ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 12;2 http://apjmt.mums.ac.ir June 2023

CASE REPORT

A Case of Pendimethalin Toxicity Mimicking Organophosphorus Toxicity

FOUAD MARWA MOHAMMED[1], ZAWILLA NERMIN HAMDY[1,2], HAMDY HATEM SHERIEF[1], ALI AHMED MAHER[1]

[1]Department of Occupational & Environmental Medicine, Faculty of Medicine, Cairo University, Egypt
[2]National Environmental and Clinical Toxicology Research Center, Faculty of Medicine, Cairo University Egypt

Abstract

Introduction: Pendimethalin is an herbicide that is used worldwide to attack certain wide leaf and grassy weeds in a variety of agricultural and non-crop regions, with a claimed very low toxicity to human. There have been some few reported cases of acute pendimethalin toxicity to date, around the world. We report a case of pendimethalin toxicity resembling and managed initially as organophosphorus poisoning.
Case Description: A 42-year-old agricultural worker was found unresponsive in his field with profuse oral secretions. The patient presented with altered mental status, where Glasgow comma scale was 10, oxygen saturation at room air was 88 %, Blood pressure measured 125/75, pulse rate was 95 beats per minute, and temperature was 37 °C. The patient's pupils were constricted, equal, regular, and reactive. Chest examination revealed scattered respiratory crepitations. The patient also had a distinct garlic odor very similar to that of Organophosphate compounds. The results of his laboratory investigations revealed only hypoxemia. The patient received atropine and supportive management, which prompted the chest secretions to clear up and allow him to restore consciousness without experiencing any neurological problems.
Conclusion: Pendimethalin toxicity can present with manifestations mimicking acute organophosphorus poisoning. Proper supportive care is needed for the management of acute pendimethalin toxicity.

Keywords: Pendimethalin, Herbicide, Acute toxicity, Organophosphorus mimic, Agricultural worker.

How to cite this article: FOUAD MM, ZAWILLA NH, HAMDY HS, ALI AM .A Case of Pendimethalin Toxicity Mimicking Organophosphorus Toxicity. **Asia Pac J Med Toxicol 2023; 12(2):77-80.**

INTRODUCTION

Pendimethalin (PM) [N-(1-ethlpropyl)-3, 4-dimethyl-2, 6-dinitrobenzamine); CAS 40487-42-1] is a dinitroaniline herbicide that is strategically used in a variety of crops and non-crop regions to combat specific wide leaf and grassy weeds [1]. It is widely used, publicly accessible, and typically sprayed to soil as a pre-emergence herbicide, however it may also be used post-emergence. It is applied on rice, peanut, soybean, cabbage, garlic, onion, radish, tomato, pea, and tobacco [2].

Pendimethalin is known to have a very low human toxicity. Indeed, the WHO classifies it as a slightly hazardous compound (Class III), and the United States Environmental Protection Agency also rates it as class III "slightly toxic" compound, as well as group C "possible human carcinogen" [3].

Pendimethalin herbicide is available in the following forms: emulsified concentrate, concentrated suspension, granular formulation, and encapsulated suspension. Some of the brand names under which it is sold include Bunker, Claymore, Prowl, and Stomp. The amount of pendimethalin in an emulsified concentrate varies depending on the product; for instance, Prowl (BASF, Germany) has 38.7% pendimethalin, whereas Stomp has 45.5% pendimethalin. Solvents, emulsifiers, surfactants, or preservatives may be added depending on the type of pendimethalin; for the emulsified concentration, pendimethalin is combined with an emulsifier and solvent. Solvents used include xylene, monochlorobenzene, naphthalene, and ethylene dichloride [4].

The exact pathogenesis for toxicity of pendimethalin in humans is not fully explored. Only few cases of its toxicity have been documented globally, to date. Farmers exposed to pendimethalin had a possible increased risk of developing lung and rectal cancer, according to an agricultural cohort research in the USA [5,6]. Another cohort study with almost 89,000 participants found a link between PM exposure and pancreatic cancer, with low users having a risk that was 1.4 times higher and strong users having a risk that was three times higher than those who never used PM [7]. In the husbands and wives of pesticide applicators, cumulative use of PM and petroleum oil has also been linked to end-stage renal disease [8]. Acute PM poisoning has caused a number of health complications, including fatalities [4, 9, 10, 11].

We report a case of pendimethalin toxicity mimicking and managed initially as organophosphorus poisoning.

*Correspondence to: Marwa Mohammed Fouad, MD, Lecturer of Department of Occupational and Environmental Medicine, Faculty of Medicine, Cairo University, Egypt.
Tel: 01004531905, Email: marwa.fouad@kasralainy.edu.eg

CASE PRESENTATION

A 42-year-old agricultural worker was found lying on the ground with altered mental status while working in the field with profuse oral secretions. A co-worker transported the patient to our Toxicology Center. At the time of arrival, with a delay of 2 hours, the patient was GCS 10, with eye opening to pain, localizing pain, and verbalizing inappropriate words. Oxygen Saturation was 88%, BP: 125/75, Pulse: 95, Temp: 37 °C. Pupils were constricted, regular, and reactive. Chest was full of scattered respiratory crepitations. There was also an evident odor very similar to the Organophosphate compounds.

Patient was immediately put on Oxygen Mask, and suction of secretions was performed. Oxygen Saturation then reached 100%. Atropine was then administered based on clinical suspicion by initial dose of 2-5 mg then the chest secretions were cleared after 10 ampoules.

Gastric suction was done revealing an orange-colored gastric aspirate, and the patient clothes were exchanged.

Laboratory investigations done to the patient on admission (table 1) revealed hypoxemia; pO2: 54 mmHg, SO2:86%, and leukocytosis; TLC: 17.6 ($\times 10^3/\mu l$).

Owing to the fact that there was no depression in the serum pseudocholinesterase level, organophosphate toxicity was excluded. By taking a thorough exposure history from the patient's coworkers, they mentioned that there is an herbicide recently used at their area called 'Stomp® Extra 45.5% CS' with active ingredient Pendimethalin consistent with the colour found in the gastric aspirate.

With continuous supportive management, the patient regained consciousness without any neurological deficit after 16 hours and then discharged.

Table 1. Laboratory investigations of the patient on admission

Laboratory Parameter	Result	Normal Range
Arterial Blood Gases		
pH	7.35	7.35-7.45
paCO2	42 mmHg	35-45 mmHg
HCO3	23 mmol/L	22-26 mmol/L
paO2	54 mmHg	75-100 mmHg
SpO2	86 %	95-100 %
RBS	124 mg/dl	80-140 mg/dl
Complete Blood Count		
Hb conc.	14.9 g/dl	13.5-18 g/dl
RBCs	5.29 ($\times 10^6/\mu l$)	4.5-6.5 ($\times 10^6/\mu l$)
Hematocrit	52.2 %	42-52 %
Plt	271 ($\times 10^3/\mu l$)	150-400 ($\times 10^3/\mu l$)
TLC	17.6 ($\times 10^3/\mu l$)	4-11 ($\times 10^3/\mu l$)
Lymphocytes	27.6 %	20-45 %
Monocytes	24.1 %	0-10 %
Granular cells	48.3 %	30-70 %
Kidney Function		
Na	145 mmol/L	135-145 mmol/L
K	4.3 mmol/L	3.5-5 mmol/L
Urea	37 mg/dl	20-40 mg/dl
Creatinine	0.8 mg/dl	0.7-1.3 mg/dl
Liver Function		
ALT	25 U/L	7-55 U/L
AST	28 U/L	8-48 U/L
PT	13.5 sec	10-14 sec
PC	100 %	80-100 %
INR	1	0.9 1.1
Serum Cholinesterase level	6000 U/L	Above 4500 U/L

DISCUSSION

Farmers in every nation must contend with weeds, which can either directly or indirectly affect a number of farming decisions. If weeds are not controlled, field crop yields might decline by more than 45% [12]. In order to improve their marketable harvest, farmers all over the world have thus steadily shifted to using herbicide [13].

Despite the WHO classification of pendimethalin herbicide as a mildly dangerous substance and its introduction to the market without adequate toxicological data, the complication rate was 23.5% in the study by Moon and Chun [4].

There have been two deaths attributed to pendimethalin: a 74-year-old woman who consumed 30 mL of the herbicide passed away from aspiration pneumonia, and a 35-year-old man who consumed an undetermined amount died from respiratory failure [9].

The current case report represents a case of agricultural worker discovered to have acute pendimethalin toxicity, found unresponsive at his fieldwork with profuse oral secretions. Presented with altered mental status of Glasgow comma scale 10, hypoxemia, constricted pupil, with chest crepitations; a presentation mimicking that of organophosphorus acute poisoning, even with the characteristic garlic odor of the organophosphorus compounds. His laboratory investigations revealed only hypoxemia. The patient received atropine and supportive management, resulting in clearance of chest secretions and regaining consciousness without any neurological complications.

There have only been a few case studies with acute pendimethalin toxicity published so far. The fatality rate was zero percent according to a retrospective observational case series involving 17 patients who had ingested pendimethalin herbicide on purpose. Altered mental status, nausea, vomiting, diarrhea, infiltrations on chest imaging, leukocytosis, QTc prolongation, hypotension, metabolic acidosis, and respiratory failure were listed as the clinical manifestations. Hypotension and respiratory failure were the two most typical complications. Some degree of similarity to our patient involved the complicated patients in the retrospective study having an altered mental state, respiratory abnormalities, leukocytosis, normal choline esterase activity, and renal functions at presentation. It is postulated that

pendimethalin may activate the immune system, leading to leukocytosis [4].

In the same study of Moon and Chun [4], unlike our case, two patients, whose starting central venous pressures were 6 and 7 mm Hg, respectively, complicated by hypotension. In addition to the possible cardiovascular toxicity of pendimethalin, hypotension is frequently explained by the effects of other combined formulations, such as combination with toluene or amitraz, but not xylene [14]. Dysrhythmia due to myocardial sensitization by solvent can develop. Hypotension may need the use of a catecholamine vasopressor; however, this should be done with caution in this case [15].

In the study of Moon and Chun [4], despite all the four complicated patients had respiratory failure, they were all released from the hospital without any aftereffects. Xylene might have caused these symptoms and signs.

Our patient also presented with neurological manifestations in the form of unconsciousness like the 25-year-old patient presented by Kumar and Verma [10], who also presented by unconsciousness in addition to delirium, associated with intractable vomiting, burning sensation, and pain in the throat and abdomen after ingesting 50 mL of pendimethalin. He had clear chest examination, normal vitals, and laboratory investigations. He was treated symptomatically and regained consciousness the next day without any sensory motor deficit.

Pendimethalin's involvement as a contributing factor to altered mental status, hypotension, and respiratory failure is unknown. In addition, the herbicide formulation containing 31.7 percent pendimethalin also includes 10.7 percent HY-410S and 58.3 percent xylene. There have been no studies on the acute toxicity of HY-401S, which is used as an emulsifier [4].

Moreover, pendimethalin herbicide may encompass multiple solvents besides xylene, such as naphthalene and monochlorobenzene, which could have a different clinical toxicity. In addition to causing methemoglobinemia, hemolysis, hemorrhage, and fever, naphthalene can also cause altered mental status [16].

Pendimethalin is regarded as generally having mild toxicity and being non-lethal to humans, but there is a paucity of data on its toxicity. Headache, nausea, vomiting, sore throat, retching, and hematemesis are the main symptoms of its toxicity in large ingestions. Its toxicity is almost often linked to oral intake. In a case report, a 73-year-old man with a history of drinking alcohol but no prior history of peptic ulcers experienced nausea, epigastric discomfort, and corrosive gastroduodenal injury two hours after accidentally ingesting a small amount of pendimethalin that had been diluted 300 times in water [11], which indicated that pendimethalin was hazardous to mammals exhibiting cytotoxicity [17]. This formulation also contains 55% xylene, which may have played a significant role in the mucosal irritation as another potential cause [18].

The herbicide pendimethalin (STOMP) is a member of the dinitroaniline group of herbicides and is chemically related to nitro substances like dinitrobenzene, which has been shown to cause methemoglobinemia in mammals. Reports of STOMP poisoning in humans are uncommon, nevertheless. Two incidents of STOMP poisoning resulted through skin and eye contact, according to an analysis of 71 cases (42 men and 29 women, mean age 43.9 +/- 2.5 y) reported to the Poison Control Center-Taiwan between September 1986 and September 1997. The others were brought on by deliberate or unintentional oral intake. The amount consumed on average was 106.1 +/- 13.4 ml. Twenty of them had no symptoms or indicators at all; 38 showed only minor symptoms like nausea, vomiting, and sore throat; and 7 showed severe symptoms including severe retching, hematemesis, and seizures. Four patients passed away as a result of consuming more herbicides (mostly organophosphates) and insufficient airway treatment. The main treatment for saving poisoned cases was adequate breathing support [9].

Unlike our patient regarding severity, according to the clinical records of a research encompassing all patients with acute herbicide poisoning during a two-year period at the Medical College Hospital in India, two individuals who self-intoxicated with pendimethalin only experienced mild symptoms including vomiting. One of the patients had mydriasis, and both had leukocytosis [19].

There is no known specific antidote for pendimethalin poisoning. Hence, supportive management is essential for acute toxicity of pendimethalin herbicide in addition to the attributed associated xylene or other solvents toxicity [4].

CONCLUSION

This case of Pendimethalin toxicity presentation mimicked greatly that of acute organophosphorus poisoning. Proper supportive care is needed for management of acute pendimethalin toxicity. Agricultural workers should be aware of the chemicals used in their field and its potential toxicity. Further studies are needed to investigate in depth the potential toxicity of Pendimethalin and risk assessment.

ACKNOWLEDGMENT

The authors would like to acknowledge the patient coworkers for their honesty and patience in detailed narration and finding the chemical present in their field.

Funding and Support: None.
Conflict of Interest: None to be declared.

REFERENCES

1. Tomlin C. The pesticide manual: incorporating the agrochemicals handbook: a world compendium. Royal Society of Chemistry. 10t ed, London, 1995.
2. Lin HT, Chen SW, Shen CJ, Chu C. Dissipation of pendimethalin in the garlic (Allium sativum L.) under subtropical condition. Bull Environ Contam Toxicol. 2007; 79: 84-6.
3. World Health Organization. WHO recommended classification of pesticides by hazard and guidelines to classification, 2019 edition. Geneva. 2020. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/rest/bitstreams/1278712/retrieve.
4. Moon J, and Chun B. Spectrum of patients intentionally poisoned with an emulsified concentrate pendimethalin herbicide. Emerg Med J. 2014; 32(8): 632-6. doi:10.1136/emermed-2014-204184.

5. Alavanja MC, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, et al. Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol 2004; 160(9):876-85.
6. Hou L, Lee WJ, Rusiecki J, Hoppin JA, Blair A, Bonner MR, et al. Pendimethalin exposure and cancer incidence among pesticide applicators. Epidemiology (Cambridge, Mass.). 2006; 17(3):302.
7. Andreotti G, Freeman LE, Hou L, Coble J, Rusiecki J, Hoppin JA, Silverman DT, Alavanja MC. Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. Int J Cancer 2009; 124(10): 2495-500.
8. Lebov JF, Engel LS, Richardson D, Hogan SL, Hoppin JA, Sandler DP. Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study. Occupational and environmental medicine. 2016; 73(1): 3-12.
9. Chuang CC, Wang ST, Yang CC, Deng JF. Clinical experience with pendimethalin (STOMP) poisoning in Taiwan. Vet Hum Toxicol 1998; 40: 149 – 50.
10. Kumar A, and Verma A. Emergence of new poisons: a case of pendimethalin poisoning from rural india. Clin Toxicol 2013; 51(5): 458-9.
11. Tsukada K, Azuhata H, Katoh H, Kuwano H. Acute gastroduodenal injury after ingestion of diluted herbicide pendimethalin. Singapore Med J 2009; 50: e105 – e106.
12. Monteiro A, and Santos S. Sustainable approach to weed management: The role of precision weed management. Agronomy. 2022; 12(1):118.
13. Kniss AR. Long-term trends in the intensity and relative toxicity of herbicide use. Nature Commun. 2017; 8(1): 1-7.
14. Dhooria S, Agarwal R. Amitraz, an underrecognized poison: A systematic review. Indian J Med Res. 2016; 144(3):348-58..
15. Lamontagne F, Cook DJ, Meade MO, Seely A, Day AG, Charbonney E, et al. Vasopressor use for severe hypotension—a multicentre prospective observational study. PLoS One. 2017; 12(1): e0167840.
16. Pannu AK, and Singla V. Naphthalene toxicity in clinical practice. Curr Drug Metab. 2020; 21(1): 63-6.
17. Patel S, Bajpayee M, Pandey AK, Parmar D, Dhawan A. In vitro induction of cytotoxicity and DNA strand breaks in CHO cells exposed to cypermethrin, pendimethalin and dichlorvos. Toxicol In Vitro 2007; 21:1409-18.
18. Rajan ST, and Malathi N. Health hazards of xylene: a literature review. Journal of clinical and diagnostic research: JCDR. 2014; 8(2): 271.
19. Raina S, Sood V, Shah B, Thakur M, Sharma R. Acute Herbicide Poisoning: An Emerging Phenomenon in Himachal Pradesh, India. Recent Adv Biol Med. 2019; 5(2019):10207.