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Acute Herbicide Poisoning: An Emerging Phenomenon in Himachal Pradesh, India

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Abstract
The clinical manifestations of acute herbicide self-poisoning have not been widely studied in India. The objective was to study the clinical profile of herbicide poisoning cases admitted in a medical college hospital located in a rural setting of Himachal Pradesh. The clinical records of all patients diagnosed with acute herbicide poisoning between January 1, 2017, and February 15, 2019, were analyzed retrospectively in this hospital-based cross-sectional study. During the study period, 20 patients were diagnosed with acute herbicide poisoning and are included in this study. There were 13 males. The mean age was 33.6 ± 13.3 years. The herbicides ingested included 2,4-D (45%), paraquat (20%), glyphosate (10%), pendimethalin (10%), atrazine (5%), butachlor (5%), and metribuzin (5%). 2,4-D is the commonest acute herbicide self-poisoning in this region. It was observed that poisoning with herbicides is usually of mild toxicity except paraquat, which is associated with high mortality.

Keywords: 2,4-D; Paraquat; Glyphosate; Pendimethalin.

1. INTRODUCTION

Herbicides are agrochemical substances used for killing weeds or inhibiting their growth. The introduction of synthetic herbicides has empowered farmers to control the crop–weed competition. The first widely used synthetic herbicide was 2,4-dichlorophenoxyacetic acid (2,4-D), and it was introduced in 1946. The chemical weed control was revolutionized with the subsequent introduction of paraquat in 1958, atrazine in 1959, metribuzin in 1968, butachlor in 1970, glyphosate in 1971, pendimethalin in 1974, and many more. Currently, around 2000 different herbicide molecules of 15 different modes of action are available in the global market. Herbicides are the largest growing segment in the crop protection market in India [1]. Increasing labor costs, labor shortage, and technological interventions are the key growth drivers for herbicides. Hand weeding is being replaced by herbicides. Rice and wheat crops are the major application areas for herbicides. Self-poisoning with agrochemicals is a major contributor to the global burden of suicide and is particularly prevalent in South Asia, South East Asia, and China [2]. Agricultural chemicals are common household items in rural India. They are a source of poisoning, being readily accessible at home, easily available in the market, and improperly stored, unaware of their potential for harm. Pesticide self-poisoning due to organophosphorus compounds, aluminium phosphide, carbamates, organochlorines, and pyrethroids is already a significant public health problem in India [3]. Herbicides self-poisoning is an emerging phenomenon and will add to the ongoing public health burden of various agrochemical poisonings. Himachal Pradesh has a rural population of 89.9% according to the 2011 census. Agriculture is a major source of income and employment in the state. Over 93% of the population depend directly upon agriculture, which provides direct employment to 71% of its population [4]. For sustained crop productivity, herbicides are gradually replacing hand-weeding workers. Over the last few years, herbicide self-ingestion is the emerging cause of acute poisoning in the state. Hence, this study was planned to analyze the clinical profile of herbicide poisoning cases admitted in a medical college hospital located in a rural setting of Himachal Pradesh, India. The study is an experience on herbicide self-poisoning in this region of the country.

2. METHOD(S)

This is a retrospective observational study conducted on patients with acute herbicide poisoning and admitted in the department of medicine of a 820-bed medical college hospital. The hospital caters to the rural population of the hilly physiogeographic zone of Shivalik and Lesser Himalayas of the state of Himachal Pradesh, India. The study period was from January 1, 2017, to February 15, 2019. We evaluated the records of all the herbicide-poisoning cases where complete information was available

as per the precoded pro forma parameters. Recorded information was entered in a precoded pro forma and included details on demography, clinical profile, treatment, and outcome. The data collected were cross-checked by two independent observers. The data obtained were entered in a Microsoft Excel sheet and analyzed with statistical software SPSS 21.0 (IBM Corp., Armonk, NY, USA). Qualitative data were calculated in the form of frequency and percentage. Quantitative data were presented as mean ± standard deviation (SD). The study was approved by the institutional ethics committee.

3. RESULTS

During the study period, 20 patients diagnosed with acute herbicide poisoning were included in the study. The herbicides included 2,4-D, paraquat, glyphosate, pendimethalin, atrazine, butachlor, and metribuzin. The different market brand names were Heera 44, Kissan 38, Superhit, and Weed for 2,4-D; Roundup for glyphosate; Milquat for paraquat; and Masstaf for atrazine. The frequency distribution of the compounds involved is shown in Table 1.

The mode of poisoning was oral ingestion in each one of the patients. Among the cases, 13 were males. The mean age was 33.6 ± 13.3 years. Mean hospital stay was 3.5 ± 1.8 days. Gastrointestinal decontamination with normal saline gastric lavage was done in all the patients. The mean time delay from ingestion to gastric lavage is shown in Table 2. The clinical profile of the patients is shown in Table 2.

The laboratory investigation profile of the patients is shown in Table 3.

Psychiatric illness was a feature in five patients that included alcohol dependence in four and adjustment disorder in another. ECG was normal in all the patients. The outcome of the patients was that 17 patients recovered completely, two expired, and one patient took a referral for another hospital. Both the patients who expired had paraquat poisoning. Four

Table 1: Frequency distribution of herbicide compounds ingested.

Type of herbicide compound consumed	2,4-D	Paraquat	Glyphosate	Pendimethalin	Atrazine	Butachlor	Metribuzin
Number of cases (percentage)	9(45)	4(20)	2(10)	2(10)	1(5)	1(5)	1(5)

Table 2: Summary of symptoms and signs in each group.

Compound	Total patients	Mean age	Gender	Mean time delay (hours)	Symptoms and signs	Outcome
2,4-D	9	37 ± 17.5	M-6 F-3	2.3 ± 1.4	Nausea, vomiting, dizziness, drowsiness, pain abdomen, hematemesis, melena, incontinence of bowel, bladder, tachycardia, mydriasis, hiccups, dryness of mouth, cerebellar dysfunction	All recovered
Paraquat	4	30.2 ± 11.3	M-3 F-1	1.5 ± 0.5	Vomiting, oral ulceration, shock, encephalopathy, acute kidney injury, acute respiratory failure, acute liver failure	Expired-2 Recovered-1 Referral-1
Glyphosate	2	26 ± 8.4	M-2	4.7 ± 6	Vomiting, pain abdomen	Both recovered
Pendimethalin	2	34.5 ± 3.5	F-2	2 ± 2	Vomiting, mydriasis	Both recovered
Atrazine	1	23	M-1	1	Vomiting, dizziness	Recovered
Butachlor	1	40	F-1	–	Vomiting	Recovered
Metribuzin	1	35	M-1	–	Vomiting, pain abdomen, tachycardia	Recovered

Table 3: Hemogram and biochemistry profile at admission (the values represented are means 6 ± SD).

Parameter	2,4 D (*n* = 9)	Paraquat (*n* = 4)	Glyphosate (*n* = 2)	Pendimethalin (*n* = 2)	Atrazine (*n* = 1)	Butachlor (*n* = 1)	Metribuzin (*n* = 1)
Hemoglobin (g%)	12.9 ± 2.3	13.2 ± 1.4	13.8 ± 0.9	11.8 ± 2.1	14.4	12.4	15.2
TLC ($\times 10^3$/mm^3)	10.3 ± 4.2	11.1 ± 6.1	12.9 ± 9.2	12.5 ± 4.8	9.9	11.2	13.9
Platelets ($\times 10^3$/mm^3)	151.7 ± 39.6	222 ± 12.3	202 ± 11.2	212 ± 11.5	179	260	150
Bilirubin total (mg/dl)	0.4 ± 0.2	7.2 ± 11.8	0.3 ± 0.3	0.4 ± 0.07	0.5	0.5	0.4
AST(IU)	44 ± 12.9	189 ± 185	43.5 ± 12	35 ± 7	48	23	68
ALT(IU)	46 ± 37.6	195 ± 199	39 ± 5.6	12 ± 2.8	54	30	37
Alkaline phosphatase (KAU)	73 ± 17.4	380 ± 375	67 ± 11.2	96 ± 21.2	92	196	95
BUN (mg/dl)	18.4 ± 9.4	103 ± 77	10.5 ± 4.9	10.5 ± 2.1	9	27	12
Creatinine (mg/dl)	0.9 ± 0.3	5.3 ± 4.1	0.8 ± 0.1	0.5 ± 0.07	0.7	0.7	0.8

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; *n*, number; TLC, total leucocyte count.

patients were misdiagnosed as organophosphorus poisoning by the primary care physicians: two had 2,4-D and one each had glyphosate and butachlor poisoning. Forced alkaline diuresis was performed in one patient with 2,4-D poisoning. Three patients with paraquat poisoning were managed by inotropic support, and two required dialysis. One of the paraquat poisoning patients having features of cardiogenic shock survived. Intentional self-harm poisoning was the reason in 15 (75%) and accidental in 5. Five patients had concomitant alcohol consumption.

4. DISCUSSION

Self-poisoning with agrochemicals such as pesticides is a global public health problem. They account for 109,700 (13.7%) of suicides, which means at least one in seven deaths globally. Pesticide self-poisoning is particularly prevalent in South Asia, South East Asia, and China. Pesticide suicides account for 38.5% of suicides in the South East Asia region [2]. The majority of deaths are from deliberate self-poisoning with organophosphorus pesticides (OP), aluminium phosphide, and paraquat [3]. The case fatality following pesticide ingestion ranges between 1% and 40% and is mainly dependent on the pesticide ingested than availability of health care [5]. The highest case fatality rates have been reported with poisoning due to aluminium phosphide, endosulfan, and paraquat. All the three are highly toxic pesticides and have no proven effective antidote at present. Between 1945 and 1989, 1012 fatal pesticide poisonings were recorded in England and Wales. The majority (77.7%) involved herbicides and predominantly paraquat [6]. Herbicides is the largest growing segment and accounts for 16% of the total crop protection chemical market in India [7]. As a result, 2000 different herbicide molecules of 15 different modes of action are easily available for human exposure. However, studies on acute herbicide human poisonings are limited. Studies, case series, and reports are available on individual herbicides such as 2,4-D, paraquat, glyphosate, and pendimethalin in India [7-23]. In this study, poisoning due to 2,4-D, paraquat, glyphosate, pendimethalin, atrazine, butachlor, and metribuzin herbicides were observed. The patients with 2,4-D poisoning had features of mild toxicity in this study. The final outcome was excellent with full recovery in all the patients. 2,4-D belongs to the chlorophenoxy herbicide group. Toxic manifestations including vomiting; abdominal pain; diarrhea; and, occasionally, gastrointestinal hemorrhage are early effects. Hypotension, coma, hypertonia, hyperreflexia, ataxia, nystagmus, miosis, hallucinations, convulsions, fasciculation, and paralysis may then ensue. Acute respiratory failure is observed in some patients. Myopathic symptoms including limb muscle weakness, loss of tendon reflexes, myotonia, and increased creatine kinase activity have been observed. Metabolic acidosis, rhabdomyolysis, renal failure, increased aminotransferase activities, pyrexia, and hyperventilation have been reported. Death has been frequently reported with this poisoning [24].

Paraquat was the second most frequent herbicide poisoning observed in this study. One of the patients developed acute kidney injury, type 1 respiratory failure, and hepatic dysfunction and was managed with hemodialysis. He died 15 days after ingestion. He had evidence of diffuse ground glass opacities and homogenous consolidation in dependent lung segments without the evidence of fibrosis on HRCT chest. The second patient developed acute kidney injury (AKI) and took a referral on the sixth day post ingestion. The third patient developed shock and encephalopathy and died within 12 h of admission. The fourth patient was a female and presented with oral ulcerations, shock, encephalopathy, and had leucocytosis at admission. She survived with medical management.

Paraquat belongs to bipyridyliums class of herbicides. Paraquat poisoning has been reported from many parts of the world including India. It has also been reported from the state of Himachal Pradesh, India, in the past [19]. Paraquat is highly

toxic and causes damage to the lungs, liver, and kidneys. The toxic manifestations include corrosive injury to the gastrointestinal tract, acute kidney injury, renal tubular necrosis, hepatic dysfunction and hepatic necrosis, respiratory failure, and pulmonary fibrosis. Paraquat poisoning is synonymous with fatality. The mortality in India and other parts of world has been reported from 35% to 100% [5]. Death may occur as late as 6 weeks after ingestion [3].

Patients with glyphosate had mild gastrointestinal symptoms. Both patients had leucocytosis. Glyphosate belongs to the amino acid derivative group of herbicides. Formulations of glyphosate can cause intoxication in humans, which may vary from different salts used.[25] In addition, toxicity may be due to the presence of surfactants such as polyoxyethyleneamine (POEA). The clinical manifestations include corrosive effects on the gastrointestinal tract, acute respiratory failure, coma, shock, myocardial injury, ventricular dysrthymias, cardiac arrest, ECG changes such as prolonged PR and QTc intervals QRS widening, acute kidney injury, elevated liver enzymes, hyperkalemia, and metabolic acidosis. Case fatality of glyphosate is 2.4% [25, 26]. A study from the Republic of Korea has reported a mortality of 9.3% after acute glyphosate herbicide ingestion [27].

The patients with pendamethalin self-poisoning had mild symptoms in the form of vomiting only. Both the patients had leucocytosis. One of the patients had mydriasis. Pendamethalin belongs to the dinitroanaline group of herbicides. Clinical manifestations are altered mental status, nausea, vomiting, diarrhea, infiltrations on chest imaging, leucocytosis, QTc prolongation, hypotension, metabolic acidosis, and respiratory failure. Pendamethalin ingestion has mild toxicity features and is nonfatal [28]. The patient with butachlor ingestion had only vomiting as manifestations. Butachlor belongs to chloracetanilide group of herbicides. Butachlor oral exposure has been found to have low toxicity. The spectrum varies from asymptomatic, gastrointestinal manifestations in the form of nausea and vomiting to central nervous system depression. Death is rare [29, 30].

Atrazine and metribuzin belong to the triazine group of herbicides. Extensive literature search did not result in any information of acute human poisoning with these agents. Preliminary information from this study is that both have mild oral toxicity. Isolated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mildly raised in patients with metribuzin and atrazin poisoning, respectively. Patient with metribuzin poisoning had leucocytosis at admission.

5. LIMITATIONS

The retrospective nature of study and the absence of sample analysis by HPLC or LC–MS are the main limitations of this study. Furthermore, the comparative analysis to self-poisoning due to insecticides or fungicides was not performed.

6. CONCLUSION

Observational studies on the herbicide poisoning are insufficient and have not been frequently reported from Himachal Pradesh. This study identified herbicides as a cause of acute poisoning in this region of India. It was observed that poisoning with herbicides is usually of mild toxicity except paraquat, which is associated with high mortality. Knowledge on this subject will allow us to discuss the clinical manifestations and focus on taking preventive measures.

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Author Contributions
SR, VC, BS, MT, and RS jointly conceived and designed the study, collected and analyzed the data, and prepared the manuscript.

Conflict of Interest
None.

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