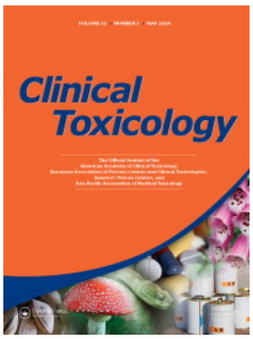

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SHORT COMMUNICATION

Tralopyril poisoning due to respiratory exposure

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ABSTRACT

Introduction: Tralopyril is a metabolite of the pesticide chlorfenapyr. Direct toxicity by tralopyril has not been described. We report two cases of tralopyril poisoning via inhalation.

Case presentations: Two workers developed heat intolerance, diaphoresis, and weight loss after occupational inhalational exposure to tralopyril. ***Patient 1:*** The exposure was due to the absence of respiratory protection. Magnetic resonance imaging showed abnormal signals in the bilateral periventricular white matter, corpus callosum, basal ganglia, brainstem, and spinal cord. The patient's blood tralopyril concentrations on days 1, 3, 5, 8, and 11 post-admission were 1.09 mg/L, 1.04 mg/L, 1.01 mg/L, 0.71 mg/L, and 0.313 mg/L, respectively. Haemoperfusion (HA330), haemoperfusion (HA380), and haemodiafiltration were performed on days 1–3, 5–8, and 9–10, respectively. ***Patient 2:*** The patient's symptoms followed inappropriate use of respiratory protection. His blood tralopyril concentrations on days 1, 4, 5, and 6 were 0.592 mg/L, 0.482 mg/L, 0.370 mg/L, and 0.228 mg/L, respectively.

Discussion: The patients presented with features typical of chlorfenapyr poisoning, which suggests that tralopyril is the main toxic metabolite of chlorfenapyr.

Conclusion: Tralopyril can be absorbed by inhalation, leading to delayed clinical symptoms and organ damage, including toxic encephalopathy and spinal cord damage.

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Chlorfenapyr; poisoning; respiratory tract; toxic encephalopathy; tralopyril

Introduction

Tralopyril (4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile), an anti-fouling biocide optimized from dioxapyrrolomycin, is an active ingredient in anti-fouling paints and is a precursor to the commercially available pro-insecticide chlorfenapyr [1,2]. Chlorfenapyr is converted into several active metabolites, such as tralopyril, AC 312094 ($C_{15}H_{12}ClF_3N_2O$), and AC 322250 ($C_{12}H_6BrClN_2O_2$) [3,4]. We present two patients with tralopyril poisoning following inhalation, the clinical features of which were similar to those described for chlorfenapyr poisoning.

Case presentations

Field investigation

Two workers were employed in the same workshop of a pesticide production company. Their workplace produces only tralopyril, using DL-4-chlorophenylglycine and trifluoroacetic acid as raw materials. A substantial amount of tralopyril dust is produced in the workplace. The workers wear long-sleeved and capped dust-proof overalls and self-absorption filter respirators. Patient 1 had worked in this workshop for one month. Two weeks before his presentation, he discovered that the anti-toxic cotton filter in his self-absorption filter respirator had disappeared after approximately 3 h of work; he noticed some white powder around his mouth and nose, but he had no obvious chest tightness or eye symptoms. Nonetheless, he changed the filter respirator, cleaned his face with water, and continued working. One week later, he experienced diaphoresis and dizziness. Patient 2 had worked in this workshop for 3.5 months. He occasionally did not change the anti-toxic cotton filter in his self-absorption filter respirators. Fifteen days before his presentation, he experienced chest discomfort and diaphoresis while working.

Patient 1

A previously healthy 51-year-old man experienced exertional diaphoresis and dizziness one week before his presentation and marked weight loss for two weeks. Subsequently, he developed reduced urinary output; sweating and dizziness increased. After two days of symptomatic treatment, he presented to our department with obvious dizziness and

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diaphoresis. On admission, examination was normal except for diaphoresis and a low-grade fever (37.5 °C). His blood tralopyril concentration was 1.09 mg/L, and DL-4-chlorophenylglycine, oxazolone, pyrrole, and chlorfenapyr were undetected. Additional results included elevated creatine kinase activity (565 IU/L; reference range, 55–170 IU/L), creatine kinase myocardial band (CK-MB) fraction concentration (13.3 μg/L; reference range, 0.3–4 μg/L), and myoglobin concentration (117.1 μg/L; reference range, 0–70 μg/L) (Table 1). The electrocardiogram and chest radiograph were normal. Dexamethasone 20 mg/day, polyene phosphatidylcholine 930 mg/day, intravenous rehydration, nutritional support and haemoperfusion were administered. On day 2, his urine volume increased; however, diaphoresis and dizziness continued. On day 4, he felt mild dizziness and displayed persistent diaphoresis. Magnetic resonance imaging (MRI) showed abnormal signals in the bilateral white matter (particularly periventricular), corpus callosum, basal ganglia, brainstem, and cervical spinal cord (Figure 1). On subsequent MRI imaging on day 11, the abnormal signals were reduced, and they disappeared on day 20. His diaphoresis was slightly improved on day 7 and significantly improved on day 14. On day 21, he was discharged but remained heat intolerant. At his follow-up visits on days 36 and 76, he had no obvious discomfort.

His tralopyril concentrations on admission days 1, 3, 5, 8, 11, 16, 20, and 36 were 1.09 mg/L, 1.04 mg/L, 1.01 mg/L, 0.71 mg/L, 0.313 mg/L, 0.093 mg/L, 0.064 mg/L, and <0.05 mg/L, respectively. Haemoperfusion (HA330, Jafron, Zhuhai, China; 2 hours/day), haemoperfusion (HA380, Jafron; 2 hours/day), and haemodiafiltration (Prismaflex ST100 set; Baxter, Deerfield, IL, USA; 4 hours/day) were performed on days 1–3, 5–8, and 9–10. No clearance data are available.

Patient 2

Fifteen days before the presentation, a 51-year-old healthy man experienced chest discomfort and diaphoresis while working. One week later, his symptoms progressed, and he developed heat intolerance and fatigue. He was admitted to our department for initial treatment. He had lost 4 kg of body weight over a period of approximately three months before admission. His vital signs and physical examination were unremarkable. His blood tralopyril concentration was 0.592 mg/L. Other laboratory test results included elevated creatine kinase activity (273 IU/L) and CK-MB concentration (32 μg/L) (Table 1). His treatments were similar to those received by Patient 1. Haemoperfusion (HA330) combined with haemodiafiltration (4 hours/day) was performed daily. On day 3, he experienced mild chest discomfort. On day 7, his chest discomfort and fatigue disappeared; however, heat intolerance persisted. His tralopyril concentration had decreased to 0.228 mg/L, and haemopurification was discontinued. On day 8, his tralopyril concentration increased to 0.445 mg/L, and haemodiafiltration was performed once. On day 14, he reported no discomfort except for heat intolerance. The results of laboratory tests and brain and chest computed tomography were unremarkable, and he was discharged from the hospital. He was followed up on day 47

Table 1. Results of investigations.

	Patient 1						Patient 2				
	On admission	Three days after admission	Seven days after admission	Nineteen days after admission	Thirty-six days after admission	Seventy-six days after admission	On admission	Three days after admission	Seven days after admission	Fourteen days after admission	Forty-seven days after admission
White blood cell count $\times 10^9$/L	5.04	5.35	5.24	4.57	6.57	7.27	5.82	4.62	6.85	5.21	9.31
Red blood cell count $\times 10^{12}$/L	4.19	4.42	4.12	3.85	4.38	4.64	3.06	3.37	3.34	3.25	4.37
Haemoglobin concentration g/L	140	145	133	125	141	145	96	105	100	98	117
Platelet count $\times 10^9$/L	149	108	96	204	212	218	274	230	174	201	292
Alanine aminotransferase activity IU/L	38	30	37	165	82	25	26	23	22	24	17
Aspartate aminotransferase activity IU/L	46	45	32	61	38	19	42	41	22	17	15
Total bilirubin concentration μmol/L [mg/dL]	10 [0.58]	8.8 [0.51]	7.7 [0.45]	6.5 [0.38]	2.7 [0.16]	8.4 [0.49]	4 [0.23]	9.4 [0.55]	8.2 [0.48]	4.4 [0.26]	3.6 [0.21]
Creatinine concentration μmol/L [mg/dl]	63 [0.71]	57 [0.64]	60 [0.68]	55 [0.62]	56 [0.63]	63 [0.71]	73 [0.83]	57 [0.64]	55 [0.62]	56 [0.63]	64 [0.72]
Blood urea nitrogen concentration mmol/L [mg/dL]	10.4 [29.12]	5.2 [14.56]	8.2 [22.96]	7.2 [20.16]	6.7 [18.76]	6.7 [18.76]	10.9 [30.52]	6.6 [18.48]	6.3 [17.64]	5.7 [15.96]	4.6 [12.88]
Creatine kinase activity IU/L	565	663	124	36	51	101	273	936	64	38	NA
Creatine kinase MB fraction concentration μg/L	13.3	8.5	1.8	1.0	0.8	1.4	32	16.3	0.9	0.7	0.9

NA: not tested.

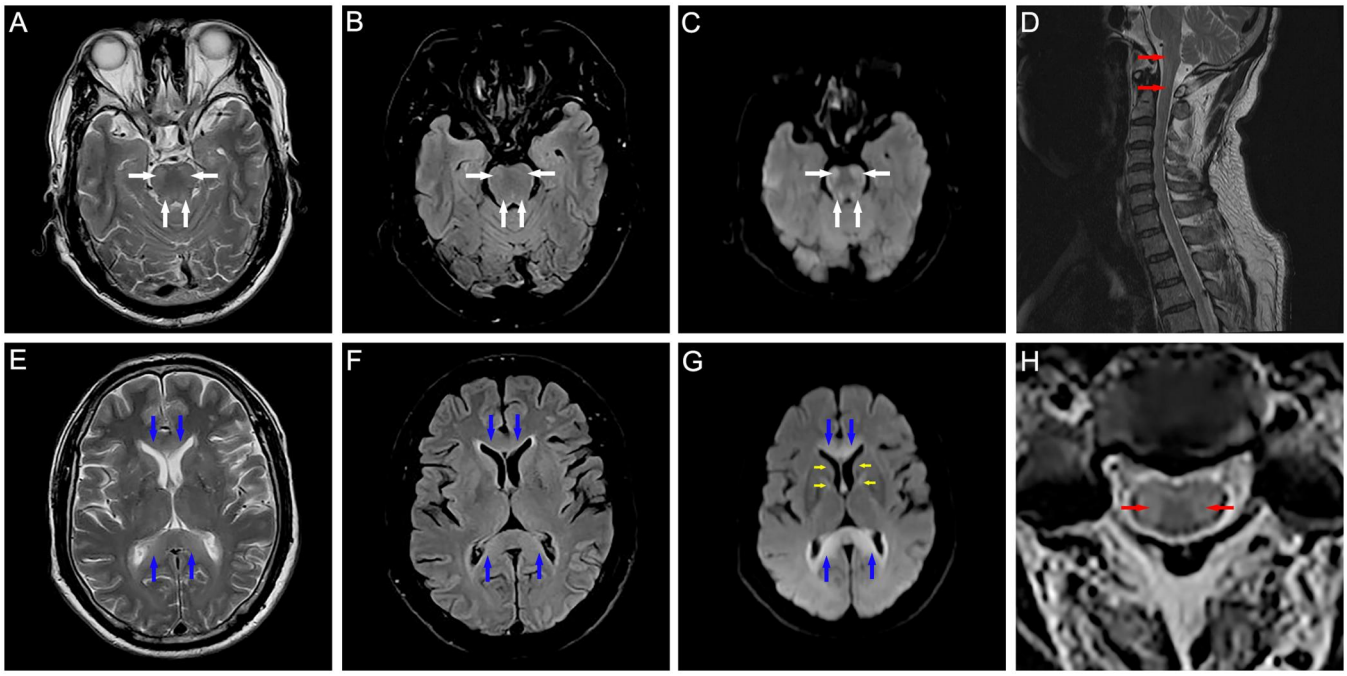

Figure 1. Brain and cervical cord magnetic resonance imaging of a 51-year-old man after approximately 20 days of exposure to tralopyril powder through the respiratory tract. Abnormalities include multiple symmetric hyperintensities of the bilateral periventricular white matter, corpus callosum (blue arrows), basal ganglia (yellow arrow), and brainstem (white arrows) on T2-weighted images and diffusion-weighted images; long segmental patchy hyperintensity in the cervical spinal cord (red arrows) on fat-saturated T2-weighted images; and patchy abnormal signal in the bilateral white matter, hypointensities on T1-weighted images, and hyperintensity on T2-weighted images and T2 FLAIR images. A, D, E, and H are T2-weighted images; B and F are T2 fluid attenuated inversion recovery (FLAIR) images; C and G are diffusion-weighted images.

and reported no discomfort. His tralopyril concentrations on days 1, 4, 5, 6, 7, 14, and 17 of admission were 0.592 mg/L, 0.482 mg/L, 0.370 mg/L, 0.228 mg/L, 0.445 mg/L, 0.05 mg/L, and $<$0.05 mg/L, respectively.

Discussion

Tralopyril has strong uncoupling activity, which decouples oxidative phosphorylation within the mitochondria and interferes with the internal and external proton balance of the mitochondrial membrane, ultimately inhibiting adenosine triphosphate production, causing cellular dysfunction and death [5]. In these two patients, myocardial, skeletal, and central nervous system injury were the main findings after tralopyril exposure. These organs or tissues, with their high energy demands, easily develop dysfunction or damage [6,7]. Notably, both patients had elevated CK-MB activities and myoglobin concentrations. However, Patient 1 had a higher tralopyril concentration and developed central nervous system injury. The damage was observed on MRI imaging, mainly involving the bilateral periventricular white matter, corpus callosum, basal ganglia, brainstem, and spinal cord, as described in previous reports of patients with chlorfenapyr poisoning [8,9]. We speculate that these regions have a higher metabolism [10] and are especially vulnerable to tralopyril. Despite inhalation being the route of poisoning in our patients, the lungs may not be the main target organ of tralopyril, as evidenced by the absence of pulmonary damage. Although no clearance data are available in our patients, removing tralopyril through haemopurification treatments might be of value and needs to be investigated further.

Conclusions

Tralopyril can be absorbed by inhalation, leading to delayed clinical symptoms and organ damage on radiological investigation, including toxic encephalopathy and spinal cord damage.

Ethical approval

This study has been approved by the Ethics Committee of Shandong University of Qilu Hospital (KYLL-202309-028). Both patients provided written informed consent to participate in this study, which included the data availability statement.

Disclosure statement

No potential conflict of interest was reported by the authors.

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