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Case report

Acute permethrin neurotoxicity: Variable presentations, high index of suspicion

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ABSTRACT

Permethrin is a synthetic Type I pyrethroidal neurotoxic pesticide that has been responsible for accidental animal deaths. Despite its widespread use, there are no published case reports on pediatric intensive care unit admissions due to permethrin exposure. We report the unusual and varied presentations of permethrin toxicity in three siblings presenting to a tertiary care pediatric intensive care unit (PICU). While there is no standard clinical diagnostic test for permethrin, accurate diagnosis was obtained by rapidly analyzing the offending agent. In the absence of a known antidote for permethrin, supportive management was initiated and resulted in a favorable outcome for all three siblings.

1. Background

Permethrin is a synthetic Type I pyrethroidal pesticide that is commonly used worldwide on crops. It is highly toxic to animals, particularly fish and cats. It is primarily a neurotoxin and its main mechanism of action is axonal sodium channel depolarization causing repetitive nerve impulses [1]. At relatively high concentrations, pyrethroids can act on gamma-aminobutyric acid (GABA)-gated chloride channels, which may be responsible for the seizures seen with severe Type II poisoning [2]. Despite its widespread use, there are few recorded cases of human toxicity and fewer reports of pediatric intensive care unit (PICU) admissions with good outcomes.

2. Patient presentations

We describe the following case summaries of three siblings who presented simultaneously to the PICU with varied clinical symptoms resulting from what was initially suspected to be organophosphate poisoning. All three patients were originally exposed to an unknown substance used to bathe a puppy. They initially presented to an outside medical facility following the exposure, which included both topical contact and ingestion. It is unknown how much of the substance was found at the location where exposure occurred. After sampling by the local Fire Department of the substance found on a trampoline, emergent analysis of the unknown substance identified it as permethrin. Subsequently, the patients were diagnosed with acute permethrin poisoning.

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Patient #1 is a five-year-old previously healthy female who, along with her siblings, had bathed a puppy, poured the unknown chemical on a trampoline, then played with it and possibly ingested some of it. Eight hours following suspected ingestion, she presented to an outside Emergency Department (ED) with symptoms of increased lacrimation, salivation, bronchorrhea, vomiting, stomach cramps, and significant respiratory depression and altered mental status. She was intubated, volume-resuscitated and administered two doses of 1 mg atropine, then transferred to the PICU at our facility. Upon admission, she manifested symptoms of excessive secretions and pinpoint pupils. Hence, she was given two further doses of 1 mg atropine with no therapeutic response. The patient continued to be comatose with no response to anticholinergic management; hence, the chemical found at the site of exposure was emergently analyzed and determined to be permethrin and not organophosphate, as initially suspected.

The existing literature was reviewed, poison control was contacted again and further treatment was discussed as being mainly supportive. Continuous bedside electroencephalogram (EEG) monitoring was performed because of the potential for permethrin to cause subclinical status epilepticus. Subsequently, benzodiazepine therapy was initiated. The patient remained comatose and on mechanical ventilation with poor deep tendon reflexes, muscle weakness, pinpoint pupils, increased secretions and diarrhea, and elevated body temperature for one week. Head computed tomography (CT) and magnetic resonance imaging (MRI) scans were reported as negative. She was started on gabapentin for possible paresthesia, a known association with permethrin toxicity. After eight days, the patient was extubated after demonstrating improved responsiveness, normal pupils, and decreased secretions.

Patient #2 is a six-year-old female with similar exposure history. As this patient was related to Patient #1, diagnosis was made again based on the chief complaint and history of present illness, suspected ingestion of permethrin. Her initial presentation was not as severe as her sister's, and did not require intubation at the outside ED. She received one dose of atropine and was transferred to the PICU for observation. After a few hours, her mental status deteriorated and she was intubated to protect her airway from excessive secretions. Unlike Patient #1, she also demonstrated signs of aspiration pneumonitis and abnormal motor movements. Her course was otherwise similar with high fever, pinpoint pupils, altered mental status, muscle weakness, profuse secretions and diarrhea. Her movements were random, non-purposeful, and very difficult to control despite sedation. She responded to a low, defasciculating dose of pancuronium with an improvement of her movements. However, she had the longest ICU course and remained mechanically ventilated for 12 days.

Patient #3 is an eight-year-old female who ingested the same chemical as the two siblings previously presented. Again, the chemical ingested was sampled by the local Fire Department and subsequently tested and identified as permethrin. However, this patient possibly did not have the same level of exposure as her siblings, as she had tried to wash the permethrin off the puppy after the other siblings had doused it. It is suspected that this patient ingested less than her siblings, as she presented with symptoms of vomiting and stomach cramps. Her total length of stay in the hospital was two days, with one day in the ICU. She never demonstrated central nervous system effects, pupillary changes or increased secretions. Her laboratory data were within normal limits. The puppy, unfortunately, was reported to have died from this exposure.

3. Discussion

This is the first report of a set of children simultaneously presenting with permethrin toxicity with differing clinical spectra with successful outcomes. Lack of standard management response to previously suspected organophosphate poisoning prompted a rapid analysis of the offending toxin, confirming the toxin as permethrin in these three cases. Unfortunately, bodily fluid analysis was not performed. However, the substance was chemically analyzed and a diagnosis of permethrin poisoning was made. It would have been useful if red blood cell acetylcholinesterase (RBC-AChE) could have been used as a confirmatory test for toxicity resulting from exposure to organophosphorus compounds, specifically in ICU management of these patients [3]; however, that test was unavailable in our geographical area.

Review of existing literature reveals a paucity of cases of human toxicity with permethrin. It appears to be particularly rare in children and the presentations may be variable; however, *in vivo*, permethrin is almost five times more acutely toxic to eight-day-old rats than to adult rats. Based on *in vivo* experiments, it is possible that children may be more sensitive to permethrin than adults [4]. A study performed at an Ohio daycare center to analyze pathways of exposure to permethrin in children concluded that children are exposed to low levels from several sources and through several routes; however, the exposure did not result in symptoms of apparent toxicity [5]. Based on these studies in combination with our patient presentations, it is suspected that lower levels of exposure to permethrin can likely cause either none or minor side effects, whereas exposure to higher doses of permethrin can lead to worsened symptoms. In addition, the detection of urinary metabolites, *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acids, have been previously used in suspected permethrin toxicity cases, however, they were not tested for in these patients, as the tests are not available in our geographical area [6].

A review of 48 cases of acute ingestion-related poisoning with pyrethroids in Taiwan revealed that gastrointestinal tract signs and symptoms were most common, found in 73% of cases [7]. Pulmonary abnormalities were found in 29% of cases, including aspiration pneumonitis and pulmonary edema [7], as evident in our second case. Central nervous system involvement, as demonstrated in the first case described here, was found in 33% cases and included confusion, coma and seizures [7].

The biodegradation of synthetic pyrethroidal compounds has been extensively studied [8–10]. Permethrin is a synthetic Type I pyrethroid with a high selectivity for insects. It has four isomers with 1R *cis*-permethrin being the most insecticidal active isomer [11]. Pyrethroids kill

insects by strongly exciting their nervous systems. They make the nervous system hypersensitive to stimuli from sensory organs. Permethrin-exposed nerves send a train of impulses, instead of a single impulse, in response to a stimulus. It does this by interacting with the voltage-dependent sodium channels and produces a prolongation of inward sodium current, and hence the channels remain open much longer, causing repetitive nerve impulses [11]. Permethrin has been shown *in vitro* and *in vivo* to increase acetylcholine and acetylcholinesterase levels [12,13]. Monoamine oxidase and ATPase enzymes are inhibited by permethrin [1,2,10]. It has been reported to inhibit the GABA receptor, producing excitability and convulsions [2,11]. At high doses, neurotoxic symptoms can include tremors, incoordination, hyperactivity, paralysis, and hyperthermia [14]. Some other effects are irritation to the eyes and skin. It is classified as a carcinogen and is a mutagen of human cell cultures [14]. The patients in this report were initially treated with atropine, which had no effect. An explanation for treatment failure could be that the atropine dose administered was not potent enough to overcome the permethrin toxin load. However, there is no literature supporting treatment of permethrin toxicity with atropine.

4. Conclusion

Permethrin is a very common and highly effective pesticide widely used around the world; however, reports of toxicity in the pediatric literature are infrequent. The most common symptoms appear to be nausea and vomiting. Neurotoxicity appears to be most clinically significant. Permethrin toxicity may mimic organophosphate poisoning because of its cholinergic actions. Treatment for permethrin toxicity is mainly supportive, including protection of the airway due to the altered mental status and significant secretions, and involves reversal of GABA receptor dysfunction with benzodiazepines. Atropine is ineffective, and may have the undesired side effect of reducing seizure threshold in these patients. Initial presentation of poisoning with permethrins may mimic that seen with exposure to organophosphates and carbamates; however, rapid analysis of the offending agent may assist with the accurate diagnosis. Thus, a high index of suspicion in patients presenting with cholinergic signs and neurotoxicity unresponsive to standard management for organophosphate poisons should suggest the possibility of permethrin toxicity. Further investigation of this form of poisoning is recommended.

Conflict of interest

Authors have no conflicts of interest related to this article. No funding was obtained for this study.

Transparency document

The Transparency document associated with this article can be found in the online version.

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