight the elevation of Total Bilirubin and Direct Bilirubin, and Complete Blood count showed the impression of neutrophilia; values are depicted below in Table 1.

Arterial Blood Gas (ABG) had tested positive for mild acidosis; values are depicted in Table 2. Liver function test and renal function test were within normal range. Urine routine, Prothrombin time/International normalized ratio (PT/INR), serum calcium and magnesium were also within normal range. An Echocardiogram (ECHO) report showed no regional wall motion abnormality and normal left ventricular systolic function, ejection fraction (EF) - 74 %.

On day 1, the patient complained of left-sided throbbing headache and a cardiovascular system (CVS) examination confirmed mild tachycardia (heart rate 107 bpm). Patient was treated symptomatically, was kept nil by mouth (NBM) and later started on plain liquids orally by day 2. Psychiatry opinion was taken and patient had counseling and psycho education in view of depression symptoms. On day 2, the patient was shifted from intensive care unit as his prognosis has improved to fair. Repeated ABG reports suggested no further acidosis. On day 4, patient was symptomatically and hemodynamically stable, and was discharged from hospital.

3. Discussion

3.1. About the patient

In this patient who ingested approximately 125 mL of a formulated product 1.9 % EB, about 47.5 mg/kg of the active compound EB has been consumed along with solvents. Clinical manifestations were mainly limited to gastrointestinal symptoms such as vomiting and sweating as well as drowsiness. With the exception of slightly elevated direct and total bilirubin, all laboratory tests were within the normal range. Psychiatric education was initiated by a psychiatrist as the patient showed signs of depression and was discharged by the fourth day without any complications.

Table 1
Elevated lab parameters with their normal range.

Lab Parameters	Results	Normal range
Total Bilirubin (TB)	1.22 mg/dL	Up to 1.2 mg/dL
Direct Bilirubin (DB)	0.43 mg/dL	Up to 0.2 mg/dL
Neutrophils	87.1 %	40–70 %

While comparing for safety, the quantity of poison that a patient consumed along with their medication and social history must be taken into consideration in cases of EB poisoning. Most fatal cases were noted in patients with chronic alcohol history. Early treatment with gastric lavage may enhance the efficacy of treatment and improve the prognosis of patients.

3.2. Past experiences

Throughout the literatures, there have only been six incidents of EB poisoning among which two humans had fatal sequelae [3,5–8].

a. First EB poisoning in human was reported by Yen and Lin, in which a 67 years old male patient consumed approximately 500 mL of diluted insecticide prepared from 100 mL of 2.15 % w/w EB concentrate and 400 mL of tap water. An hour after ingesting the insecticide, he reports experiencing nausea, vomiting, cramping abdominal pain, and mild confusion. Fortunately, the patient's general condition improved the next day and was discharged a week later without any complications [3].
b. In the literature by Yadav GK et al., a 6 years old female patient weighing 20 kgs consumed 5 g of 5 % w/w EB which is approximately 250 mg/kg. The patient had mild symptoms of disturbance of consciousness and gastrointestinal distress, was discharged on the third day and a review after a week showed no complications [5].
c. The Godhiwala P et al., had published a case report of 40 years old male who was chronic alcoholic with no known co-morbidities, allegedly consumed 500 g of EB 5 % Soluble Granules (SG). Inj. Levetiracetam 500 mg twice daily was administered to address myoclonic jerks with generalized seizure along with Inj. Flumazenil 0.25 mg, a benzodiazepine antagonist was also given intravenously over 15–30 seconds. However, on third day, the patient succumbed to death despite aggressive resuscitative efforts with severe metabolic acidosis, shock and ventricular tachycardia [6].
d. Park JM also had reported an unfortunate case of EB poisoning of a 75 years old male who consumed 100 mL of undiluted 2.5 % EB, having a history of major depressive disorder and was on alprazolam, donepezil, paroxetine, and quetiapine. He presented with gastrointestinal (GI) symptoms, hypotension and hypoxemia but no CNS depression. Intensive treatment was provided as patient developed quick onset of metabolic acidosis but following a cardiac arrest, the patient had fatal outcome [7].

A case series published by Khatri A reported a case of multi organ dysfunction syndrome (MODS) in a patient. A 52 years old male patient who consumed 50 g of 5 % EB under the influence of alcohol developed severe symptoms from acute respiratory failure to MODS within two days of consumption. He was on mechanical ventilator for eight days, underwent nine hemodialysis treatments and got discharged after one month without any sequelae. Whereas a 22 years old female patient who consumed 200 g of 5 % EB did not have any complications and got discharged after four days in the hospital without any complications [8].

3.3. Pharmacokinetics & pharmacodynamics considerations

As EB is a relatively large molecule, it is not completely absorbed when taken orally, and poorly absorbed when applied topically, and rapidly eliminated in the feces, with whole-body half-lives of roughly 1.5 days. While EB is not significantly metabolized in mammals, the minimal knowledge on its metabolites suggests that EB is not detoxified by metabolism. In animals LD_{50} range from 53 to 237 mg/kg and the plasma half-life is 20–51 hours. 94 % of the compound eliminates through feces and less than 1 % through urine [1].

Research suggests that EB was rapidly removed from the plasma of rats, with half-lives ranging from roughly 15–28 hours following oral or

Table 2
ABG chart on Day 1–3.

Day	pH (7.35–7.45)	pCO_2 (35–45 mm Hg)	pO_2 (80–100 mm Hg)	HCO_3 (22–26 mmol/L)	Lactate mmol/L)	Anion Gap (4–12mmol/L)	SPO_2 (95–99 %)
1	7.327	33.1	50.0	16.8	1.2	24.0	81.5
	7.384	36.9	92.2	22.3	0.8	17.8	95.3
2	7.385	35.6	88.2	21.8	0.7	13.8	96
3	7.421	36.6	104	23.4	0.7	−2.8	97.3

intravenous administration. Residues were broadly distributed throughout the body, with the largest amounts in the lungs. Furthermore, following high dose oral exposures, relatively significant amounts of EB residues were found in the gastrointestinal system, indicating that oral absorption was limited. Based on the time course of residues following intravenous and oral administration, approximately 40–60 % of the orally administered EB was absorbed. Despite the fact that the nervous system is clearly the target of EB toxicity, residues in the brain and spinal cord were extremely low in comparison to most other tissues. EB and one N-demethylated metabolite were nearly entirely eliminated in the feces, with very little parent or metabolite identified in the urine. In a study done on goats, tissue assay showed highest EB concentrations in the liver and kidney and majority was excreted through feces with only few concentrations found in the urine [1].

The tissue distribution of EB after a single oral dose in Atlantic salmon was also investigated by means of whole-body autoradiography and scintillation counting (distribution study). EB concentration gradually dropped from the completion of treatment (day 7) to day 70, with half-lives in muscle, plasma, and mucus of 9.2, 10.0, and 11.3 days, respectively [5,9].

The literature states EB is a macro cyclic lactone and a broad-spectrum insecticide used in vegetables with rapid paralytic action in insects leading to their death. However, wide safety margin has been established in mammals which may be attributed to the presence of GABA mediated nerves only in the CNS whereas in invertebrates, such nerves are present along the peripheral muscles [3]. This safety may be attributed to less sensitivity due to lack of GABA receptor affinities and their impermeability to cross blood brain barrier [2]. Also, humans having larger body surface area may play a significant role in lesser toxicity as compared to other invertebrates.

GABA neurotransmitters i.e., by stimulating the release of γ-aminobutyric acid, an inhibitory neurotransmitter causes irreversible paralysis, which leads to cessation of feeding and killing of the organism in 2–4 days [2,3]. This process causes minimal damage to the crops as the insects cease feeding [2,10]. As EB is believed to enhance GABA, the use of sedative agents such as benzodiazepines and barbiturates are avoided while treating an EB poisoning case as it has a chance of causing CNS depression.

The mechanism of action of EB involves disruption of the neurotransmitter GABA causing irreversible paralysis in invertebrates. Furthermore, GABA receptors with high affinity are thought to be stimulated by EB, which also enhances membrane chloride ion permeability to the opening of the ion channel into the neuronal cells resulting in the disruption of nerve impulses and loss of cell function. EB additionally enhances activity of GABA in the CNS, which may result in CNS depression [2,3].

3.4. Management

In cases of EB poisoning, first resuscitation was initiated, coupled with supportive and symptomatic therapy. Uses of any CNS depressants were avoided as EB is believed to enhance GABA receptors. Levetiracetam was given as a treatment in case a patient develops seizures. Due to scarcity of management of EB poisoning, in all reported cases, only supportive and symptomatic managements were given.

4. Conclusion

In a situation of EB poisoning, early initiation of gastric lavage may improve patients' overall prognosis as it aids in removing the toxins from the body. In general, lack of specific antidote is usually a predictor for untoward prognosis. However, concurrent use or presence of CNS depressants in the patients i.e., benzodiazepines, barbiturates and alcohol could prove otherwise. In case a patient develops seizures, levetiracetam may be utilized for treatment. Side-effects of EB poisoning can range from simple gastrointestinal distress to severe CNS manifestations, and cardiac distress which might result in death. Fatal cases and unfortunate prognosis were reported more with EB poisoning when consumed along with alcohol. Emergency physicians should be made aware of the likelihood of rapid worsening in patients due to an underlying ailment or related substance abuse that might further oppress CNS. Through this paper, the researchers aim to contribute to the existing knowledge on EB poisoning, highlighting the necessity for further in-depth studies. More research is needed to determine the exact pathophysiology and effects of EB on humans, which would aid in the development of a standard treatment strategy to reduce mortality.

CRediT authorship contribution statement

Renthlei Lalmalsawmi: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Data curation. **Madhan Ramesh:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis. **P.M. Mariyam Shihuna:** Writing – original draft, Investigation, Data curation. **M. Mahesh:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Y.S. Ravikumar:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Sri Harsha Chalasani:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

No data was used for the research described in the article.

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