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Emamectin-Chlorfenapyr-Induced Fatal Leukoencephalomyelopathy with Delayed Hyperthermia: Insecticide Endanger Public Safety

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Case Study

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ABSTRACT

Background: Emamectin-chlorfenapyr is a compound comprising chlorfenapyr and emamectin benzoate that is widely used in agriculture. Chlorfenapyr toxicity has been verified in animals; however, its true mechanism and progression in humans remain to be elucidated. Cases of emamectin-chlorfenapyr poisoning are very scarce.

Case presentation: We present a case of a 65-year-old female who attempted suicide by consuming 30 g of 9.5% chlorfenapyr and 0.5% emamectin benzoate 14 days before admission to our hospital. Laboratory tests revealed extremely high creatinine kinase levels upon admission. Magnetic resonance imaging revealed diffuse and symmetric T2 hyperintensities in the entire white matter tract of the brain and spinal cord, and cytological smears of the cerebrospinal fluid showed abnormal lymphocyte aggregation. The patient died 19.5 hours after admission owing to cardiopulmonary arrest and hyperthermia.

Conclusion: Further research is needed on how to perform flow cytometry in patients with emamectin-chlorfenapyr intoxication and to elucidate the immunological mechanism underlying the inflammatory response caused by emamectin-chlorfenapyr and provide new insights into antidote development.

Keywords: Emamectin-chlorfenapyr; Hyperthermia; Lymphocyte; Fatal outcome; Leukoencephalomyelopathy

INTRODUCTION

Emamectin-chlorfenapyr is a compound of 9.5% chlorfenapyr and 0.5% Emamectin Benzoate (EB). EB (C104H154N2O28) is a broad-spectrum insecticide and pesticide used in agriculture [1]. It acts as a Gamma-Aminobutyric Acid (GABA) receptor agonist and alters membrane chloride ion permeability [2]. Chlorfenapyr (C15H11BrClF3N2O) is a pyrrole insecticide widely applied in vegetable and fruit farming [3]. Chlorfenapyr can block normal oxidative phosphorylation in mitochondria and cause Adenosine Triphosphate (ATP) reduction and failure of oxygen-demanding organs [4].

Agriculture is an important pillar of industry in the Asia-Pacific region. The widespread use of pesticides facilitates access to these poisons and they can be ingested accidentally or by suicidal intent. Clinical symptoms may not be obvious during the early stages of poisoning. Approximately 7 days after exposure, a delayed onset of toxicity may occur. Both EB and chlorfenapyr can lead to nervous system depression [5]. Other typical manifestations of chlorfenapyr poisoning include hyperthermia and rhabdomyolysis [6].

EB poisoning may not be lethal; however, chlorfenapyr exposure has caused high mortality in the Asia-Pacific region and the USA [4,6-8]. Although chlorfenapyr toxicity has been verified in animals, the true mechanism and progression of chlorfenapyr toxicity in humans remain unclear. Furthermore, cases of emamectin-chlorfenapyr poisoning are very scarce. Herein, we present a fatal case of a 65-year-old female who consumed a bottle of emamectin-chlorfenapyr in her suicide attempt. This case report presents cerebrospinal fluid test results and cytological smears, which have not been included in previous studies on chlorfenapyr and EB poisoning.

CASE PRESENTATION

A 65-year-old female was brought to our emergency room with urinary incontinence and a 5-day history of weakness and hypoesthesia that gradually increased in the lower extremities. She had a previous history of hypertension, type 2 diabetes mellitus and depression. The patient had attempted suicide by consuming 30 g of 9.5% chlorfenapyr and 0.5% EB orally 14 days before admission to our hospital.

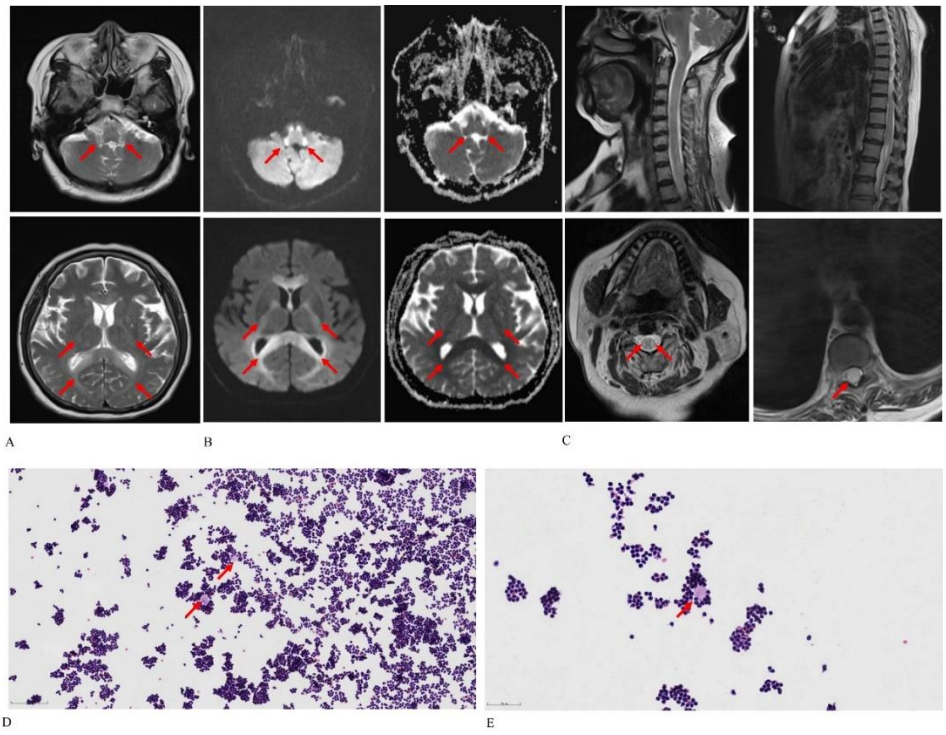
Electrocardiogram monitoring showed the following values for the vital signs: Body temperature, 37.6℃; heart rate, 73 beats/minute; respiratory rate, 22 breaths/minute; and blood pressure, 140/69 mmHg. Neurological examination revealed motor weakness in both legs (grade 0/grade 0) and reduced acupuncture pain below the T8 dermatome. Patient was completely conscious and Glasgow Coma Scale (GCS) score was E4, V5, M6.

Toxicity screening showed sparse chlorfenapyr and emamectin benzoate; screening for cholinesterase inhibitors, illicit drugs and benzodiazepines yielded negative results. Previous computed tomography of the chest and abdomen proceeded in our emergency room revealed no obvious abnormalities. Laboratory tests indicated an extremely elevated creatine kinase level of 2406 IU/L (normal, 40-200 IU/L) and slight liver dysfunction, with an aspartate aminotransferase level of 85 IU/L (normal, 13-35 IU/L) and alanine transaminase level of 47 IU/L (normal, 7-40 IU/L). Routine blood tests revealed a white blood cell count of 9.93*10^9/L (normal, 3.5-9.5*10^9/L) and a Neutrophils Percentage (NEU%) of 82.7% (normal, 40%-75%). The procalcitonin level was mildly abnormal at 0.081 ng/mL (normal, 0-0.046 ng/mL).

It performed Magnetic Resonance Imaging (MRI) of the patient's brain and spine with a 3.0T unit (MAGNETOM Skyra; Siemens Healthcare GmbH, Erlangen, Germany). The brain MRI revealed diffuse and bilaterally symmetrical leukoencephalopathy in the dentate nucleus of the cerebellum, ventral medulla, bilateral inferior cerebellar

peduncles, pons, midbrain, bilateral cerebral peduncles, bilateral corticospinal tracts, corpus callosum and bilateral parieto-occipital white matter (Figure 1). T2-Weighted Imaging (T2WI) revealed lesions with an increased signal intensity (Figure 1A). Diffusion-weighted imaging and an apparent diffusion coefficient map revealed cytotoxic edema and reduced Brownian movement (Figure 1B). The entire spinal cord presented with turgid and hyperintense lesions on T2WI, especially in the cervical spinal cord and conus medullaris (Figure 1C). A lumbar puncture was completed in the emergency room; the patient's cerebrospinal fluid pressure was 240 mm H_2O and the cerebrospinal fluid was a yellowish, cloudy liquid with visible flocculent material. The total cell count in the cerebrospinal fluid was 6000*10^6/L, with a white blood cell count of 5200*10^6/L and NEU% of 94%. The data collected for the cerebrospinal fluid were as follows: Chloride, 114 mmol/L (normal, 120 mmol/L -132 mmol/L); glucose, 2.37 mmol/L (normal, 2.5 mmol/L-4.5 mmol/L); lactate, 7.7 mmol/L (normal, 0.6 mmol/L-2.2 mmol/L); and protein, 1.57 g/L (normal, 0.15 g/L-0.45 g/L). Next-generation sequencing of the cerebrospinal fluid showed no pathogens. Autoimmune encephalitis-related antibodies, demyelinating disease-related antibodies, paraneoplastic nerve syndrome antibodies, cerebrospinal fluid oligoclonal bands and serum oligoclonal bands were absent. A cytological smear of the cerebrospinal fluid revealed an interesting phenomenon of some lymphocytes surrounding the protein-like material and collecting in a wreath-like pattern (Figures 1D and 1E).

Figure 1. Chlorfenapyr and emamectin benzoate-induced leukoencephalomyelopathy in a 65-year-old female patient. **Note:** (A) Axial T2-weighted images showing diffuse and bilaterally symmetrical leukoencephalopathy in the dentate nucleus of the cerebellum, ventral medulla, bilateral inferior cerebellar peduncles, pons, midbrain, bilateral cerebral peduncles, bilateral corticospinal tracts, corpus callosum and bilateral parieto-occipital white matter; (B) Cytotoxic edema and reduced Brownian movement are observed on axial diffusion-weighted imaging and an apparent diffusion coefficient map; (C) Sagittal T2-weighted images of the spine show swelling and hyperintensity of the entire spinal cord, especially in the cervical spinal cord and conus medullaris. (D and E) A cytological smear of the cerebrospinal fluid (optical microscope: Hematoxylin-eosin stained, 100 × D, 200 × E) showing lymphocytes surrounding the protein-like material and collecting in a wreath-like pattern, as marked by the red arrow.



Based on these imaging and laboratory findings, we suspected toxic leukoencephalomyelopathy. The patient's condition deteriorated on day 2 and 16 hours after admission, hyperthermia occurred with the body temperature rising to 39°C-40°C without the administration of antipyretic medication proving effective. The Glasgow Coma Scale (GCS) score was determined as E3, V3, M5, leading to progressive onset of impaired consciousness being recorded. Tachycardia (heart rate, 110 beats/minute) and tachypnea (respiratory rate, 30 breaths/minute) with shallow breathing occurred 18 hours after admission and we initiated steroid pulse therapy. The percutaneous oxygen saturation fluctuated between 80% and 90%. A venturi mask (10 L/minute) was used to improve oxygenation. Nineteen hours after admission, hypoxemia was detected by arterial blood gas examination (pH, 7.31; partial pressure of CO_2, 50 mmHg; partial pressure of O_2, 44 mmHg; HCO_3, 26.5 mmol/L). The patient appeared to be in a deep coma, with a GCS score of E1, V1, M1. She was immediately transferred to the intensive care unit, where tracheal intubation was performed. The patient died 19.5 hours after admission as a result of cardiopulmonary arrest. Her family members issued do-not-resuscitate instructions.

RESULTS AND DISCUSSION

Reports concerning the full spectrum of manifestations of emamectin-chlorfenapyr poisoning in humans is scarce. The literature was reviewed to identify the features of such poisoning, yielding a total of 19 reported cases of emamectin-chlorfenapyr poisoning. The details are shown in Table 1. Among these cases, the age of patients was 46.11 ± 15.82 years (mean ± standard deviation) and the hyperthermal temperature was 40.08 ± 1.46°C. Only three cases in which the patient survived have been reported, with the mortality rate thus being 84.21%. More than half of the patients died in hospital within 1 day of admission.

Table 1. List of reports documenting toxicity due to emamectin-chlorfenapyr.

Reference	Country	Age (years)	Sex	Route	Amount of poisoning	Highest BT (°C)	AMS	Elevated CK (IU/L)	AKI	Management	LOS (days)	Outcome
Han et al. [9]	Korea	49	Male	Dermal	Unknown	41.5	Yes	Yes (4484)	Unknown	Intubation, sedation and analgesia, intravenous administration of paracetamol and tepid sponging	0.46	Mortality
Kang et al. [10]	Korea	41	Female	Oral	20 mL	40.7	Yes	Yes (3081)	No	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	0.83	Mortaliy
Kwon et al. [11]	Korea	49	Male	Oral	200 mL	40	Yes	Yes (14336)	Unknown	Intubation and mechanical ventilation	7	Mortality
Tharaknath et al. [12]	India	28	Female	Oral	Unknown	Unknown	Yes	Unknown	Unknown	Gastric lavage and supportive treatment, intubation	1	Mortality
Ku et al. [13]	Korea	61	Female	Oral	10 mL	38.3	Unknown	Yes (859)	Unknown	Gastric lavage and activated charcoal	19	Survival
Chomin et al. [7]	Korea	44	Female	Oral	Unknown	Unknown	Unknown	Unknown	Unknown	Steroid pulse therapy	Unknown	Survival
Choi et al. [4]	Korea	55	Male	Oral	250 mL of 10% chlorfenapyr	40.9	Yes	Yes (10507)	Yes	Gastric lavage and activated charcoal and intubation	5	Mortality
Lee et al. [14]	Korea	74	Male	Intra-abdominal injection	20 mL	Unknown	Unknown	Unknown	Unknown	Emergency surgery and fluid drainage	Unknown	Mortality
Baek et al. [6]	United States of America	42	Male	Oral	Approximately 300 mL of 21% chlorfenapyr and 500 mL vodka	Unknown	Yes	Unknown	Unknown	Gastric lavage and activated charcoal	Unknown	Mortality
Park et al. [15]	Korea	44	Female	Oral	10 mL-20 mL	Unknown	Unknown	Unknown	Unknown	Gastric lavage and high-dose intravenous corticosteroid pulse therapy	Unknown	Survival

Jingfang et al. [16]	China	11	Male	Oral	Unknown	Unknown	Yes	Yes	No	Gastric lavage and high-dose intravenous corticosteroid pulse therapy	4	Mortality
Liao et al. [8]	China	21	Male	Oral	Unknown	39	Yes	Yes (933.74)	No	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	1	Mortality
Liao et al.[8]	China	55	Male	Oral	60 mL	37.3	Yes	Yes (820.48)	No	Emergency surgery and fluid drainage, intubation	<1	Mortality
Zhaohuan et al. [17]	China	66	Male	Oral	20 mL	38.5	Yes	Yes (8174)	Yes	Gastric lavage and supportive treatment, intubation	5	Mortality
Xianghu et al. [18]	China	66	Male	Oral	30 mL-50 mL	42.1	Yes	Yes (4271)	Unknown	Gastric lavage and high-dose intravenous corticosteroid pulse therapy, intubation	<1	Mortality
Gong et al. [19]	China	50	Female	Oral	60 mL	40	Yes	Yes (1960)	Unknown	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	<1	Mortality
Gong et al. [19]	China	50	Male	Transnasal	Unknown	41	Yes	Yes (1590)	Unknown	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	<1	Mortality
Gong et al. [19]	China	38	Male	Transnasal	Unknown	40	Yes	Yes (5945)	Unknown	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	<1	Mortality
Gong et al. [19]	China	32	Female	Oral	5 mL	41.8	Yes	Yes (3762)	Unknown	Intravenous fluid hydration and urine alkalinisation, intubation and mechanical ventilation	1	Mortality

Mammalian species have a low sensitivity to Electricity Board (EB) because of the chemical's low affinity for gamma-aminobutyric acid and the blood-brain barrier's relative impermeability to it [5]. Chlorfenapyr, known to be moderately hazardous, inhibits the transformation of adenosine diphosphate to ATP by acting on the mitochondria, interrupting the production of ATP and causing energy retardation; these activities lead to cell dysfunction and death [6]. Emamectin-chlorfenapyr is a type of pesticide that is mixed to delay the development of resistance among insect pests and increase the synergism. EB plays a synergistic role in the death process of oxidative phosphorylation decoupling caused by chlorfenapyr [9]. This mechanism may account for the primary characteristics of emamectin-chlorfenapyr poisoning, including a decreased level of consciousness, respiratory failure, rhabdomyolysis and demyelination of the brain and spinal cord, as well as its apparent targeting of organs with high energy requirements. In previous reports on chlorfenapyr poisoning, the clinical course included a latent period of up to 14 days, followed by a rapid progressive period before death [10-12]. Kang et al., surmised that the incubation period for chlorfenapyr poisoning is related to the time required for the pro-insecticide to be metabolized to the active toxicant [10]. Our patient also had a latent period, of approximately 9 days, with no obvious symptoms until patient experienced paraplegia. Moreover, the precise lethal dosage of chlorfenapyr or emamectin-chlorfenapyr is still unknown because of the different medical environments and individual biochemical features. In a case of survival after chlorfenapyr intoxication, a dose of approximately 10 mL was consumed; the patient had no hyperintensity in the central nervous system and was immediately rescued using early gastrointestinal decontamination with gastric lavage and whole-bowel irrigation [20]. Our patient had an occult course and her brain and spinal cord were severely damaged by the

time she arrived at the hospital; she had missed the optimal opportunity for treatment. EB may also play a synergistic role in this lethal process.

Other typical clinical features of chlorfenapyr poisoning are rhabdomyolysis and hyperthermia, which we observed in our patient. Delayed hyperthermia is commonly observed in chlorfenapyr intoxication cases and in a case report from China, as in our case, tracheal intubation seemed to accelerate deterioration [21]. The precise mechanisms remain unclear. Rhabdomyolysis and hyperthermia are symptoms of malignant hyperthermia, a rare syndrome that occurs when certain anesthetics are injected. In this patient, we did not administer any anesthetic or medication that could cause malignant hyperthermia. We believe that lipophilic chlorfenapyr accumulates in striated muscle and uncouples oxidative phosphorylation in the mitochondria, disrupts ATP production, causes cellular death and raises creatine kinase levels. This results in non-shivering thermogenesis in brown adipose tissue, which leads to hyperthermia [11]. Few cases of chlorfenapyr intoxication in humans that include integrated radiological data have been reported. Tharaknath et al., reported a case of chlorfenapyr poisoning with diffuse and bilateral hyperintensity in the white matter of the brain and spinal cord on T2WI MRI; their case was very similar to ours [12]. Baek et al., reported a case of survival after chlorfenapyr intoxication and found reversible signal changes in the white matter tracts throughout the brain, brainstem and spinal cord after 75 days of follow-up visits [6]. Other similar radiological features reported by Kang et al., also indicated a low white matter density in the whole brain tissue on computed tomography scans [10]. In a previous animal experiment involving rats with chlorfenapyr poisoning, vacuolar myelopathy and mild myelin sheath swelling were found in a variety of structures ranging from the subcortical areas to the brainstem and spinal cord in neurohistopathological examinations; this is consistent with MRI findings in clinical case reports [22]. However, the pathophysiology of the susceptibility of the white matter tracts alone is unknown. We presume that chlorfenapyr tends to invade and accumulate in the myelin sheath owing to its weak lipophilic acid features and causes myelin disintegration, the presence of which is shown on MRI. In addition, heat-regulating centers in the hypothalamus are believed to be involved in chlorfenapyr cases, causing hyperthermia [16-18].

Clearly few case reports that present cerebrospinal fluid consequences have been published. Baek et al., reported that the cerebrospinal fluid test results of a patient with diffuse abnormal signals in the brain and spinal cord were normal [6]. However, using next-generation sequencing and cytometric bead array, it confirmed that the cerebrospinal fluid of our patient showed a secondary inflammatory process with no pathogenic microorganisms or related antibodies [16,19]. In the cytological smear of the cerebrospinal fluid, we observed that some lymphocytes surrounded the protein-like material and lined up in a wreath-like pattern. We speculated that the protein-like material may be a type of myelin tissue that has been shed and that contains abundant chlorfenapyr. In addition, chlorfenapyr could activate some lymphocyte subsets, which, in turn, could gather around the exogenous substance. Only one case report of methadone intoxication may provide some evidential support of our speculations. Repple et al., performed flow cytometry on the cerebrospinal fluid of methadone-intoxicated patients and found cell composition alterations that were characterized by the transformation of monocytes from the classical ($CD14^{+}CD16^{-}$) to the non-classical ($CD14^{+}CD16^{+}$) and a switch from $CD56^{bright}$ non-killing cells to $CD56^{dim}$ non-killing cells [21]. Notably, $CD14^{+}CD16^{+}$ monocytes and $CD56^{dim}$ non-killing cells are pro-inflammatory cells that may be involved in delayed encephalopathy. These findings from Repple et al., may explain the lymphocyte aggregation observed in the current case, which provides the first reported cerebrospinal fluid findings of chlorfenapyr intoxication [21,22].

CONCLUSION

We present a fatal case of leukoencephalomyelopathy induced by emamectin-chlorfenapyr with delayed hyperthermia and rapid deterioration. The latent period from emamectin-chlorfenapyr exposure to paraplegia onset was less than 9 days and MRI revealed bilateral, symmetric and diffuse T2 hyperintensity of the entire white matter tract in the brain and spinal cord. In the cytological smear of the cerebrospinal fluid, we observed that some of the lymphocytes gathered in a wreath-like pattern surrounding a protein-like material; this is the first report of cerebrospinal fluid microscopic characteristics in emamectin-chlorfenapyr intoxication. Further research is needed to clarify how to perform flow cytometry on patients with emamectin-chlorfenapyr intoxication, to elucidate the immunological mechanism underlying the inflammatory process caused by emamectin-chlorfenapyr and to provide new insights into antidote development.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The patient's legal guardian approved the publication of identifying information and images in an online open-access publication and signed an informed consent form.

AUTHOR CONTRIBUTION STATEMENT

Xun Li and Yun Yang wrote the manuscript. Yajing Zhang, Xuebin Zhang and Na Zhao prepared Figure and Table. All authors reviewed the manuscript and Wei Yue revised the manuscript.

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DATA AVAILABILITY STATEMENT

No data was used for the research described in the article.

CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors declare no conflict of interest.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from the patient's next of kin.

ADDITIONAL INFORMATION

No additional information is available for this paper.

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