DOI: 10.7860/JCDR/2016/22756.8773

Case Report

Pharmacology Section

Pharmacokinetic Potentiation of Mixed Organophosphate and Pyrethroid Poison Leading to Prolonged Delayed Neuropathy

MEENAKSHI SRINIVASAN[1], RUHUL AMIN[2], GIRISH THUNGA[3], SHIVASHANKAR KANIYOOR NAGIRI[4], CHANDRASHEKAR UDYAVARA KUDRU[5]

ABSTRACT

Organophosphate (OP) and mixed pesticide poisoning remains an important cause of hospital admission. Therefore, physician must be aware of atypical presentations of delayed neurological complications of poisoning by taking proper patient history. We report a case of a 23-year-old female who presented with high stepping gait and muscle wasting in hands. Patient history revealed consumption of approximately 4ml of mixed pesticide, consisting of 50% chlorpyrifos with synthetic pyrethroid, 5% cypermethrin. The prolonged and severe nature of delayed peripheral neuropathy, persisting at two years of follow-up, suggests that even small quantities of OP taken in combination with a pyrethroid can result in significant morbidity and is irreversible.

Keywords: Chlorpyrifos, Cypermethrin, Mixed poisoning

CASE REPORT

A 23-year-old woman presented to the hospital complaining weakness of lower limbs. On further investigation, the patient revealed consumption of a mixed poison with intent to commit suicide, seven months ago.

Documents obtained from the previous hospital and the patient herself confirmed having taken a small amount of approximately 4ml of a fixed dose pesticide containing organophosphate chlorpyrifos 50% with synthetic pyrethroid, cypermethrin 5%. On hospital admission, the patient was given gastric lavage immediately. Following symptoms of cholinergic crisis, respiratory depression and a low pseudocholinesterase level, she was intubated and admitted in the Intensive Care Unit (ICU). She was found to have persisting muscle weakness and developed intermediate syndrome. Four weeks later, symptoms of delayed neuropathy had set in. She was unable to stand and experienced both upper and lower limb weakness. On being stabilized, she was started with in-hospital physiotherapy and was subsequently discharged.

She continued regular physiotherapy at home. However, as her condition failed to improve after seven months, she was referred to our hospital. A thorough motor system examination found foot drop to be present. Additionally, the patient had clawing of both hands, hand grip was weak and muscle wasting was present. Examination of the small muscles of the hand revealed weakness. The patient demonstrated a high stepping gait. Ankle reflexes were absent, while knee jerk reflexes were brisk. Lower limb tone was found to be increased. Truncal weakness was present. There was no sensory system involvement. Bowel and bladder irregularities were not present. Nerve conduction study was suggestive of axonal and predominantly motor demyelinating neuropathy which was greater in lower limbs. Distal weakness was greater than proximal weakness. Magnetic Resonance Imaging (MRI) of the spine was normal. Additional laboratory investigations to rule out other causes of neuropathy including complete blood count and other hematological tests, Vitamin B_{12} levels, electrolytes and immunological markers were done which were essentially normal. Electromyography (EMG) was not done. The patient was treated conservatively with muscle relaxant oral Baclofen and vitamin B complex. Physiotherapy and occupational therapy was continued throughout the length of stay. The patient was discharged, with minimal improvement in functional status and continues to have signs of delayed neuropathy.

DISCUSSION

Organophosphate Induced Delayed Neuropathy (OPIDN) is a rare toxicity resulting from exposure to large quantities of certain organophosphorus esters. It is a sensory motor distal axonopathy which occurs after 1-4 weeks following a single or short term exposure [1]. Although OPIDN after chlorpyrifos ingestion in large doses has been reported [2], delayed neuropathy at a low dose of 40 mg/kg has not been reported. The delayed neuropathy persisted at two years of follow-up. The combination of two poisons might have contributed to this phenomenon. The uniqueness of this case lies in the extremely low quantity of ingestion of chlorpyriphos which lead to delayed neuropathy probably because of being taken along with cypermethrin and presentation with exclusively motor symptoms with no sensory involvement.

Acute poisoning from organophosphate pesticides remains an important cause of severe toxicity and death in rural Asia [3]. Studies indicate that over 2,00,000 deaths occur due to pesticide poisoning each year in developing nations [4]. This value is likely to be an underestimation in today's scenario, where these agents are easily available and accessible cheaply in India. Pyrethroids are generally considered safe, however their effects are potentiated in combination with organophosphate (OP) compounds [5,6]. Due to the emerging resistance among agricultural pests to pyrethroids, certain fixed dose pesticide combinations of OP and pyrethroids are widely available in India [7]. Chlorpyrifos is a moderately hazardous (class II) pesticide with an LD_{50} of 135 mg/kg. Cypermethrin, a synthetic pyrethroid is also a class II pesticide with an LD_{50} of 250 mg/kg [8]. The combination of 4ml of 50% chlorpyrifos and 5% cypermethrin accounts for an ingested dose of 40 mg/kg and 4 mg/kg respectively. Phosphorylation and aging of around 70% of Neuropathy Target Esterase (NTE), a protein in the nervous system, initiates OPIDN [9]. OP activated by CYP450 enzymes, inhibit esterases involved in the detoxification pyrethroids, leading to a greater than additive toxicity [6]. Taken together, the carboxylesterase mediated metabolism of cypermethrin is inhibited, thus increasing its tissue concentration and reducing the urinary excretion of its metabolites [10]. Additionally, the toxic metabolite of chlorpyrifos, known as chlorpyrifos oxon inhibits the hydrolysis of permethrin irreversibly, resulting in the potentiation of permethrin toxicity [11]. An extensive literature search revealed only one other mixed OP- pyrethroid poisoning case series, where patients showed

predominantly pyrethroid effects of choreo-athetosis, excessive salivation and seizures [12].

When taking mixed poisons together, due to the above mechanism it is expected to see signs and symptoms of pyrethroid toxicity. However, signs of OP were predominantly seen. This could have been due to the high OP: pyrethroid ratio of 10:1 in our case as compared to the methyl parathion: lambda-cyalothrin ratio of 1:4 in the other study. At two years of follow-up, the indexed patient continues to have signs of spastic ataxia. Studies have confirmed that OP-pyrethroid mixed poisoning is definitely more toxic than either compound taken alone [13]. This case report emphasizes that OP-pyrethroid poison in the current concentration, even taken in small amounts is highly toxic which can lengthen the usual course of delayed neuropathy.

CONCLUSION

This case report is the first report to document prolonged delayed neuropathy with mixed poisoning when ingested at low doses. Since chlorpyrifos was present in higher concentration in this combination, OP poisoning symptoms and signs were more pronounced. OPIDN may present as pure motor neuropathy with no sensory manifestations. The treating physician must be aware of the composition of the poison and the possibility late neurological manifestations with low quantities of mixed poisoning.

REFERENCES

[1] Lotti M, Moretto A. Organophosphate-induced delayed polyneuropathy. *Toxicological Reviews*. 2005;24(1):37-49.
[2] Thivakaran T, Gamage R, Gunarathne KS, Gooneratne IK. Chlorpyrifos-induced delayed myelopathy and pure motor neuropathy: a case report. *The Neurologist*. 2012;18(4):226-28.
[3] Thunga G, Sam KG, Khera K, Xavier V, Verma M. Profile of acute mixed organophosphorus poisoning. *The American Journal of Emergency Medicine*. 2009;27(5):628-e1.
[4] Eddleston M. Self poisoning with pesticides. *BMJ*. 2004;328(7430):42-44.
[5] Bradberry SM, Cage SA, Proudfoot AT, Vale JA. Poisoning due to pyrethroids. *Toxicological Reviews*. 2005;24(2):93-106.
[6] Hernández AF, Parrón T, Tsatsakis AM, Requena M, Alarcón R, López-Guarnido O. Toxic effects of pesticide mixtures at a molecular level: their relevance to human health. *Toxicology*. 2013;307:136-45.
[7] Martin T, Ochou OG, Vaissayre M, Fournier D. Organophosphorus insecticides synergize pyrethroids in the resistant strain of cotton bollworm, Helicoverpaarmigera (Hübner)(Lepidoptera: Noctuidae) from West Africa. *Journal of Economic Entomology*. 2003;96(2):468-74.
[8] WHO recommended classification of pesticides by hazard and guidelines to classification 2009. Geneva: World Health Organization; 2010.
[9] Johnson MK. Organophosphates and delayed neuropathy—is NTE alive and well? *Toxicology and Applied Pharmacology*. 1990;102(3):385-99.
[10] Wielgomas B, Krechniak J. Toxicokinetic interactions of alpha-cypermethrin and chlorpyrifos in rats. *Polish Journal of Environmental Studies*. 2007;16(2):267.
[11] Choi J, Hodgson E, Rose RL. Inhibition of trans-permethrin hydrolysis in human liver fractions by chloropyrifosoxon and carbaryl. *Drug Metabolism and Drug Interactions*. 2004;20(4):233-46.
[12] Tripathi M, Pandey R, Ambesh SP, Pandey M. A mixture of organophosphate and pyrethroid intoxication requiring intensive care unit admission: a diagnostic dilemma and therapeutic approach. *Anaesthesia & Analgesia*. 2006;103(2):410-12.
[13] Iyyadurai R, Peter JV, Immanuel S, Begum A, Zachariah A, Jasmine S, et al. Organophosphate-pyrethroid combination pesticides may be associated with increased toxicity in human poisoning compared to either pesticide alone. *Clinical Toxicology*. 2014;52(5):538-41.

PARTICULARS OF CONTRIBUTORS:
1. Intern, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India.
2. Postgraduate Student, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India.
3. Assistant Professor (Senior Scale), Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India.
4. Professor, Department of Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
5. Associate Professor, Department of Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Girish Thunga,
Assistant Professor (Senior Scale), Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences, Manipal University, Manipal-576104, Karnataka, India.
E-mail: girishthunga77@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 14, 2016**
Date of Peer Review: **Aug 02, 2016**
Date of Acceptance: **Aug 29, 2016**
Date of Publishing: **Nov 01, 2016**