

A fatal case of chlorfenapyr poisoning and a review of the literature

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Abstract

Background: Chlorfenapyr is a widely used pesticide and is classified as moderately hazardous to human health. Ingestion usually leads to mortality in humans. However, chlorfenapyr toxicity has a variable course and mechanism of action.

Case presentation: We report the case of a 79-year-old female who ingested chlorfenapyr with the intent to commit suicide. The liquid was ingested 2 hours before she was brought to our emergency department. Gastric lavage was immediately performed. On admission, laboratory examinations revealed mildly elevated liver enzyme and creatinine kinase levels. Acute fever occurred on day 7; on day 8, the patient died of progressive respiratory distress and conscious disturbance. Chlorfenapyr toxicity leads to high rates of mortality (75%) and causes damage to the liver and the nervous system.

Conclusions: It is necessary to observe patients with chlorfenapyr toxicity for 3 weeks because no significant abnormalities occur in the early phase. The onset of fever and deterioration of consciousness is a warning sign of a sudden fatal outcome. We review the literature and discuss neurologic and cardiopulmonary impairment in the clinical course of chlorfenapyr poisoning.

Keywords

Chlorfenapyr, hyperthermia, pesticide, poisoning, fever, fatal outcome

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Introduction

Chlorfenapyr ($C_{15}H_{11}BrClF_3N_2O$)¹ is a pyrrole insecticide that is classified as moderately hazardous. Its mechanism of action is mainly related to its oxidative compound – CL 303268. CL 303268 uncouples oxidative phosphorylation at the mitochondrial level, leading to toxicity.

Chlorfenapyr is widely used in America, Europe, the Asia-Pacific region (China, Japan, Korea, India, Australia, Indonesia, Thailand, the Philippines, Malaysia, and Vietnam), Africa, and the Middle East to protect crops from insects and mites. Because its mechanism is different from that of other insecticides, chlorfenapyr is currently used against insect strains with resistance to traditional insecticides, such as insects that cause malaria.²

The multi-system toxicity of chlorfenapyr has previously been reported in animals.³ In humans, chlorfenapyr toxicity leads to a high incidence of mortality, with only two previously reported case of survival.⁴ The actual mechanism of action and course of progression of toxicity leading to mortality is still unknown. Herein, we report a case of chlorfenapyr toxicity that led to mortality. This case report will assist physicians in managing cases of chlorfenapyr poisoning in clinical practice.

Case report

A 79-year-old female with a previous history of lumbar spondylosis with root compression, type 2 diabetes mellitus, and hypertension was brought to our emergency department. The patient had attempted suicide by drinking 250 mL of 10% chlorfenapyr 2 hours prior to being transported to the hospital.

On arrival, her vital signs were as follows: body temperature: 37°C, heart rate: 97 beats/minute, respiratory rate: 18 breaths/minute, blood pressure (BP): 181/91 mmHg. She was

fully conscious (Glasgow coma scale (GCS) E4V5M6).

A physical examination revealed no obvious abnormalities. Toxin screening for illicit drugs and benzodiazepines showed negative results. A chest X-ray showed left ventricular hypertrophy, and the lung fields were clear. An abdominal plain film X-ray revealed that the gas pattern was normal.

Her laboratory data indicated mildly elevated liver function (aspartate aminotransferase (AST): 104 IU/L (normal: 15–41 IU/L)) and an elevated lipase level (52 IU/L (normal: 22–51 IU/L)). No other toxins were detected during toxin screening. Nasogastric tube insertion and irrigation were performed immediately. She was admitted to the intensive care unit for further observation and treatment.

On day 1, the patient experienced no discomfort, and all vital signs were stable. She was transferred from the intensive care unit. Gastroduodenoscopy was performed, which revealed multiple erosions and erosive ulcers in the antrum and body. The patient had neither abdominal pain nor peritoneal signs during the entire hospital course.

Pantoprazole was administered orally (40 mg every 24 hours). Follow-up laboratory data on day 3 revealed mildly elevated creatinine kinase (CK) (581 IU/L, normal range of 38–397 IU/L), liver function test (69 IU/L, alanine aminotransferase 53 IU/L, normal: 14–40 IU/L), and lipase (70 IU/L) levels. Abdominal ultrasound revealed a moderate degree of fatty liver. The patient was in good spirits and was symptom-free without fever or tachycardia during the first 5 days. Her oxygen saturation was between 91% and 95% without subjective dyspnea.

On day 6, the patient started to complain of mild epigastric pain along with back pain. No fever, tachypnea, or tachycardia was noted. At 8 AM on day 7, the first sign of increasing fever was noted, and her body temperature reached 38.0°C without

additional symptoms. Her body temperature decreased upon administration of oral antipyretics (acetaminophen, 500 mg every 6 hours). Administration of empirical antibiotics (flomoxef, 1 g every 8 hours) was started. Blood test results revealed elevated liver enzyme levels (AST: 133 IU/L, alanine aminotransferase: 85 IU/L). No abnormality was found on chest and abdomen radiography. At 8 PM on day 7, aggravated and fluctuating hyperthermia, between 38.3°C and 38.6°C, was recorded. Her body temperature was quite high despite administration of oral acetaminophen (500 mg) and diclofenac (25 mg) every 6 hours. At 8 AM on day 8, the patient was in a lethargic state (GCS: E3V5M6), and she experienced tachypnea (respiratory rate: 24 breaths/minute) with shallow breathing at 2 PM. Her arterial oxygen saturation decreased to between 88% and 92%, and a nasal cannula (2 L/minute) was applied.

At 3 PM, she was hypertensive (184/85 mmHg) and febrile (38.8°C) with a subsequent decrease in oxygen saturation to between 86% and 88%; oxygen was applied through a non-rebreathing mask (15 L/minute). Three hours later, she was disoriented (GCS: E3V3M6) and had strenuous breathing. Hypoxemia was reported via arterial blood gas examination (pH: 7.38, partial pressure of CO₂: 46 mmHg, partial pressure of O₂: 45 mmHg, HCO₃: 27.2 mmol/L, O₂ saturation: 80%). Exaggerated persistent hyperthermia, hypertension, and tachypnea with intermittent wheezing occurred simultaneously. The patient went into a deep coma (GCS: E1V1M1). Thirty minutes later, she died of cardiopulmonary arrest in accordance with her family's do-not-resuscitate order.

Discussion

Chlorfenapyr intoxication has rarely been reported in humans and has mainly occurred through oral ingestion. We conducted

a literature review of chlorfenapyr poisoning to identify a potential management strategy (Table 1). The mean ± standard deviation age of patients was 52.2 ± 15.6 years old, and the highest body temperature was 40.8 ± 1.1°C. A difference between the sexes was also observed. The length of hospital stay was 10.3 ± 6.1 days, and the mortality rate was 80%. Only two cases of survival have previously been reported.^{4,5}

Chlorfenapyr toxicity has been studied in animals, with reported involvement of various systems. In 1994, a rat, mouse, and rabbit model showed no biological effects on the respiratory, cardiovascular, autonomic nervous, skeletal muscle, and gastrointestinal systems and blood coagulation.⁶ In the mouse and rat models, hepatocellular necrosis and infarction were reported, and liver enzyme elevation was also found (AST and gamma-glutamyl transpeptidase).⁶ Furthermore, hemograms showed elevated blood urea nitrogen and total protein levels. Prominent neurotoxicity was also revealed, and the mechanism of toxicity was studied. Chlorfenapyr can cause oxidative removal of the N-ethoxymethyl group to form CL 303268. This toxin can uncouple oxidative phosphorylation in the mitochondria, which leads to a decrease in or total loss of adenosine triphosphate production. Organs with high energy requirements are more severely affected by chlorfenapyr.^{7,8} The LD₅₀ was measured in various species in previous studies.² Moreover, the dose that causes toxicity in humans was reported to be very low in a previous review, and detergents (such as 0.5% carboxy methyl cellulose) may have a synergic effect on human morbidity and mortality.⁷

Neurotoxicity was dose-dependent, and the effects could vary based on sex. Both acute and chronic neurotoxicity induce multiple clinical symptoms such as a decrease in spontaneous motor activity, gait abnormality, and abnormal arousal. In a study conducted by Metruccio, abnormal posture,

Table 1. List of articles describing chlorfenapyr poisoning.

Reference	Year	Country	Age (years)	Sex	Route	Amount that caused poisoning	Hypotension in triage	Hyperthermia (°C)	Highest BT (°C)	AMS	Elevated CK (IU/L)	AKI	Management	LOS (days)	Outcome
[4]	2015	Korea	61	Female	Oral	10 mL	No	Yes	>38.3	No	Yes (859)	No	Gastric lavage within 1 hour	19	Survival
[5]	2016	Korea	44	Female	Oral	Oral without swallowing, 10%	No	Unknown	No	Unknown	No	Steroid pulse therapy	Unknown	Survival	Survival
[9]	2013	India	28	Female	Oral	Unknown	Unknown	Yes	Not available	Yes	Unknown	Unknown	Neurobion Methylprednisolone Antibiotics: ceftriaxone	10	Mortality
[10]	2012	Korea	49	Male	Oral	200 mL 6%	No	Yes	40.0	Yes	Yes (14,336)	No	Pantoprazole Gastric lavage within 1 hour	18	Mortality
[12]	2018	USA	42	Male	Oral	350 mL 21%	No	Yes	42.2	Yes	Yes (432)	No	Gastric lavage within 2 hours N-acetylcysteine Coenzyme Q Dialysis	6	Mortality
[13]	2010	Korea	55	Male	Oral	250 mL 10%	No	Yes	40.9	Yes	Yes (10,507)	Yes	Gastric lavage within 2 hours Urine alkalinization Dialysis	5	Mortality
[14]	2013	Korea	74	Male	Intra-abdominal injection	20 mL Unknown, dissolve in Kocosol-100	No	Yes	Not available	Unknown	Unknown	Unknown	Surgery, abdominal irrigation, drain insertion Antibiotics: third generation cephalosporin and metronidazole	12	Mortality
[15]	2014	Korea	41	Female	Oral	20 mL	No	Yes	40.7	Yes	Yes (3081)	Unknown	Urine alkalinization	14	Mortality
[16]	2019	Hong Kong	49	Male	Dermal	Unknown (arm, anterior chest, abdomen for several hours) 10%	No	Yes	41.5	Yes	Yes (4484)	Unknown	Intubation Sedation: remifentanyl infusion Antipyretics: intravenous paracetamol, tepid sponging	0.46	Mortality
[This case]	2019	Taiwan	79	Female	Oral	250 mL 10%	No	Yes	39.2	Yes	Yes (581)	No	Gastric lavage Pantoprazole Antibiotics: flumoxef	8	Mortality

AMS = altered mental status; AKI = acute kidney injury; LOS = length of stay; BT = body temperature; CK = creatinine kinase; Normal range: 38–397 IU/L.

decreased activity, and hyperthermia were observed before salivation, convulsion, and death caused by large-dose chlorfenapyr intoxication in male rats.⁶ The clinical neurologic signs differed in mice and rats; a change in the pupil size was only found in mice, and convulsion was only observed in rats. Regarding neurohistopathological findings, vacuolar myelinopathy was observed in various structures ranging from the subcortical regions to the brain stem and spinal cord.⁶ Insult to the hypothalamus caused by a large dose may partly explain hyperthermia during the clinical course of chlorfenapyr poisoning. The elevated CK level (4966 ± 5978.4 IU/L) that we found in our study (Table 1) was not mentioned in previous animal studies. We presumed that neurotoxicity might play a role in the terminal stage of cardiopulmonary instability because of acute leukoencephalopathy, as previously reported.^{5,9,10} Importantly, chlorfenapyr is presumed to cause brain injury in patients with acute poisoning. Sympathetic cardiac activation was found to be related to white matter lesions in the case of multiple sclerosis.⁸ Aside from the hypothalamus, thermoregulation may also partly be influenced by white matter lesions.¹¹ The current presentation exhibited some differences from previously reported cases. Kwon et al. and Baek et al. reported focal neurologic changes such as consciousness disturbance, bilateral leg weakness, and urinary incontinence.^{5,10} Rhabdomyolysis, metabolic acidosis, and pancreatitis were also reported.^{4,5,12} In most cases, organ function changes were similar to those reported herein. In the acute phase (<6 days), liver impairment and elevated CK levels were the first signs and symptoms; these ranged from minor to severe. In the subacute phase, neurotoxicity (including hyperthermia, cardiopulmonary instability, and mortality) was revealed.^{4,5,9,10,12}

In this case, however, a rapid increase in BP occurred before cardiac arrest (164/76 to 219/93 mmHg). In the case reported by

Kwon et al. severe diaphoresis was recorded during the period of hypotension.¹⁰ However, this was the only case that presented hypotension. The differing patterns and development of cardiopulmonary and neurologic impairment in the terminal stage may be attributed to the different stages and extent of leukoencephalopathy. Differences in the location and severity of white matter lesions may have induced varying terminal presentations. In the terminal stage, the course of the condition was non-specific and unpredictable. Kwon et al. reported a patient with relative hypotension (BP: 100/60 mmHg) on day 7, which worsened on day 10 (90/60 mmHg). The patient then recovered on day 12 (BP: 140/100 mmHg), but he eventually died of sudden asystole.¹⁰

The time between symptom onset and the rapid deterioration of health is our major concern, and the range is quite broad (5 to 19 days).^{4,5,9,10,12} In the current case, an initial low-grade fever and lethargy were followed by a rapid deterioration of health over approximately 1 day. Compared with previous reports in humans and animals, hyperthermia may be an early sign of rapid deterioration. The mortality rate of chlorfenapyr toxicity is relatively high and involves the onset of a rapid deterioration cascade. In our case, the patient deteriorated over 30 minutes, and we had no time to perform further examinations such as lumbar puncture and magnetic resonance imaging. Previously, survival has been reported in only two cases of chlorfenapyr poisoning. However, early gastric decontamination within 1 hour saved the patients' lives.^{4,5}

Antidotes and interventions in the late phase of toxicity are lacking; no survivors have previously been reported. Regarding intervention in the late phase, dialysis may be a possible treatment method. The parent compound of chlorfenapyr was found in fecal matter. However, its metabolite was excreted in the urine.³ Chomin et al.

performed hemodialysis on a patient on day 6 but could not halt the onset of deterioration or progression to mortality.¹²

Conclusion

Chlorfenapyr toxicity leads to a high mortality rate (75%) and causes damage to the liver and the nervous system. A rapid onset of tachycardia, hypertension, tachypnea, and diaphoresis resulted from paroxysmal sympathetic hyperactivity, and it led to a life-threatening situation and deterioration of this patient. Early gastric decontamination could be used as a rescue treatment strategy. Although clinical signs are not present in the early phase, prolonged dialysis may be a possible method to prevent deterioration.

It is necessary to observe patients with chlorfenapyr toxicity for at least 3 weeks because no significant abnormalities are present in the early phase. The onset of fever and deterioration of consciousness are warning signs of a sudden fatal outcome.

Ethics statement

The requirements for informed consent and ethics committee review were waived because the patient was deceased.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

Dr. Shih-Chun Chien and Dr. Shih-Chao Chien drafted the report. Dr. Yu-Jang Su revised the report and is responsible for all correspondence. All authors discussed the contents of this report.

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