症例報告

Fatal chlorfenapyr poisoning：A case report

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——Summary——（Jpn J Clin Toxicol 2017；30：379–382）

Context：The mortality rate after chlorfenapyr ingestion is high, and a treatment strategy has not yet been determined. Whether acute blood purification is effective for chlorfenapyr poisoning remains unknown.

Case details：A 74–year–old man who had ingested 100–200 mL of 10% chlorfenapyr in a suicide attempt was treated by gastric lavage by a local physician. He was transferred to our intensive care unit with nausea, diaphoresis, and tachypnea. He was treated with intravenous fluids and activated charcoal. Acute blood purification therapy including online hemodiafiltration, slow plasma exchange, and continuous hemodiafiltration was started. Although the patient did not appear severely affected, his heart rate suddenly decreased and he died on hospital day 5 despite early intensive care.

Discussion：We surmise that acute blood purification therapy was ineffective because of the lipophilic nature of chlorfenapyr and its metabolites. If so, then intravenous lipid emulsion therapy might be more effective as it might prevent the accumulation of lipophilic metabolites in tissues. Basic laboratory and experimental animal studies are required to elucidate the pathophysiology of chlorfenapyr poisoning to establish an appropriate treatment strategy.

Key words：chlorfenapyr poisoning, blood purification therapy, suicide

Introduction

Around 30% of the 800,000 individuals who commit suicide every year do so using pesticides, according to the World Health Organization. Chlorfenapyr belongs to a new class of pyrroles that is widely applied；it is a pro–insecticide activated by the oxidative removal of an N–ethoxymethyl group. The activated form is a lipophilic, weakly acidic pyrrole metabolite that interferes with mitochondrial oxidative phosphorylation, resulting in disrupted ATP production and cellular death. Almost all instances of human intoxication with chlorfenapyr in the literature have resulted in death[1)～6)]. Details of chlorfenapyr toxicity in humans remain scant, and an effective antidote and the value of blood purification after chlorfenapyr poisoning remain unknown. We describe a patient for whom chlorfenapyr ingestion was fatal after blood purification therapy.

Case report

A 74–year–old man with depression attempted to

Table 1 Laboratory data on admission

WBC	7,400/μL	AST	30 IU/L
Hb	14.2 g/dL	ALT	13 IU/L
Ht	41.1%	LD	212 IU/L
Plt	26.9 × 10^4/μL	BUN	11.2 mg/dL
F_IO_2	0.21	Cr	0.79 mg/dL
pH	7.47	CK	370 IU/L
$PaCO_2$	28.3 mmHg	CK-MB	16 IU/L
PaO_2	77.9 mmHg	Na	139 mEq/L
HCO_3^-	20.8 mmol/L	K	4.9 mEq/L
BE	－3.1 mmol/L	Cl	104 mEq/L
Lactate	1.0 mmol/L	BG	150 mg/dL
		CRP	0.12 mg/dL

commit suicide by ingesting 100–200 mL of 10% chlorfenapyr. Four hours later, he felt ill and consulted a local doctor, who treated him with gastric lavage and then transferred him to a nearby hospital. His vital signs were stable, but because his condition was likely to worsen, he was transported to our emergency department nine hours after ingestion. Upon admission, he had nausea, warmness, and diaphoresis. His vital signs and other values were as follows：blood pressure, 137/79 mmHg；pulse, 82 bpm；respiratory rate, 30/min；body temperature, 36.8℃；oxygen saturation（SpO_2）, 100% in room air；Glasgow Coma Scale value, 15. Laboratory findings showed serum creatine kinase（CK）, 370 IU/L；serum CK-MB, 16 IU/L；and blood glucose, 150 mg/dL. Arterial blood gas analysis revealed pH, 7.47；pCO_2, 28.3 mmHg；HCO_3^-, 20.8 mmHg；and lactic acid, 1.0 mmol/L. Other laboratory data were unremarkable. Initial findings comprised slight mitral valve regurgitation with normal wall motion on echocardiography and no abnormalities on electrocardiography and chest radiography. However, abdominal radiography revealed gas in the intestines. **Table 1** shows the laboratory data on admission. He was administered intravenous fluids and activated charcoal in the emergency room, and then transferred to the intensive care unit due to the poor prognosis of chlorfenapyr poisoning. We continued supportive care and started online hemodiafiltration（HDF）during the daytime and slow plasma exchange. The nausea disappeared on the following day, but the sensation of warmness and diaphoresis persisted. Despite continuous HDF, laboratory data on day 3 revealed increases in serum creatinine and serum CK to 1.39 mg/dL and 3,883 IU/L, respectively. Continuous HDF during the nighttime was started. Repeated echocardiography did not show any remarkable changes despite the high serum CK-MB value. He was administered 40 g of activated charcoal every four hours until hospital day 3, when he developed abdominal pain and bloating. We administered cathartic medicines, but had to stop the activated charcoal（total dose, 600 g）administration on hospital day 4 due to bloating. His vital signs remained relatively stable until the evening of hospital day 5, when the patient suddenly became confused and disoriented. About 30 minutes later, his heart rate suddenly decreased and he fell into cardiac arrest. We immediately started advanced cardiac life support, but his extremities rapidly stiffened and he died 50 minutes later.

Discussion

Chlorfenapyr poisoning causes fever, nausea, vomiting, diaphoresis, tachypnea, neurological changes, rhabdomyolysis, and renal failure, being ultimately fatal. Chlorfenapyr poisoning does not seem to cause extreme, obvious effects during the early phase, but symptoms arise and worsen until death occurs between 5 and 30 days after ingestion. The lethal dose

Table 2 Published case reports of chlorfenapyr poisoning

Author	Age/Sex	Chlorfenapyr dose	Elapsed time until death
Endo, et al[1]	45	80 mL	54 hr
	63	≤ 100 mL	77 hr
	84	≥ 250 mL	36.5 hr
	25	100 mL (dilute solution)	20–44 hr
	49	100 mL	46 hr
	52	375 mL	87.5 hr
	30	250 mL	96–120 hr
	71	80–125 mL	10 hr
Choi, et al[2]	55/M	250 mL, oral	5 day
Kwon, et al[3]	49/M	200 mL	16 day
Lee, et al[4]	74/M	20 mL, intra-abdominal injection	12 day
Kang, et al[5]	41/F	20 mL, oral	14 day
Ku, et al[6]	61/F	10 mL, oral	Alive

of chlorfenapyr for humans has not yet been defined, but published case reports indicate that 20–250 mL could be lethal, whereas 10 mL is not (**Table 2**)[1)~6)]. Our patient ingested 100–200 mL of 10% chlorfenapyr. We understood before this patient arrived at our hospital that this dose could be fatal, that there is no antidote, and that the effects of blood purification are unknown. We therefore believed that an aggressive approach was necessary. Animal studies have shown that chlorfenapyr has the feature of enterohepatic circulation, and thus we treated him with repeated activated charcoal administration. We also treated him with online HDF because the molecular weight of chlorfenapyr is 407.6 g/mol. However, the rate of chlorfenapyr binding to protein is unknown, and if it was high, it would not have been removed. Therefore, simultaneous slow plasma exchange was started. However, the patient died despite these aggressive approaches. The fact that therapy was started about 12 hours after chlorfenapyr ingestion might have been related to the poor outcome in this patient. Experimental animal studies have shown that the chlorfenapyr concentration reaches a maximum in most tissues due to its lipophilic nature between one and eight hours after ingestion and that it is higher in tissues than in plasma[7)]. One study has suggested that intravenous lipid emulsion (ILE) therapy is effective against poisoning with highly lipid-soluble drugs, when indicated by a log P (octanol：water partition coefficient) > 2[8)]. Since the log P of chlorfenapyr is 5.28 (20℃), ILE therapy might be effective for treating chlorfenapyr poisoning[7)8)]. This type of therapy is emerging as a potential antidote to the toxic effects of other lipophilic drugs such as local anesthetics, beta-blockers, calcium-channel blockers, and tricyclic antidepressants[9)10)]. Cave et al. argued that ILE therapy could be considered in the event of extreme cardiovascular instability resulting from lipophilic toxin poisoning, particularly in the absence of a response to conventional measures[9)]. To apply ILE therapy against chlorfenapyr poisoning seems logical as a last resort, because the mortality rate associated with conventional treatments is very high. Nevertheless, basic laboratory and experimental animal studies are required to define the effectiveness of ILE therapy.

Conclusions

We described a patient with chlorfenapyr poisoning who suddenly fell into cardiac arrest and died on day 5 of hospital admission. Acute blood purification at this point in the development of chlorfenapyr toxicity might be ineffective. Therefore, further effort is required to establish novel treatment modalities for chlorfenapyr poisoning including ILE therapy.

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None.

Declaration of interests

The authors have no interests to declare.

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要 旨

クロルフェナピル中毒は予後不良で，治療方法は確立されていない。急性血液浄化療法の有効性も不明である。症例は74歳，男性。自殺目的にクロルフェナピルを推定100～200 mL服用し，近医で胃洗浄を受け，当院に紹介入院した。入院時，悪心，発汗，多呼吸を認めた。補液を行い，活性炭を投与し，急性血液浄化療法（on line HDF，緩徐血漿交換）を開始した。入院中，全身状態は比較的安定していたが，第5病日に突然心停止をきたし，死亡した。クロルフェナピルおよびその代謝産物が脂溶性であるため，急性血液浄化療法が有効でなかったと考えられる。脂溶性という特性を考慮すると，脂肪乳剤中和療法が有効かもしれない。治療法を確立するためにも，さらなる病態解明が必要である。