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Acute liver injury associated with Oxyfluorfen toxicity

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Abstract

Oxyfluorfen is a phenoxyphenyl-type herbicide which is used for broad-spectrum control of broadleaf and grassy weeds. Ingestion of toxic dose of oxyfluorfen can be fatal among animals. However, toxicity to humans are rare in literature. The alterations in haem biosynthesis (anaemia) and in liver are the primary toxic effects. There are no specific antidotes and none of the current treatments have proven efficacious till date. Therefore, prevention needs to be the utmost priority, and on exposure, aggressive decontamination should be initiated. Herein, we described an oxyfluorfen toxicity with acute hepatic injury in a young woman who presented with a deliberate self-harming with an oxyfluorfen poisoning in Sri Lanka.

Keywords

Liver toxicity, Oxyfluorfen, liver transaminases

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Introduction

Oxyfluorfen is a commercially available pesticide which is commonly used for weed control in crop production. The carcinogenic and teratogenic effects are well described in literature among animals.[1,2] The potential toxic effects such as liver cancer, liver failure and haematological effects are recognized in animal models.[3] One case of an oxyfluorfen poisoning is reported in literature in young man.[4] Herein, we described an oxyfluorfen toxicity complicated with acute liver injury in a young woman who presented with a deliberate self-harming with an Oxyfluorfen poisoning in Sri Lanka.

Case history

A 20-year-old previously healthy woman was admitted to an emergency unit of district general hospital in Northern Sri Lanka with a history of nausea, vomiting and throat discomfort after an one of oxyfluorfen poisoning. She had ingested 150 mL of an oxyfluorfen following quarrelling with her husband. Poison was identified by medical professional via empty bottle labelled with an Oxyfluorfen which was brought by patient and relatives. On examination, she was conscious with Glasgow coma scale of 14/15 (GCS 14/15).[5] Her pupils were equally reacting to light and were 3 mm in size. Her blood pressure was 112/65 mmHg and pulse rate was 86 beats per minute. Her respiratory rate was 12 breaths per minute and core body temperature was 36.8°C. The rest of the systemic examinations were unremarkable. Gastric lavage was performed and single dose of activated charcoal was administrated. Her biochemical investigations were within normal limits (Table 1). She was observed in highly dependency care unit for 24 h. She was counselled and was discharged on day 3 of admission.

Four days later, she was admitted to medical ward with a history of right hypochondrial pain, nausea, vomiting and constitutional symptoms. She denied any history of paracetamol overdose. On examination, she was conscious with GCS 15/15. She had pink conjunctiva and no icterus or no flapping tremor. Her blood pressure was 120/60 mmHg and pulse rate was 80 beats per minute. Her respiratory rate was 16 breaths per minute and core body temperature was 36.8°C. Her abdominal examination showed right hypochondrial tenderness. The rest of the systemic examinations were unremarkable. Her full blood count showed white cell count of

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Table 1. The biochemical profile of patient is shown with clinical progression of disease.

Biochemical investigations	First Day 1	Admission Day 3	Day 1	Second Day 2	Admission Day 3	Day 4	Day 7	Day 10	Day 14
Full blood count									
White cell count (4,000–11,000/mm^3)	6,230	7.7	7,460	13,500	8,000	11,790	10,800	8,900	9,000
Neutrophils (50%-70%)	72	74	78	83	68	68	50	54	65
Lymphocytes (20%–40%)	27	14	10	8.9	23	18	29	32	23
Haemoglobin (12–16 g/dL)	12.1	12.9	14	13.2	12.8	12.5	12.5	12.3	11.1
MCV (80–100 fL)	82	83	81	83.6	87	82	83	84	85
Red cell count (400,000–550,00 mm^3)	445,000	471,000	420,000	432,000	420,000	408,000	418,000	408,000	467,000
Platelets (150,000–450,000 mm^3)	284,000	267,000	428,000	379,000	330,000	258,000	247,000	255,000	287,000
Renal functions tests									
Blood urea (18–55 mg/dL)	35	37	26.2	19	25	12.9	20	23	34
Serum Creatinine (0.7–1.5 mg/dL)	1.1	1.0	0.91	0.64	0.78	0.71	0.98	1.0	1.1
Serum electrolytes									
Serum sodium (135–145 mmol/L)	135.3	138.1	134.8	134.9	135.6	138.2	134.9	135.0	134.8
Serum potassium (3.5–5.0 mmol/L)	4.3	4.48	3.78	4.1	4.2	4.08	4.1	4.2	4.7
Liver profile									
Serum AST (0–45 U/L)	19	24	418.5	1815.6	2201	1366	732	212	47
Serum ALT (0–35 U/L)	15	26	482.4	1658.6	2112	1728	991	347	39
Serum bilirubin (0–2.0 mg/dL)	0.70	0.64	1.0	1.90	2.58	1.23	1.65	1.0	1.1
Direct bilirubin (0–0.2 mg/dL)	0.10	0.14	0.30	0.7	0.60	0.20	0.55	0.2	0.3
Indirect bilirubin (0.2–0.6 mg/dL)	0.6	0.50	0.7	1.2	1.98	1.0	1.10	0.8	0.8
Serum protein (6.4–8.3 g/dL)	7.1	7.0	7.48	6.53	5.22	6.14	6.99	7.1	7.0
Serum albumin	4.5	4.4	4.49	3.98	3.24	3.67	4.02	4.0	4.3
Serum globulin	2.6	2.6	2.99	2.55	1.98	2.47	2.97	3.1	2.7
PT/INR (<1.4)	1.1	1.1	1.4	1.95	2.45	1.83	1.27	1.23	1.1

MCV-Mean Corpuscular Volume; AST-Aspartate Transaminase; UL-Unit/Litre; ALT-Alanine Transaminase; PT/INR-Prothrombin Time/Internationalized Ratio.

7,460/ mm^3, haemoglobin of 14.0 g/dL and platelets of 428,000/mm^3. Her inflammatory markers were normal (C-reactive protein (CRP): 0.3 mg/dL, erythrocyte sedimentation rate (ESR): 15 mm/1st hour). Her septic screening was negative. Her aspartate aminotransferase (AST) was 418.5 U/L and aminotransferase (ALT) was 482.5 U/L. Her serum electrolytes showed sodium of 134.8 mmol/ L and potassium of 3.78 mmol/L . Her blood urea was 26.2 mg/dL and serum creatinine was 0.91 mg/dL . Her PT/INR was 1.0 and APTT was 32 . Her total bilirubin was 1.77 mg/dL with indirect bilirubin of 1.27 mg/dL. Her liver enzymes (AST- 2201 IU/L, ALT-2112 IU/L) and serum bilirubin (Total- 2.58 mg/dL, indirect -1.98 mg/dL), PT/INR (2.45) were gradually elevated. Her investigations were shown in Table 1. Her USS scan of abdomen showed acute hepatic injury. Her hepatitis A antibody, Hepatitis Bs Antigen, Hepatitis C antibody, Hepatitis E antigen, Epstein-Barr virus (EBV) antibody, cytomegalovirus (CMV) antibody, HIV screening, Venereal Disease Research Laboratory (VDRL) screening, dengue antigen and antibody were negative. She was managed with *N*-acetyl cystenine 6.25 mg/kg/hourly infusion for 72 h, fresh frozen plasma 15 mL/kg for 5 days and intravenous vitamin K 10 mg for 5 days. Her liver enzymes were gradually improved with therapy and were back to normal on her discharge. She was discharged on day 10 and followed up at medical clinic.

Discussion

Oxyfluorfen is a diphenyl-ether herbicide which is used for broad spectrum pre- and post-emergent control of annual broadleaf and grassy weeds in a variety of tree fruit, nut, vine, and field crops. It is structurally related to lactofen and acifluorfen which inhibits protoporphyrinogen oxidase, involved in haeme biosynthesis pathway.[6] The toxicity occurs through acute oral, dermal and inhalation methods. The moderate

toxicity can occur by ingestion and slightly toxicity can occur by dermal absorption.[7] The potential adverse effects are liver cancer, liver injury and bone marrow toxicity.[8] Oxyfluorfen inhibits haem production which results in a variety of anaemias. Haem is the part of the haemoglobin molecule that contains iron and binds oxygen. It disrupts protoporphyrinogen oxidase enzyme which is involved in haeme biosynthesis pathway as it primary mechanism of action. The person who has genetic inherited disease; variegate porphyria has high risk to oxyfluorfen exposure due to defect of protoporphyrinogen oxidase enzyme.[9] The anaemia was usually mild with varying hematologic abnormalities described in the rat, mouse, and dog studies in literature.[10,11]

Several chronic oral toxicity studies showed hepatic toxicity among mice fed diets which includes increased absolute liver weight, necrosis, regeneration, and hyperplastic nodules.[8,12] Furthermore, chronic toxicity includes effects on the nervous system, immune system, endocrine function, development and reproduction and carcinogenicity or mutagenicity as well.[1,13–15] It is neurotoxicant that interrupts the function of nerves either interacting with nerves directly or by interacting with supporting cells of nervous system.[13] It can trigger an immune system and adversely impact the immunity as well.[13] The exposure to high concentrations of oxyfluorfen has been associated with adverse effects on adrenal, thyroid and thymus glands.[14] However, no further systemic effects were not observed except liver injury in our patient.

Moreover, it is recognized cause for human carcinogen based on combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study.[15] The pathophysiology of hepatic injury among animal models were well described. The increase in serum alkaline phosphatase and increase in liver weight in dogs fed were described.[1] Oxyfluorfen has high affinity and causes inhibition of protoporphyrinogen oxidase in mouse liver mitochondria which causes biochemical changes consistent with those observed in variegate porphyria.[8,9] However, exact pathophysiology of hepatic injury associated with an oxyfluorfen toxicity among human was not well described in literature.[1]

There are isolated case reports of other herbicide injections such as paraquat and glyphosate-surfactant as well.[16–19] There are cases reports of hepatic injury associated with paraquat and glyphosate-surfactant in literature.[20,21] We have found one previous reports on oxyfluorfen injections to the forearm among human in literature in which oxyfluorfen produced a chemical burn to the fascia and subcutaneous tissue of the forearm.[4] There are major diagnostic and therapeutic challenges among hepatic injury associated with herbicide-poisoning.[20,22] However, there were no cases reported hepatic injury associated with an oxyfluorfen toxicity among humans. The clinical consequences of oxyfluorfen are not very well described among humans.

The management of oxyfluorfen toxicity is mainly supportive as there is no known antidote. Gastric lavage, adsorbents such as activated charcoal should be initiated as early as possible to prevent the absorption of the poison.[22] The outcome depends on the severity of the poisoning and the time taken to avail medical help. The high mortality rates are due to the toxicity of the compound itself and the lack of a specific antidote.[22]

This case illustrates first case of hepatic injury following oxyfluorfen toxicity among human. Therefore, such information is valuable for clinicians, regulatory authorities and the public at large. Furthermore, clinical outcomes depend on early recognition and aggressive supportive management since there is no antidote available.

Conclusion

In the case of oxyfluorfen toxicity; anaemia and hepatic injury are the most serious but uncommon complications. The clinical consequences of oxyfluorfen are not very well described among humans. Therefore, such information is valuable for clinicians, regulatory authorities and the public at large. Furthermore, clinical outcomes depend on early recognition and aggressive supportive management since there is no antidote available.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images

Declaration of conflicting interests

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Ethical approval

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Informed consent

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Availability of data and materials

All the data generated or analysed during this study are included in this article and its supplementary information files.

References

1. Antra-Cordone M, King C, Klotzbach J, et al. Oxyflurofen-human health and ecological risk assessment (Final report). USDA Forest service, 2005, https://www.fs.fed.us/foresthealth/pesticide/pdfs/122205_Oxyfluorfen.pdf

2. Abd El-Rahman GI, Ahmed SAA, Khalil AA, et al. Assessment of hematological, hepato-renal, antioxidant, and hormonal responses of Clarias gariepinus exposed to sub-lethal concentrations of oxyfluorfen. *Aquat Toxicol* 2019; 217: 105329.
3. De Vasconcelos Lima M, de Siqueira WN, Silva HAMF, et al. Cytotoxic and genotoxic effect of oxyfluorfen on hemocytes of Biomphalaria glabrata. *Environ Sci Pollut Res Int* 2019; 26(4): 3350–3356.
4. Couceiro J, Garcia-Portal G and Garcia O. Subcutaneous injection of Oxyfluorfen herbicide to the forearm: case report. *Surg J* 2017; 3(4): e188–e190.
5. Jennett B and Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975; 1(7905): 480–484.
6. Poletika NN, Kramer VJ and Wright JP. *Dow AgroSciences' response to the U.S. EPA's environmental fate and effects division science chapter for Oxyfluorfen*. Indianapolis, IN: Regulatory Laboratories: Indianapolis Lab, Dow AgroSciences LLC, 2001.
7. Cheng T. *[Carbon 14]-Oxyfluorfen: dermal absorption study in male rats*. Final report: Lab project no. HLA 6228-105; Report 89RC-1019; Protocol 88P-279, MRID42142306, Hazleton Laboratories America, 1989.
8. Krijt J, Stranska P, Maruna P, et al. Herbicide-induced experimental variegate prophyria in mice: tissue porphyrinogen accumulation and response to porphyrogenic drugs. Canadian J Physiol Pharmacol 1997; 75(10–11): 1181–1196.
9. Birchfield NB and Casida JE. Protoporphyrinogen oxidase: high affinity tetrahydrophthalimide radioligand for the inhibitor/herbicide-binding site in mouse liver mitochondria. *Chem Res Toxicol* 1996; 9(7): 1135–1139.
10. Adler IL, Jones BM and Wargo JP Jr. Fate of 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl) benzene (Oxyfluorofen) in rats. *J Agric Food Chem* 1997; 25(6)): 1339–1341.
11. Dhabe SP and Deshmukh US. Haematological and biochemical assessment of oxyfluorfen toxicity in female rat Rattus norvegicus. *Biosci. Biotech Res Comm* 2014; 7(1): 32–36.
12. U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). Human health effects division, science chapter on Oxyfluorfen, 2001. https://www3.epa.gov/pesticides/endanger/litstatus/effects/oxyfluorfen/oxyfluorfen_analysis.pdf
13. Durkin PR and Diamond G. *Neurotoxicity, immunotoxicity, and endocrine disruption with specific commentary on glyphosate, triclopyr, and hexazinone: final report*. SERA TR 01-43-08-04, 2002, https://nanopdf.com/download/neurotoxicity-immunotoxicity-and-endocrine-disruption-with-specific-commentary-o_pdf
14. Stroh J, Wan MT, Isman MB, et al. Evaluation of acute toxicity to juvenile pacific coho salmon and rainbow trout of some plant essential oils a formulated product and the carrier. *Bulletin of Environmental Contamination and Toxicology* 1998; 60(6): 923–930.
15. Goldenthal EI and Wazeter FX. *Twenty month dietary feeding study in mice*. IRDC no. 285-012, April. Mattawan, MI: International Research and Development Corporation, 1977.
16. Fernando R. Survival of a patient after self-injection of paraquat and surgical excision of the injection site. *Ceylon Med J* 2015; 60(2): 66.
17. Weng SF, Hung DZ, Hu SY, et al. Rhabdomyolysis from an intramuscular injection of glyphosate-surfactant herbicide. *Clin Toxicol* 2008; 46(9): 890–891.
18. U.S. EPA/OPP (U.S. Environmental Protection Agency/Office of Pesticide Programs). Health effects division, Oxyfluorfen: revised occupational and residential non-cancer and cancer exposure and risk assessments for the reregistration eligibility decision (RED) document. 2001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=100046TG.TXT
19. Janeela MA, Oommen A, Misra AK, et al. Paraquat poisoning: case report of a survivor. *J Family Med Prim Care* 2017; 6(3): 672–673.
20. Vadysinghe AN and Bandara HMYY Thilakarathne SMNK Liyanag LMM. Acetaminophen overdose followed by ingestion of an herbicide: a case of unique combination. *Forensic Scien Intern Report* 2019; 1(11);: 100031.
21. Mills PJ, Caussy C and Loomba R. Glyphosate excretion is associated with steatohepatitis and advanced liver fibrosis in patients with fatty liver disease. *Clin Gastroenterol Hepatol* 2020; 18(3): 741–743.
22. Ghosh S, Singh A, Dewan H, et al. Herbicide poisoning: a diagnostic challenge. *Indian J Crit Care Med* 2012; 16(1): 52–54.