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원 저

Aryloxyphenoxy propionate 계열 제초제 중독환자의 임상 양상

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임준영 · 문정미 · 전병조

Clinical Characteristics of Patients after Aryloxyphenoxy Propionate Herbicide Ingestion

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Purpose: No studies have been conducted to investigate the acute toxicity of aryloxyphenoxypropionate herbicides in humans following ingestion. Therefore, this study was conducted to investigate the clinical characteristics of aryloxyphenoxypropionate herbicide poisoning and provide guidance for physicians treating patients who have ingested these types of herbicides.

Methods: A retrospective observational case series was conducted using ten patients with history of aryloxyphenoxy propionate herbicide. Data were collected for clinical manifestation, management and final outcome.

Results: The most common symptoms were gastrointestinal irritation and an altered mental state (Glasgow Coma Scale<15). An elevated lactate level was a common laboratory abnormality, and prolonged QTc interval was commonly observed. These clinical features normalized within one day of supportive treatment.

Conclusion: The acute toxicity of aryloxyphenoxypropionate herbicides in humans is manageable with supportive treatment. However, physicians should take into account depressed consciousness, the possibility of arrhythmia, and an elevated lactate level when planning their treatment strategy.

Key Words: Aryloxyphenoxy propionate herbicide, Poisoning, Acetyl-CoA carboxylase

Introduction

Worldwide, pesticides are one of the most frequently used methods of suicide and account for an estimated 300,000 deaths in Asia each year[1,2]. After paraquat was banned, glyphosate and other new herbicides replaced it as a cause of acute herbicide poisoning[3].

Aryloxyphenoxypropionate post-emergence herbicides inhibit the acetyl-CoA carboxylase (ACC) enzyme in grasses, and this enzyme catalyzes the first step in fatty acid synthesis and is important for cell membrane synthesis[4,5]. Aryloxyphenoxypropionate herbicides include clodinafop-propargyl, cyhalofop-butyl, diclofop-methyl, fenoxaprop-P-ethyl, fluazifop-P-butyl, haloxyfop-R-methyl, propaquizafop, and quizalofop-P-ethyl[6].

In mammals, ACC exists as two tissue-specific

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isozymes, ACC1 and ACC2[7,8]. The inhibition of ACC1 in mammals results in the inhibition of fatty acid synthesis, while the inhibition of ACC2 can stimulate mitochondrial fatty acid β-oxidation[7,8]. Mice embryos with a genetically deleted ACC1 gene died[9]. ACC2 knock-out mice showed lower glucose and triglyceride levels and a very low-density lipoprotein level in serum compared with wild mice[10].

Despite concerns about the toxic effects of these herbicides in humans, which stem from the essential role of ACC in the body, English-language studies on the acute toxic effects in humans are lacking. One study reported on the effects of acute fenoxaprop-P-ethyl coformulated with ethoxysulfuron in humans[3]. The published toxicity of aryloxyphenoxypropionate herbicides in animals is related to the carcinogenic effect in cases of chronic exposure[11]. Most studies concerning aryloxyphenoxypropionate herbicides have focused on the degradation or detection of these herbicides in soil or water[12,13].

This study aimed to review the clinical course of patients who ingested aryloxyphenoxypropionate herbicides.

Methods

This study was approved by the institutional review board at ○○ National University Hospital (○○, South Korea). A single-center, retrospective review of electronic medical record identified twelve adult patients (18 years or older) who had presented to the emergency department (ED) within 24 hours of ingesting an aryloxyphenoxypropionate herbicide between February 2009 and February 2016. Aryloxyphenoxypropionate herbicide ingestion was diagnosed based on the patient- or witness-reported history of ingestion and on the patient's hospital record, in which the physician had recorded the commercial name of the herbicide taken from the bottle brought by the patient or witness. Of these twelve patients, one had ingested cyhalofop-P-ethyl coformulated with propanil and was treated with methylene blue at admission due to propanil-induced methemoglobinemia. This patient was excluded from the study. Another patient intentionally ingested 100 ml of herbicide which contained cyhalofop-P-ethyl and was discharged against doctor's order after refusing any medical evaluation or treatment. Although survival was confirmed by a phone call, this patient also was excluded because of the lack information about the clinical course.

The analysis was performed on the remaining 10 patients, all of whom were considered to have ingested only an aryloxyphenoxypropionate herbicide.

The medical records were reviewed for the following data: age, gender, cause of exposure, estimated amount of ingestion, time interval from ingestion to presentation, symptoms, electrocardiogram (EKG) and laboratory results, administration of gastric decontamination and specific treatment, medical complications, length of hospitalization, and survival outcome. The ingested volume of the herbicide was estimated as a spoonful (5 mL), a mouthful (25 mL), a cup (100 mL), or a bottle (300 mL). 15 The EKG was interpreted by one emergency physician. A prolonged QTc interval was defined as greater than 440 ms[16]. Medical complications included acute kidney injury (absolute increase in the serum creatinine of ≥ 0.3 mg/dL or a percentage increase in the serum Cr ≥50% from baseline); respiratory failure (the need for mechanical ventilation); hypotension (the need for pressor support to maintain blood pressure after admission); and metabolic acidosis (pH〈7.35 and HCO_3^-〈20 mmol/L)[15]. In addition, any condition encountered during the review of the patients' medical records that was deemed to be serious and clinically significantly by the investigator was rated as a medical complication. Survival outcomes were evaluated through phone calls to the patient and/or their family members.

Data are presented as the frequency for categorical variables and the median with interquartile range for continuous variables.

Results

The ages and genders of the 10 patients included in this analysis are shown in Table 1. All patients

Table 1. Basic characteristics and initial symptoms of patients

Patient No	Age Sex	Active ingredient	Amount* (mL)	Ethanol Co ingestion	Time interval† (hr)	Sys BP‡ (mmHg)	GCS§	Other symptoms	EKG findings QTc interval (ms)/Rhythm
1	64/F	Cyhalofop-P-ethyl	unknown		3	140	15		505/First AV block‖
2	44/F	Cyhalofop-P-ethyl	300	+	1	120	15		385/ Normal rhythm
3	73/M	Cyhalofop-P-ethyl	100		3	120	15		453/Normal rhythm
4	51/M	Cyhalofop-P-ethyl	150		3	130	15		421/Atrial fibrillation
5	67/F	Fenoxaprop-P-ethyl	200		3	160	3	Diarrhea	442/Normal rhythm T wave inversion
6	85/M	Fenoxaprop-P-ehtyl	60		2	130	15		473/Normal rhythm
7	48/M	Fenoxaprop-P-ethyl	100		3	160	14	Abd pain	406/Normal rhythm
8	65/F	Fenoxaprop-P-ethyl	50	+	1.5	140	15		508/ Sinus tachycardia
9	88/F	Fenoxaprop-P-ethyl	100		6	140	14	Abd pain, Salivation, Nausea.Vomting	446/T wave inversion
10	33/F	Fluazifop-p-butyl	100		2	110	15	Nausea,Vomiting	469/Normal rhythm

*: amount of ingestion
†: Time interval from ingestion to arrival to our hospital
‡: systolic blood pressure at presentation
§: Glasgow Coma Scale at presentation
‖: first degree atrioventricular block

Table 2. The results of the patients' laboratory analyses at presentation

Patient No	WBC ($\times 10^3/mm^3$)	pH	$PaCO_2$ (mmHg)	Base excess (mmol/L)	HCO_3^- (mmol/L)	Lactate (mmol/L)	AST (U/L)	ALT (U/L)	Glucose (mg/dL)	CK (U/L)	TroponinI (ng/mL)
	(4.8-10.8)	(7.35-7.45)	(35-48)	(-2 -+2)	(21-28)	(0.7-2.1)	(5-37)	(5-40)	(60-100)	(35-175)	(0-0.05)
1	13.7	7.44	29.8	-4.6	20.1	3.7	9	18	136	63	0.034
2	8.0	7.44	35.5	-0.3	23.8		28	18	115	127	0.02
3	4.0	7.42	39.0	0.8	25.5	3.2	23	21	131	69	0.015
4	10.4	7.46	32.5	-0.4	22.9	1.2	24	19	103	218	0.02
5	18.8	7.42	35.5	-1.7	23.0	1.6	24	12	136	77	0.01
6	5.0	7.40	43	1.8	26.1	0.7	14	15	97	112	
7	8.6	7.49	28.0	2.4	21.0	2.8	28	18	87	245	0.01
8	8.3	7.34	25.2	-11.	13.5	6.6	45	17	57	103	0.036
9	18.2	7.41	36.0	-1.8	23.8	1.6	24	9	127	40	0.017
10	7.6	7.38	35.6	-4.6	20.5	2.6	16	10	93	98	0.01

The number in parenthesis is normal range of each parameter.

were transferred from their primary hospital to our ED after intentional ingestion of an aryloxyphenoxypropionate herbicide. Five patients ingested fenoxaprop-P-ethyl, four ingested cyhalofop-P-ethyl, and one ingested fluazifop-p-butyl.

Gastrointestinal (GI) tract irritation was the most common symptom (40.0%) and was resolved with symptomatic treatment (Table 1). However, patients who complained of GI irritation were treated with gastric lavage at their primary hospital. Three patients (30.0%) demonstrated a depressed mental state (Glasgow Coma Scale (GCS) score〈15) at presentation, and brain computer tomography evaluations of these patients revealed no remarkable findings. One patent with a GCS score of 13 returned to baseline mental status 24 hours after presentation, and two patients with GCS scores of 14 recovered within 2 hours of presentation without any specific treatment (Table 1).

The most common abnormal EKG finding was a prolonged QTc interval (70.0%) followed by T-wave inversion (20.0%), and these findings had resolved within 1 day after admission (Table 1). Cardiac enzymes (troponin I, creatine kinase, and creatine kinase-MB) remained within the normal range during the admission period (Table 2).

Common abnormal laboratory findings at presentation included an elevated lactate level (50.0%) and leukocytosis (30.0%) (Table 2). Hypoglycemia and metabolic acidosis developed in patient #7, who co-ingested ethanol. These laboratory abnormalities returned to normal limits following supportive care, such as hydration. The red blood cell and serum cholinesterase activities were evaluated at admission in three patients (30.0%) and were found to be within the normal range.

Gastric lavage was administered to seven patients at their primary hospital, and activated charcoal was administered to one patient (Table 3). Supportive treatment, such as hydration and the administration of antiemetics or pain medication, was provided. No patient experienced any complications, and all patients were discharged at an average of 2 days (2.0-3.3 days) after admission without any sequale (Table 3).

Discussion

This is the first study evaluated the clinical features and outcomes of patients who had ingested aryloxyphenoxypropionate herbicides. There were no critical complications during admission, and all patients were discharged without any sequelae after conservative treatment. Similar to our results, Zawahir et al reported that 86 patients with acute poisoning from a combination herbicide (fenoxaprop-P-ethyl, 69 g/L, and ethoxysulfuron, 20 g/L) did not require intensive care treatment, and the case fatality rate was zero[3].

The symptoms related to GI tract irritation in

Table 3. Treatment and final patient outcome

Patient No	Gastric lavage* (min)	Administration of activated charcoal† (min)	Hospital day‡	Survival
1			3	Survival
2	60		2	Survival
3	60		2	Survival
4	40		2	Surviv al
5	120		4	Survival
6			2	Survival
7	60		2	Survival
8			5	Survival
9	120		2	Survival
10	30	120	2	Survival

*:Time interval from ingestion to gastric lavage

†: Time interval from ingestion to administration of activated charcoal

‡: duration of hospitalization

patients with aryloxyphenoxypropionate herbicide intoxication may be due to gastric lavage. A decreased GCS score at presentation was observed in three patients who had ingested only the fenoxaprop-P-ethyl herbicide. The patients with decreased GCS scores did not co-ingested ethanol, and their serum osmolality at presentation was within the normal range (280-295 mOsm/kg). Although there can be exceptions, chemicals with a lower molecular weight and a higher lipophilicity can easily penetrate the blood brain barrier[17]. Table 4 shows the chemical properties of three aryloxyphenoxypropionate herbicides. The molecular weight and lipophilicity of fenoxaprop-P-ethyl is in the middle of these three aryloxyphenoxypropionate herbicides that were ingested by the patients in our study. Another potential contributor to the decreased GCS score in these patients was the solvent. Intoxication with either naphtha, found in fenoxaprop-P-ethyl and fluazifop-P-butyl, or xylene, found in cyhalofop-butyl, can cause central nervous system (CNS) depression[18]. Although it remains unclear whether CNS depression results from the active ingredient, either alone or in combination with the solvent, or from some other factor, the physician should monitor the level of consciousness in patients who have ingested aryloxyphenoxypropionate herbicides, particularly fenoxaprop-P-ethyl, because of a risk of aspiration. Because CNS depression develops in fenoxaprop-P-ethyl-intoxicated patients, a future study with a larger number of patients is needed to determine whether intoxication with other aryloxyphenoxypropionate herbicides, such as fluazifop-P-butyl, that have a higher lipophilicity than does fenoxaprop-P-ethyl causes CNS depression.

Although the mechanism of QTc prolongation remains unclear, it is associated with adverse cardiovascular events or mortality in poisoning cases[19]. In the repeated EKGs, QTc prolongation, which was the most common EKG finding regardless of the type of aryloxyphenoxypropionate herbicide that was ingested, disappeared by the time of discharge. This implies that active or other ingredients in these herbicides may disturb the repolarization of the ventricle and may indicate the possibility of arrhythmia or sudden death, which warrants close cardiac observation of these patients.

An elevated lactate level and leukocytosis were observed in some patients in our study, regardless of the type of herbicide ingested. An elevated lactate level after aryloxyphenoxypropionate herbicide ingestion may be explained by the competition between lactate and fatty acids for oxidation to generate energy in the mitochondria. Increasing fatty acid oxidation by inhibiting ACC2 decreases lactate utilization[20]. Stress, which can result from herbicide ingestion or the administration of gastric decontamination, may also contributed to both an elevated lactate level and leukocytosis[21,22].

The metabolic acidosis, hypoglycemia, and elevated lactate identified in patient #7 can be explained by the effect of co-ingesting ethanol rather than by the inhibition of ACC by fenoxaprop-P-ethyl herbicide. Unfortunately, the serum level of ethanol was not

Table 4. Chemical characteristics of three aryoxyphenoxy propionate herbicides ingested by the patients in this study

	Fenoxaprop-P-ethyl	Fluazifop-P-butyl	Cyhalofop-butyl
Molecular weight (g/mol)	361.8	383.4	357.4
Log Kow at 25°C*	4.58	>5.3	3.31
WHO hazard classification†	Not listed	III	Not listed
Oral LD50 (mg/kg) for rat	5,000	4,096	>5,000
Herbicide with active ingredient			
Type of herbicide	Emulsifiable concentrate	Emulsifiable concentrate	Emulsifiable concentrate
Concentration of active ingredient (%)	7	17.5	5
Solvent	Naphtha	Naphtha	Xylene

*: the log value of the octanol/water partition coefficient at 25°C

†: World Health Organzation hazard classification

measured. However, this patient's serum osmolality at presentation was 340 mOsm/kg and had decreased to 290 mOsm/kg at discharge.

The low toxicity potential of aryloxyphenoxypropionate herbicides on humans in this study may be partially explained by the different structure of ACC, which is targeted by herbicides, in plants and in humans. In plants, ACC is a multisubunit enzyme, while humans have a single-unit, multi-domain enzyme[23]. However, this study was confined to aryloxyphenoxypropionate herbicides and did not include insecticides that inhibit ACC enzymes, such as spirodiclofen and spiromesifen. Most eukaryocytes, including insects, have a multi-domain ACC structure.

There is no specific antidote for aryloxyphenoxypropionate herbicide ingestion, and treatment is symptomatic. Given that intoxication by this class of herbicides appears to be less toxic and that transient CNS depression can develop after ingestion, gastric decontamination may be indicated when another toxic drug is co-ingested.

This study has several limitations. First, symptoms could have been missed because of the retrospective nature of the study. However, significant symptoms that required treatment were recorded in the medical record and would not be missed. Second, the relationship between the amount of herbicide ingested and the severity of acute toxicity was not studied because the blood concentration of the herbicide was not determined. In addition, the diagnosis of aryloxyphenoxypropionate herbicide poisoning was based on the patient's history and not on an analytic blood test. The resources to check a patient's blood level of a pesticide are not available in most EDs. Only patients whose medical record indicated the commercial name of the herbicide and included a history provided by the patient or a witness were included in this study. Third, the number of patients was not sufficient to draw any strong conclusions.

In conclusion, aryloxyphenoxypropionate herbicide intoxication can cause gastrointestinal irritation, a transient disturbance of consciousness, EKG abnormalities and an elevated lactate level. Supportive care is the appropriate treatment.

Disclosure statement

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