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FATAL INTOXICATION AFTER DELIBERATE INGESTION OF 2-METHYL-4-CHLOROPHENOXYACETIC ACID (MCPA)

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Abstract

Although intentional poisonings with 2-Methyl-4-chlorophenoxyacetic acid (MCPA) are relatively rare and in most cases cause moderate toxicity, deaths have been described, mainly due to cardiorespiratory arrest. Treatment is generally supportive, with opposing effects from the application of urinary alkalization and other methods for secondary elimination of the poison.

Case report. Herein we report a case of an adult female who was admitted to theUniversity Clinic for Toxicology several hours after a suicidal ingestion of an unknown toxic agent that resulted in vomiting and loss of consciousness. After MCPA ingestion was confirmed, she received supportive care, urinary alkalinization, and hemodialysis.

Despite this, the patient was hypotensive, after which signs of acute kidney injury, rhabdomyolysis, hyperamylasemia, hepatic lesion, electrolyte abnormalities, metabolic acidosis, disseminated intravascular coagulation, and respiratory failure developed. Despite applied mechanical ventilation and inotropic support, the patient died several days later.

Conclusion: MCPA is a poisonous herbicide that can cause severe forms of poisoning and fatal outcome especially after large intentional ingestions.

The availability of rapid qualitative toxicological confirmation of the xenobiotic can contribute to early etiological diagnosis and initiation of appropriate therapeutic measures that would improve survival even in more severe forms.

***Keywords*:** 2-Methyl-4-chlorophenoxyacetic acid, herbicide, poisoning, treatment

Introduction

Chlorophenoxy compounds in the form of acids, salts and esters are the most widely used herbicides for the destruction of weeds in agriculture [1].

Signs of poisoning and systemic effects in humans may occur after dermal and inhalation exposure, but more severe forms of poisoning have been noted in patients after intentional ingestion [2].

The clinical presentation is broad due to involvement of multiple systems and organs, but most fatal case reports show the presence of renal injury, acidosis, electrolyte disturbances, and subsequent multiorgan damage [3].

In the acute phase, due to the non-specific symptoms, it resembles other poisonings, most often poisoning with anthocholinesterase agents, which is the reason for misdiagnosis and mistreatment, especially in the absence of rapid toxicological confirmation [2].

In the absence of an antidote for poisoning with this herbicide, treatment is mainly supportive. Early application of urinary alkalization (UA) contributes to successful treatment in severe poisonings after ingestion of chlorophenoxy compounds[3].

Early hemodialysis (HD) is also recommended especially in critically ill patients in whom large fluid intake should be avoided,but not as first-line therapy [4,5].

We present the case of an adult woman who was admitted to the University Clinic for Toxicology after a suicidal ingestion of an unknown substance, later determined to be 2-Methyl-4-chlorophenoxyacetic acid (MCPA). Despite treatment with early applied UA, performed HD and other supportive therapy the result was unfavorable.

Case report

We present a case of a 64-year-old female patient who was brought to the University Clinic for Toxicology in a coma with a heteroanamnastic history of poisoning by an unknown substance.

She was found by the family in an unconscious state, with emetic contents around her and an empty bottle of alcohol. She was initially taken to a local medical center where a CT scan was performed with normal findings and transferred to the toxicology clinic for further treatment after 12 hours of ingestion. She had no abnormal body movements, fever, diarrhea and sweating.

The patient had a history of schizoaffective disorder and was on regular therapy with biperiden, valproic acid, flurazepam, olanzapine and clonazepam. Despite that, she had suicidal thoughts in the last 4 years.

On admission to our clinic, the patient was unconscious.

Her vital parameters were: BP 80/60 mmHg, PR 102/min, RR 20/min and SPO_2 92% on ambient air. Physical examination revealed: GCS of 7 out of 15, pupils were isochoric, fixed with preserved light response.Lung auscultation showed vesicular breathing with dry scraping bronchitic murmurs bilaterally basally. Abdominal status was unremarkable. Her electrocardiogram showed only sinus tachycardia of 102/min without conduction disturbances.

Neurological examination showed absent Babinski, coma and signs of metabolic encephalopathy.

Laboratory analyses showed a normal hemogram with leukocytosis, with a gradual decrease in the number of red blood cells, hemoglobin, hematocrit and platelet count in the following days. The random glucose was elevated but with normal HbA1C. Additional biochemical analyses showed the presence of acute kidney injury, rhabdomyolysis, moderate hepatic toxicity and electrolyte abnormalities.

The results of the biochemical analysesare shown in Table 1.

Table 1. Most prominent biochemical findings at several time points.

Parameter / Reference range	**Day of hospitalization**					
	Day 1	**Day 2**	**Day 3**	**Day 5**	**Day 7**	**Day 9**
RBC (10^{12}/L)4.20-5.20	4.30	4.1	3.59	3.36	2.72	3.47
HGB (g/L)120-180	129	128	109	97	81	104
WBC (10^9/L) 4.00-9.00	13.3	9.8	10.4	7.9	5.1	3.6
LYMPH (%) 15-50	6.7	7.7	10.1	9.4	6.3	4.9
NEUT (%) 35-80	91.1	90.7	86.3	87.5	90.2	86.3
PLT (10^9/L)150-450 150-450	295	334	240	101	29	10
CRP (mg/L)- 6	6	29.6	82.5	48.8	39.5	39.2
LDH (U/L) до 248	230	356	820	1160	803	598
CK-MB (U/L) - 25	33.91	91	138	448.2	N.A.	N.A.
CK (U/L) 24-173	90	3791	9079.32	10994	3494	1156
ALT (U/L) 10-45	21	35	43	67	84. 04	95
AST (U/L)10-34	20	65	124	174	177.6	70

Ca (mmol/L)2,1-2,6		2.30	1.7	1.27	1.48	2.1	1.67
K (mmol/L)3,8-5,5		5.58	5.4	5.6	4.53	3.1	3.30
Creatinine (umol/L)	**45-109**	96	199	460	537	254.2	356
Urea (mmol/L)2,7-7,8		10.9	26.1	54.6	51.3	23. 77	31.1
Glucose (mmol/L)3,5-6,1		9.5	5.6	10.5	4.3	9.97	10
Myoglobin (ng/ml)	**<75,0**	2978	2978.36	3627.76	638.9	N.A.	N.A.
Albumin (g/L)35-50		46	42	27	33	27.4	26
Total proteins (g/L)	**63-83**	74	64	60	59	47.8	49

***N.A. - Not available**

Cholinesterase levels were normal (ChE 4925.2 U/L), thus ruling out the possibility of anticholinesterase poisoning. Troponin was normal. Amylase was elevated (1071 U/L), while lipase was normal (30 U/L). TSH and FT4 were normal, but PTH value was 473.7 pg/ml and was significantly higher than the reference range(r.r. 10.0-69.0 pg/ml), while Vit. D3 was 8.29 ng/ml, which is below the normal range (r.r. 10-75 ng/ml). Potassium was slightly elevated and total calcium (1.27 mmol/L) and ionized calcium (0.63, 1.01 mmol/L) were lower. Urine culture confirmed bacterial infection with *Enterococcus* and *Escherichiacoli*, which was treated according to antibiogram.

Hemostasis showed signs of DIC with a drop in PLT and a rise in D-dimers to 18933. Arterial blood gas analyses showed metabolic acidosis (pH 7.212, SO_2 89.3%, HCO3 15.9 mmol/L, BE -10.8 mmol/L, lactate 4.52 mmol/l). CTM showed no abnormalities, and lung CT showed only chronic peribronchitic changes bilaterally chylobasally.

Toxicology screening showed increased concentrations of benzodiazepines but without response to antidote therapy. Additional toxicological analyses performed at the Institute of Forensic Medicine showed the presence of metabolites of the drugs for her underlying disease and metabolites of MCPA determined by the gas chromatography-mass spectrometry (GC/MS) method.

The patient was treated with crystalloid solutions, corticosteroids, PPIs, oxygen therapy, diuretics, intravenous NaHCO3 for urine alkalinization, MgSO4, Ca-gluconate, flumazenil, dopamine stimulation, anticoagulants and antibiotics. Macromolecular solutions and aminoplasmal solution were also added.

Hemodialysis was performed on the second and fourth day of hospitalization.

Despite the measures taken, the patient's hypotension worsened; she became anuric with worsened blood gas analyses and coagulation tests, and her state of consciousness remained unchanged. She was transferred to the intensive care unit (ICU), intubated and placed on mechanical ventilation.

Another curative hemodialysis was performed, and the patient was placed on vasopressor and inotropic support with noradrenaline and adrenaline. Despite all efforts, hemodynamic instability persisted. Cardiovascular destabilization with hypotension and bradycardia occurred on the 10th day, but despite attempts at cardiopulmonary and cerebral resuscitation, the patient died.

Discussion

Numerous compounds containing chlorophenoxy herbicides are on the market in various forms and concentrations and are sold under various trade names. Poisonings with chlorophenoxy compounds in humans have been studied in detail for more than two decades [4].

However, mortality data differ in different reports and for different formulations. Thus, a prospective case study that studied the outcome of intentional poisonings with MCPA and included 181 patients reported a mortality of 4.4% [6]; another epidemiological study with the same formulation on 1653 patients detected a mortality of 5.5% [7].

Another study from China that studied the outcome of poisoning with another chlorophenoxy formulation 2,4-dichlorophenoxyaceticacid (2,4-D) in 852 patients reported a very high mortality of 99.17% [8], implying that MCPA poisonings are quite mild. Although there are more published fatal case reports in the literature after poisoning with 2,4 D than with MCPA, it is reasonable to assume that all

chlorophenoxy herbicides have a similar mechanism of action and share a similar clinical presentation. In spite of the fact these poisonings are not very common, ingested in high doses they can be potentially fatal, especially if not diagnosed and treated early. Their toxic effects involve the heart, central and peripheral nervous systems, liver, kidneys, muscles, lungs, and endocrine system [9].

The exact mechanism of chlorophenoxy herbicides is not sufficiently elucidated. Some of the most important mechanisms include dose-dependent cell membrane damage, disruption of acetyl coenzyme-A metabolism, and uncoupling of oxidative phosphorylation. It also implies dose-dependent damage to the central nervous system through disruption of the blood-brain barrier with consequent accumulation of the herbicide in the brain [9, 10,11].

Uncoupling of oxidative phosphorylation can also be fatal in some poisonings because it leads to increased oxygen consumption and heat production out of proportion to the generation of adenosine triphosphate [12].

Increased mitochondrial respiration and subsequent decreased ATP levels are not sufficient for basic cellular functions such as active transport of pumps such as Na-K ATPase. This can cause a loss of cellular ion and volume regulation and if ATP is not delivered in a timely manner, the effect is irreversible and cell death occurs [6].

Signs of systemic toxicity can also appear after inhalation and dermal exposure, but ingestion is considered the most relevant route of exposure associated with more severe forms of poisoning [1,2].

The most logical explanation behind this lies in the fact that chlorophenoxy compounds are absorbed well from the gastrointestinal tract, less well from the lungs, and minimally after dermal exposure [3].

Other pharmacokinetic characteristics of these herbicides are: insignificant fat storage, almost complete elimination through urine and a high percentage of binding to plasma proteins and distribution to other tissues [13, 14].

The average half-life under normal conditions differs for different formulations and ranges from 13-39 hours, but varies depending on urinary pH. It accelerates in alkaline urine, and slows down at 70-90 hours in acidic urine. Also, higher doses and prolonged exposure prolong the half-life of chlorophenoxy herbicides [3].

Mild gastrointestinal and peripheral neuromuscular symptoms were noted after inhalation exposure, while signs of gastrointestinal irritation and mixed sensorimotor neuropathy were recorded after dermal exposure [10].

Numerous manifestations of systemic toxicity from chlorophenoxy compounds have been noted following intentional suicidal ingestions of large amounts of these herbicides. Most reports indicate the involvement of renal failure, acidosis, electrolyte imbalance, and subsequent multiorgan failure as causes of death [3].

Other authors, in addition to metabolic acidosis and respiratory failure, also list massive rhabdomyolysis, refractory hypotension and coma as markers of severe toxicity [1].

Bradberry *et al*. found that coma was a consistent feature of fatal cases, although it was also present in one-third of non-fatal cases after ingestion of chlorophenoxy herbicides [4].

Toxicological confirmation and quantitative evidence of chlorophenoxy compounds in blood and urine in patients who had impaired consciousness showed large differences in concentrations ranging from 80-1,000 mg per liter, and therefore if the clinic indicates a massive ingestion/exposition, the initiation of appropriate treatment as soon as possible is recommended without waiting for chemical confirmation of the absorbed poison [3].

Roberts DM *et al*. also found changes in mental status in more severe patients as well as higher mortality mainly due to cardiorespiratory arrest, with no significant correlation between MCPA concentrations on admission and markers of severe toxicity [6].

Other authors found higher mortality in older patients with higher oral intakes, and did not find significant differences between the value of GCS score and AKI in healthy and deceased [7].

There is a similar clinical presentation of poisonings with chlorophenoxy herbicides and anticholinesterase agents, which makes differential diagnosis difficult and may underestimate the number of these poisonings [1, 2].

On the other hand, poisonings with organochlorine compounds, fungicides, mushrooms and opioids resemble poisoning with organophosphorus compounds, so early identification of the type of xenobiotic (availability of basic toxicological tests) is crucial for the outcome of the poisoning because it prevents wrong classification and wrong treatment [2].

Management of these poisonings is mainly supportive because no specific antidote is available. It consists of decontamination measures with charcoal and gastric lavage after oral ingestion of large amounts of chlorophenoxy herbicides, rehydration and vasopressors in hypotension unresponsive to crystalloid treatment, correction of acidosis and electrolyte abnormalities [6,15,16].

Controversy among clinicians exists mainly over methods of secondary elimination of the poison, due to lack of evidence based on randomized, controlled clinical studies for this type of treatment [15].

Early application of urinary alkalinization was used with success in poisonings with chlorophenoxy compounds [3,9,17].

This treatment allows accelerated excretion of poisons that are weak acids, with intravenous administration of sodium bicarbonate to produce urine with a pH $\geq$ 7.5. Therefore, numerous experts from the American Academy of Clinical Toxicology (AACT) and the European Association of Poison Centers and Clinical Toxicologists (EAPCCT) recommend UA and high urine flow (approximately 600 mL/h), i.e., forced diuresis in a patient that should achieve clinically important elimination of the chlorophenoxy herbicide, accompanied by electrolyte control and their substitution [17,18].

Other authors consider that hemoperfusion is a superior method over UA and that it leads to a faster recovery of CNS symptoms, reduces damage to other organs and reduces mortality in severe 2,4-D poisoning [8].

Although some authors refer to a favorable outcome and survival after early application of hemodialysis in patients poisoned with high doses of 2,4-D [5], it should be considered in severe cases, especially where excessive fluid administration is not advised, and not as first line therapy [4].

However, three-compartment kinetics and extensive plasma protein binding can interfere with the efficacy of hemodialysis [4,11].

Therefore, in case of severe toxicity, hemoperfusion, hemodialysis and plasmapheresis can be used [4,5].

We have presented a case of severe MCPA poisoning for which the initial hetero-amnestic data indicated alcohol intoxication. Shortly after admission, the possibility of alcohol poisoning, poisoning with anthocholinesterase agents and benzodiazepines was ruled out.

The etiological diagnosis of the poisoning was later confirmed by qualitative evidence of the presence of MCPA metabolites in the patient's blood. Findings from clinical investigations, biochemical and blood gas analyses indicated the existence of a severe form of poisoning with this herbicide. Markers for severe toxicity such as coma, hypotension and advanced age were present in the patient from the beginning. Later, signs of rhabdomyolysis, acute kidney injury, moderate hepatotoxicity, hyperamylasemia, metabolic acidosis, DIC, respiratory depression, and cardiac arrest developed as causes of death.

Although hepatic injury is a rare manifestation of MCPA poisoning, there are authors who have described toxic-induced mixed hepatocellular and cholestatic liver damage occurring after acute/chronic MCPA exposure for 6 months, proven clinically, biochemically, and histopathologically [19].

An increase in parathormone was also registered in our patient, but due to the rapid deterioration of the clinical picture, no additional investigations were performed.

Thus, have no explanation whether it was due to another reason or was related to the poisoning. Chronic exposure to various pesticides, including chlorophenoxy herbicides, is known to disrupt normal hormonal function. Until now, the literature has described a negative impact on the thyroid gland and reduced secretion of thyroid hormones [20], as well as negative toxic effects on male and female reproductive capacity [21], but the impact of intentional single large ingestions has not been described, yet.

Although deaths following intentional ingestion of MCPA are less frequently described in the literature compared to other formulations of chloro-phenoxy herbicides, they have been described following ingestion of pure and combined preparations containing MCPA [22, 23] and indicate the real possibility of relentless progression to severe poisoning in humans with these herbicides.

Accordingly, in our patient, despite the timely supportive measures, urinary alkalization and hemodialysis, a fatal outcome occurred on the tenth hospital day.

Conclusion

Although rare, MCPA poisonings are potentially life-threatening conditions that lead to multisystemic and multiorgan involvement, especially after an oral ingestion of large amounts of herbicide.

Knowledge about the acute toxicity of these herbicides is still limited and additional research is needed that will clarify all mechanisms of toxicity, which will probably contribute to a more successful treatment.

The early qualitative confirmation of the herbicide in biological material can help in establishing a correct diagnosis, and taking supportive therapeutic measures as soon as possible and combined methods for secondary elimination of the poison can be a prerequisite for lower mortality from these poisonings.

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