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A clinical warning in the treatment of chlorfenapyr poisoning

Yuelei Cheng [a,1], Yunlai Zhao [a,2], Hao Li [b,3], Minmin Duan [a,4], Lianxiang Li [a,5], Song Zhou [a,6], Qingbin Tang [a,7], Wei Xie [a,*,8], Jixue Shi [b,9]

[a] Department of Emergency, Central Hospital Affiliated to Shandong First Medical University, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China
[b] Department of Emergency, The Second Affiliated Hospital of Shandong First Medical University, Tai'an, China

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ABSTRACT

Chlorfenapyr, an arylpyrrole-based insecticide, disrupts mitochondrial oxidative phosphorylation to deprive the target organism of energy. Chlorfenapyr poisoning in humans causes distinct clinical signs such as hyperhidrosis, malignant hyperthermia, rhabdomyolysis, and delayed neurological symptoms that worsen over time and can be fatal. When treating acute chlorfenapyr poisoning, physicians must consider the latent period and not assume that a patient is safe after an initial response to treatment. It is important to take measures before sudden, fatal symptoms appear. This paper presents three cases of chlorfenapyr poisoning as a warning for physicians to understand its clinical course and treatment.

1. Introduction

Chlorfenapyr is a broad-spectrum insecticide for which no specific antidote or antagonist currently exists. The World Health Organization (WHO) has classified chlorfenapyr as a moderately hazardous (i.e., Class II) insecticide [1]. Chlorfenapyr (with trade names including Chujin, Pirate, Stalker, Alert, and Kotetsu) is an arylpyrrole-based pro-insecticide that can interfere with the oxidative phosphorylation of the mitochondria [2,3]. This interference leads to energy deprivation of the target organism and ultimately to its mortality [4,5]. Chlorfenapyr is used to control various insects and mites on cotton, ornamental plants, and various vegetable crops [2,6,7]. It is accepted for routine application to crops/plants according to federal regulations in a number of countries, including Brazil, Australia, Mexico, the United States, Japan, and South Korea [8]. Reports of chlorfenapyr poisoning are relatively rare both in China and internationally. Acute toxicity after ingestion of technical-grade chlorfenapyr is categorized as category I toxicity in mice and as category II toxicity in rats [9]. In humans, chlorfenapyr poisoning produces distinctive clinical symptoms, chiefly presenting as hyperhidrosis, malignant hyperthermia, rhabdomyolysis, and severe delayed neurological impairments, which worsen progressively until death [4,10–15]. Herein, we have profiled three cases of chlorfenapyr poisoning and provided a brief narrative literature review on chlorfenapyr poisoning in the discussion.

2. Case reports

We present three cases of chlorfenapyr poisoning (Cases 1, 2, and 3; see Table 1 for the results of comprehensive clinical evaluations) wherein the patients received active gastrointestinal decontamination,

* Corresponding author.
E-mail addresses: xpestx@126.com (Y. Cheng), yunlaizhao@126.com (Y. Zhao), lihaonan2564335@163.com (H. Li), duanminmin@126.com (M. Duan), lilianxiang688@163.com (L. Li), woshizhousong@126.com (S. Zhou), tyfytqb@163.com (Q. Tang), wxie@sdfmu.edu.cn (W. Xie), shijie3@163.net (J. Shi).
[1] http://orcid.org/0000-0001-9518-5156
[2] http://orcid.org/0000-0002-7196-9551
[3] http://orcid.org/0000-0002-4469-8338
[4] http://orcid.org/0000-0002-4772-3375
[5] http://orcid.org/0000-0003-2049-4215
[6] http://orcid.org/0000-0001-8362-932X
[7] http://orcid.org/0000-0002-4932-2372
[8] http://orcid.org/0000-0002-1887-1897
[9] http://orcid.org/0000-0002-8742-4230

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Table 1
Results of comprehensive clinical evaluation.

Indicator	Case 1	Case 2	Case 3
Arterial blood gas analysis			
pH	7.32	7.31	7.40
Partial pressure of oxygen (mmHg)	91	88	98
Partial pressure of carbon dioxide (mmHg)	32	31	40
Lactic acid (mmol/L)	2.2	2.5	1.0
Bicarbonate (mmol/L)	18.3	18.7	25
Base excess (mmol/L)	−7	−7	1
Blood biochemistry			
Urea nitrogen (mmol/L)	12.24	6.36	5.12
Creatinine (μmol/L)	87.6	58.7	66.9
Creatine kinase (U/L)	9754	10207	89
Creatine kinase isoenzymes (U/L)	176	189	3
Aspartate aminotransferase (U/L)	121	288	31
Alanine aminotransferase (U/L)	54	103	63
Albumin (g/L)	36.1	44.3	32.1
Total bilirubin (μmol/L)	11.7	14.1	6.8
Serum amylase (U/L)	99	111	46
K+ (mmol/L)	3.81	3.82	3.50
Na+ (mmol/L)	140	138	134
Cl- (mmol/L)	106	106	101
Mg2+ (mmol/L)	0.94	0.92	0.93
Ca2+ (mmol/L)	2.14	2.23	2.06
C-reactive protein (g/L)	26.60	5.00	39.06
Glucose (mmol/L)	7.9	10.3	6.9
Cholinesterase (U/L)	4891	7781	8843
Troponin (ng/mL)	0.072	0.025	0.045
Procalcitonin (ng/mL)	0.066	0.040	0.053
Routine blood tests			
White blood cells (×109/L)	10.05	7.29	9.33
Neutrophil percentage (%)	88.6	73.0	70.7
Hemoglobin (g/L)	116	130	83
Platelets (×109/L)	151	267	269
Cerebrospinal fluid	Elevated cell count	-	-
Anti-acetylcholine receptor antibodies	Negative	-	-
Electrocardiogram	No abnormalities	No abnormalities	No abnormalities

Note: 1 mmHg = 0.133 kPa.

blood purification, and symptomatic and supportive care at their local hospitals in the early stages of chlorfenapyr poisoning. None of the three patients were tested for poison after early poisoning.

2.1. Case 1

A 51-year-old woman ingested approximately 40 g of chlorfenapyr and was initially discharged after five days of treatment. On day 11, she was admitted to our hospital after developing bilateral lower extremity paralysis and weakness, loss of sensation, hyperhidrosis, and bowel and bladder incontinence. After admission, her neurological symptoms progressively worsened, and she exhibited persistent hyperthermia (maximum temperature: 41 °C) that responded poorly to conventional antipyretics. Contrast-enhanced magnetic resonance imaging (MRI) of the spinal cord (Fig. 1) revealed spinal cord lesions. On day four after admission, the patient experienced cardiac arrest and died after failed resuscitation. The patient's total disease duration was 14 days.

2.2. Case 2

A 50-year-old woman ingested approximately 5 g of chlorfenapyr and was discharged from her local hospital after three days of treatment. On day 10, she developed drowsiness, bilateral lower limb weakness, sweating, and chest tightness. On day 13, the patient was admitted to our hospital with bilateral lower limb paralysis, loss of sensation, and hyperhidrosis. Brain and chest computed tomography did not reveal meaningful abnormalities. After admission to our hospital, the patient received intravenous administration of human immunoglobulin (20 g once a day.), adenosine triphosphate (ATP) disodium (20 mg once a day), and methylprednisolone (480 mg once a day), as well as other symptomatic and supportive care. Her neurological symptoms progressively worsened, and she exhibited hyperthermia (maximum temperature: 40 °C). On day three, after admission, the patient experienced cardiac arrest and died after unsuccessful resuscitation. The patient's total disease duration was 15 days.

2.3. Case 3

A 56-year-old man ingested approximately 5 g of chlorfenapyr, which was followed by amnesia on day two and bilateral lower limb weakness on day nine. He was then transferred to our hospital. A brain MRI revealed ischemic foci in the bilateral frontal lobe, but no meaningful abnormalities were evident in the other brain regions. After admission, the patient was administered ATP disodium (40 mg once a day), vitamin C (10 g/day) via a microinfusion pump, vitamin B6 (3 g/day) via a microinfusion pump, and other symptomatic and supportive care. Muscle weakness did not show marked progression and gradually improved on day five after admission. The patient was discharged on day 12 without hyperthermia, sweating, or neurological symptoms. The patient's total disease duration was 21 days. He was followed up two months after discharge, where he showed normal function with no discomfort. Vitamin B and vitamin C, as indispensable substances in the human body, play a vital role in life activities and can play a role in antioxidation and enzymatic reactions. Under the premise of fully obtaining the informed consent of patients, a large dose of treatment is given to try to enhance the effects mentioned above. This treatment is an example, and there are no other cases reported at present; thus, it is impossible to accurately evaluate whether it plays a role in improving patients. The factors influencing the survival of Case 3 are uncertain. During the drug treatment, the patient refused to carry out relevant further examination for better evaluation, and only the clinical manifestation was taken as the sole criterion.

3. Discussion

Chlorfenapyr can trigger multiple mechanisms of toxicity, including dose-dependent cell membrane damage, oxidative phosphorylation uncoupling, and disruption of acetyl coenzyme A (CoA) metabolism. Thus, chlorfenapyr can inhibit the conversion of adenosine diphosphate to ATP at the mitochondrial level, thereby terminating the life functions of cell synthesis due to lack of energy [5,14,16,17]. This energy deprivation can severely damage energy-intensive vital organs (e.g., muscles and kidneys as well as the brain and the heart) [11,16–19]. It has been mentioned in some literature that bromopyrrolonitrile is the only metabolite with toxicological significance after toxicological evaluation, and its toxicity is 10 times that of chlorfenapyr [20,21]. However, almost all the literature retrieved so far is related to agriculture, mainly focusing on the study of crop residues and dietary intake risks, which has little clinical significance, and no relevant reports on bromopyrrolonitrile poisoning have been retrieved. The clinical course of patients with chlorfenapyr poisoning can be divided into acute toxicity symptoms such as nausea, vomiting, metabolic acidosis, rhabdomyolysis, and renal failure, and delayed toxicity symptoms such as hyperthermia and the gradual worsening of neurological symptoms (e.g., hyperreflexia, ataxia, nystagmus, miosis, hallucinations, convulsions, and paralysis) [14,17,22–26]. Reports from countries outside of China have indicated that chlorfenapyr poisoning in humans is generally fatal and that a small dose of commercial chlorfenapyr can lead to death; most patients die after a latent period of 7–20 days [14,22–24,27]. The specific mechanisms underlying the delayed toxicity of chlorfenapyr poisoning remain

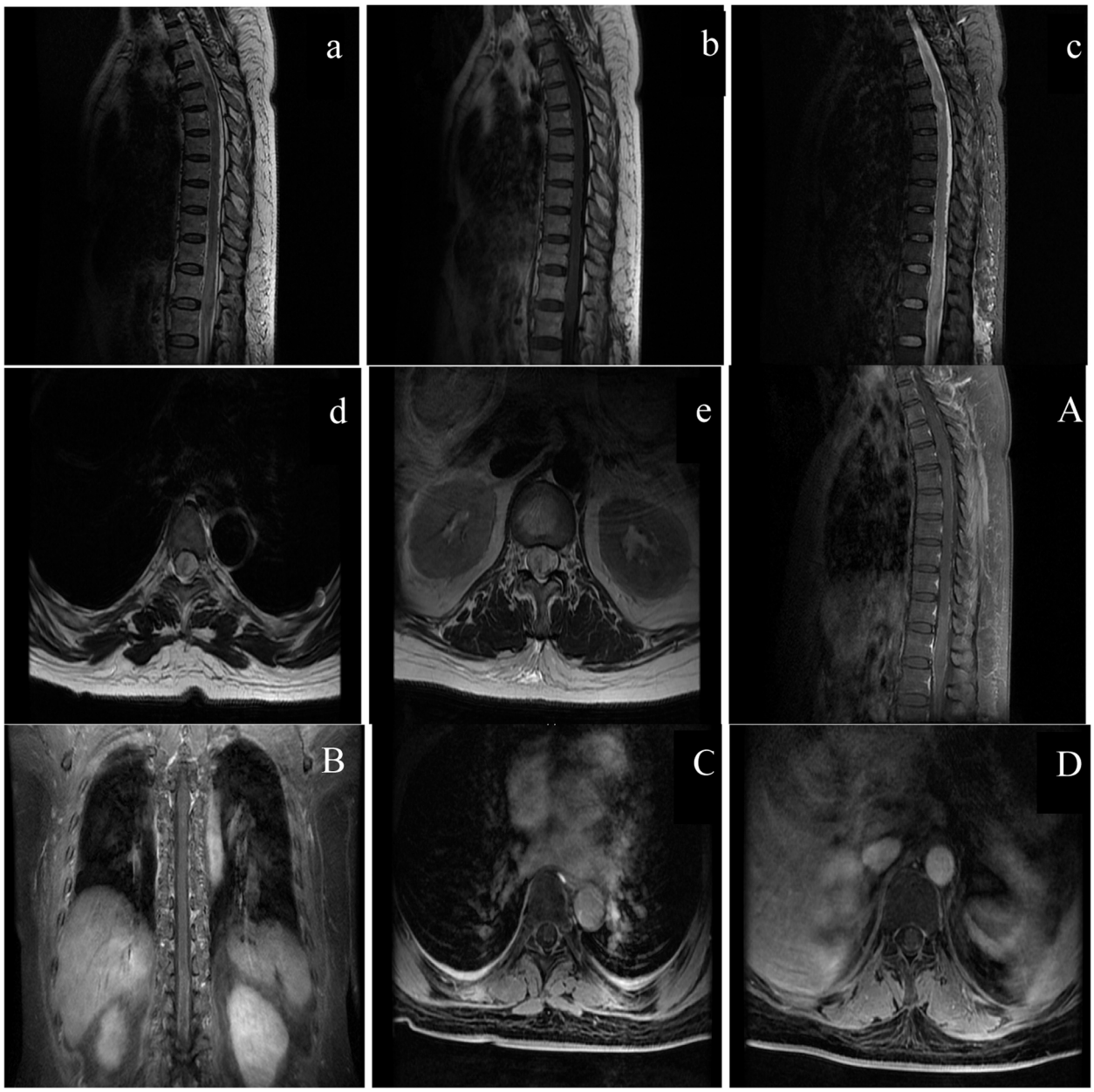

Fig. 1. Magnetic resonance imaging (MRI) findings. Sagittal T2-weighted (WI) image (a), sagittal T1WI image (b), sagittal fat-suppressed image T2WI image (c), and axial T2WI images (d, e). The spinal cord showed irregular thickening, heterogeneous signals, multiple patchy long T1 and T2 signal intensities, and hyperintensities on fat-suppressed imaging. Contrast-enhanced MRI findings in the sagittal (A), coronal (B), and axial (C, D) planes. The spinal cord showed multiple patchy enhancements, particularly in the lower half.

unclear. They may be related to the lipid solubility of chlorfenapyr, which can facilitate its widespread absorption and distribution in the body. Thus, after the initial removal of toxins from the blood, the toxins absorbed by various organs are slowly released into the blood, thereby causing recirculating rebound toxicity [16]. A previous study [24] demonstrated that chlorfenapyr needs time to be converted into its active form via the oxidative removal of its *N*-ethoxymethyl group through mixed-function oxidases, thereby resulting in the formation of a toxic metabolite (CL303268) that leads to delayed toxicity symptoms. This finding suggests that chlorfenapyr metabolites may exhibit delayed adverse effects on energy-intensive vital organs [28]. Additionally, hyperthermia may result from increased glucose consumption and elevated cellular metabolism as a compensatory response to ATP consumption [5]. Moreover, uncontrolled hyperthermia may be a cause of death due to chlorfenapyr poisoning. Moreover, studies have demonstrated that chlorfenapyr ingestion by rats results in brain neurotoxicity after 18 days [29] and that chlorfenapyr poisoning leads to neurological damage in dogs [30]. Other studies [11,17,22,24,31] have indicated that chlorfenapyr poisoning can induce neurological lesions, which are mainly limited to the white matter of the central nervous system (CNS). Several cases of chlorfenapyr-induced leukoencephalopathy have been reported in the literature to date [11, 14,18,23,24]. In these patients, brain MRI revealed bilateral symmetrical lesions in the white matter, hyperintensities on fluid-attenuated inversion recovery (FLAIR) imaging, restricted diffusion on diffusion-weighted imaging, and apparent diffusion coefficient maps. Tharaknath et al. [24] reported on one patient with chlorfenapyr poisoning in whom MRI revealed changes in the white matter in the cerebrum and brainstem, whereas T2WI MRI revealed diffuse edema and hyperintensities in the spinal cord; this was similar to the findings

reported for Case 1 in the present paper. Kramer et al. [32] also obtained similar imaging findings in a one-year chlorfenapyr dietary neurotoxicity study in rats. In another case of chlorfenapyr poisoning documented in Japan [5], the patient presented with delayed impairment of consciousness, hyperhidrosis, and hyperthermia and eventually died due to chlorfenapyr poisoning. Postmortem examination revealed liquefaction necrosis of the cervical and thoracic spinal cord, as well as hyperemia and hemorrhage, which are lipophilic poisons [10]. Given that the white matter consists of nerve fibers running along lipid-rich myelin sheaths, chlorfenapyr can be easily distributed across lipid-rich white matter and can cause organic damage to nerve fibers, thereby causing CNS damage [5]. Chlorfenapyr poisoning can cause delayed leukoencephalopathy and lead to severe neurological symptoms. However, Baek et al. [13] previously reported a case of radiologic reversibility that was verified through a follow-up MRI conducted after 71 days. Moreover, Sivasubramanian et al. [33] demonstrated that abnormal imaging findings in drug-induced toxic leukoencephalopathies can be reversed after discontinuation of the offending agent; these researchers referred to this disease as "acute reversible toxic leukoencephalopathy." In addition, an increasing number of studies on leukoencephalopathies have reported the increased use of chemotherapeutic agents [33]. The causes of restricted diffusion in toxic leukoencephalopathy are known; however, we note that this condition may also be caused by the putative mechanisms of intramyelin edema (i.e., myelin vacuolation) and cytotoxicity occurring due to endothelial injury or direct toxic demyelination [13,31]. In view of the factors mentioned above, autonomic neuropathy resulting from injury to the brainstem and cervicothoracic spinal cord may be one cause of cardiac arrest in chlorfenapyr poisoning [5,14].With regard to the lethality of chlorfenapyr, specific individualized treatment plans for individuals exposed to this substance are lacking (apart from routine interventions for poisoning). Animal experiments in rats have demonstrated that ingested chlorfenapyr is absorbed via the digestive tract and excreted into bile for enterohepatic circulation [34]. This finding suggests that the repeated administration of active charcoal is an effective treatment for chlorfenapyr poisoning. Moreover, given the lipophilicity of chlorfenapyr, the administration of hemoperfusion in the early stages of poisoning should theoretically ensure its rapid and effective removal [35]. However, in Cases 1 and 2, the patient's conditions showed an initial remission after treatment, followed by rapid deterioration that involved persistent hyperthermia, progressive worsening of neurological symptoms, and eventually death. Respiratory, urinary, and neurological infections, as well as cerebrovascular accidents, were excluded from the differential diagnosis during this period. Thus, these clinical presentations were considered to have resulted from delayed toxicity due to chlorfenapyr poisoning. Based on the properties, distribution, and metabolic characteristics of chlorfenapyr, the appropriate administration of slow plasma perfusion after hemoperfusion should facilitate further removal of redistributed toxins with relatively low concentrations. The high lipophilicity of chlorfenapyr suggests that the administration of lipid emulsions may be beneficial [34]. To our knowledge, no current studies support the clear efficacy of ATP in improving body metabolism and participating in the metabolism of fat, protein, sugar, nucleic acids, and nucleotides. Simultaneously, it is the main source of energy in the body. When energy is needed for absorption, secretion, muscle contraction, and biochemical synthesis in the body, adenosine triphosphate is decomposed into adenosine diphosphate and phosphate groups, and energy is released simultaneously. This product can inhibit the slow calcium influx of slow-response fibers and block or delay the forward conduction in the atrioventricular node re-entry pathway. It may also block or delay the forward and reverse conduction of bypass at large doses. In addition, it also has a short-term and strong effect of enhancing the vagus nerve so that it can terminate arrhythmia caused by atrioventricular node re-entry and bypass the re-entry mechanism. Given the toxic effects of chlorfenapyr, this approach can be used as part of symptomatic treatment. However, caution should be exercised to prevent adverse effects caused by excessive and rapid supplementation. Cases involving the administration of N-acetylcysteine and coenzyme Q10 have also been reported, but the efficacy of these treatments remains inconclusive [36]. Some clinicians have started administering intravenous pulse glucocorticoid therapy as adjuvant therapy for symptom relief. However, neurological symptoms continue to progress despite treatment; hence, the efficacy of this treatment remains questionable [13]. To our knowledge, there are no reports regarding treatment with intrathecal injections of glucocorticoids, and chlorfenapyr-induced hyperthermia responds poorly to drug treatment [14]. Thus, physical cooling with an ice blanket or cold-saline infusion (at 4 °C) can be considered. In addition, patients with chlorfenapyr poisoning often exhibit varying extents of metabolic acidosis, which can be treated with appropriate alkalinization therapy [17,21].Currently, there are no reports on the treatment of chlorfenapyr poisoning with hyperbaric oxygen. Therefore, further investigation on this topic is necessary. Finally, we note that piperonyl butoxide is a synergist for many pesticides, and it exhibits inhibitory effects on cytochrome P450 enzymes in the target organism. Insect studies [37,38] have demonstrated the antagonistic effects of this agent on chlorfenapyr. More specifically, it can interfere with the conversion of chlorfenapyr to toxic metabolites and may, therefore, be a promising candidate as an antidote for chlorfenapyr poisoning. However, additional investigations are necessary to determine its efficacy in humans. [4]. In recent years, cases of chlorfenapyr poisoning have become increasingly common. However, at present, there is no substantial progress in the treatment of chlorfenapyr poisoning, and there is still no targeted poison inspection, auxiliary inspection, or treatment plan. We can only focus on the general treatment principles of poisoning and gradually improve and support treatment according to the changes in the disease during the entire disease process. Although chlorfenapyr is classified as moderately toxic, it is clinically found that chlorfenapyr poisoning is generally fatal, regardless of the exposure route. The exposure dose is one of the factors influencing the prognosis of acute chlorfenapyr poisoning (although the poison was imported but not swallowed, it was still fatal). First-aid measures such as removing contaminated clothes, thoroughly washing contaminated parts, inducing vomiting, gastric lavage, and blood purification, as well as their start-up time, can also affect its prognosis. After an incubation period of 5–7 days, most patients developed sweating, high fever, rhabdomyolysis, and severe neurological symptoms and died of cardiac arrest within 14–21 days. Creatine kinase is an important index for determining prognosis. The earlier the index increases abnormally, the worse the prognosis. In agricultural operations, chlorfenapyr is diluted and used to kill insects. At present, the toxic dose of chlorfenapyr in the human body is still unknown, and there are no reports of poisoning caused by eating contaminated food.

4. Clinical warning

The three cases presented here, together with other relevant reports, indicate that physicians should uniformly have a better understanding of the clinical course of chlorfenapyr poisoning. Physicians must consider the latent period typical of chlorfenapyr poisoning [4,6,14,35] to avoid being lulled into a false sense of security after a patient's initial positive response to treatment. We recommend treating and observing patients with close supervision while simultaneously adopting appropriate measures before the onset of sudden, rapidly progressing, and potentially fatal manifestations. Most cases of chlorfenapyr poisoning involve oral ingestion. Therefore, emphasis should be placed on early and thorough gastrointestinal decontamination. This treatment should be followed by continuous and moderate gastrointestinal decontamination owing to the distribution patterns and metabolic characteristics of chlorfenapyr. Visual impairment due to skin contact with chlorfenapyr [6] and death due to exposure to chlorfenapyr vapor [27] have also been reported. Therefore, after skin contact with chlorfenapyr, removing contaminated clothing and rinsing exposed areas are critical life-saving

measures. Emergency physicians must keep in mind that even in cases of skin contact, all patients with chlorfenapyr poisoning are at risk of irreversible disease progression and death. Reports on chlorfenapyr poisoning in China and abroad did not include MRI scans in the early stages. Neurological symptoms after poisoning are often delayed because of the absence of these symptoms at initial presentation and because of the clear symptom-free interval prior to the onset of the renewed symptomology that occurs in the course of chlorfenapyr poisoning. Therefore, physicians should conduct predictive MRI evaluations of the CNS for early diagnosis of toxic leukoencephalopathy induced by chlorfenapyr poisoning. Similar radiologic findings can also be observed in mitochondrial neurogastrointestinal encephalomyopathy [39], which can be used for differential diagnoses. In clinical practice, patients with unexplained sweating, high fever, rhabdomyolysis, worsening nervous system symptoms, and unexplained white matter lesions should consider chlorfenapyr poisoning. Based on the factors mentioned above, we believe that chlorfenapyr is highly toxic to humans and that its application may need to be subjected to restrictions similar to those enacted for paraquat. Agricultural workers are advised to use this insecticide with caution and should be provided with adequate protective gear when placed in situations where they may be exposed to this insecticide. In addition, to prevent poisoning crimes, vigilance is needed against criminals, who may exploit the delayed neurological damage and lethality of chlorfenapyr.

CRediT authorship contribution statement

Minmin Duan: Investigation. **Lianxiang Li:** Project administration. **Qingbin Tang:** Resources. **Wei Xie:** Validation. **Hao Li:** Data curation. **Yuelei Cheng:** Writing – original draft. **Yunlai Zhao:** Conceptualization. **Song Zhou:** Formal analysis. **Jixue Shi:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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