Vol. 1 / Issue 1 / 2024

FEZ MULTIDISCIPLINARY JOURNALS

Journal of Nursing, Education Sciences, and Medical Practice

ISSN: 3009-5867

Journal homepage: https://fmjpublishing.com/index.php/JNESMP

Case Study

Rare Cardiotoxicity in a Child Following Accidental Alphachloralose Ingestion: A Case Study with *In-Silico* Insights

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Abstract

Cardiotoxicity associated with alphachloralose is poorly understood, and its underlying mechanisms remain unclear. Only a few cases have been reported in the literature. We present the case of a 5-year-old child who experienced moderate alphachloralose poisoning following accidental ingestion. Cardiac involvement was identified through elevated troponin levels, with a favorable outcome following symptomatic treatment. The interaction between alphachloralose and cardiotoxicity was evaluated using in silico methods. Alphachloralose potentially induces cardiotoxicity through 15 key overlapping targets, including STAT3, MMP2, and CASP3, identified via database integration and correlation analysis. STAT3, MMP2, and CASP3 emerge as critical targets in alphachloralose-induced cardiotoxicity, offering potential avenues for therapeutic intervention.

Keywords: alphachloralose, cardiotoxicity, case study, *in silico*, STAT3, MMP2, CASP3

Citation: Hasnae Houmman, Hajar El Ammari, Mohamed Chebabi, Sanae Achour. Rare Cardiotoxicity in a Child Following Accidental Alphachloralose Ingestion: A Case Study with In-Silico Insights. Journal of Nursing, Education Sciences, and Medical Practice. 2024, 1, 1-6. https://doi.org/10.69998/JNESMP5

Edited by: Insaf Mabchour

Abbreviation

ECG: Electrocardiogram

GABA: Gamma-Aminobutyric Acid

CPK-MB: Creatine Phosphokinase-MB

STAT3: Signal Transducer and Activator of Transcription 3

MMP2 : Matrix Metallopeptidase 2

CASP3 : Caspase 3

PPI : Protein-Protein Interaction

ECM: Extracellular Matrix

JAK/STAT: Janus Kinase/Signal Transducer and Activator of Transcription

MCL1: Myeloid Cell Leukemia 1

IL2: Interleukin 2

LGALS3: Galectin-3

HSP90AA1: Heat Shock Protein 90 Alpha Family Class A Member 1

MMP1: Matrix Metallopeptidase 1

1. Introduction

Alphachloralose is a synthetic compound belonging to the convulsant rodenticide family. Initially synthesized in 1889, it was originally employed as a hypnotic and anesthetic in human medicine but was later discontinued due to its adverse effects. Today, it is used as a rodenticide and avicide, typically formulated as a powder or bait with concentrations ranging from 10% to 100% (Isackson and Irizarry, 2024). Alphachloralose acts by inducing sedation in the central nervous system while simultaneously causing hyperactivity in the spinal cord. This paradoxical effect is often described as a state of a "sedated brain and hyperactive spinal cord" (Iken et al., 2018).

The mechanism of action of alphachloralose involves modulation of the GABAergic system, where it acts as a central nervous system depressant, combined with its excitatory effects on peripheral motor pathways (Bates, 2020). These dual effects make alphachloralose an effective agent for immobilizing small animals, such as rodents and

Received: 26 December 2024; **Revised:** 29 December 2024; **Accepted:** 30 December 2024; **Published:** 31 December 2024

birds. However, its widespread use has raised concerns regarding its potential for accidental poisoning, particularly in children, due to its availability in households and agricultural settings (Cullen, 2000).

Acute poisoning by alphachloralose is characterized by neurological symptoms, including seizures, myoclonus, and altered consciousness. Other manifestations include bronchorrhea, and hypothermia (Windahl et al., 2022). The toxic dose in children is estimated at 20 mg/kg, making even small amounts of ingestion potentially dangerous (Bergrath et al., 2019). Treatment is primarily symptomatic and includes the administration of activated charcoal, benzodiazepines for seizure control, and respiratory support in severe cases. Early recognition and prompt intervention are critical for favorable outcomes (Gerace et al., 2012).

Accidental ingestion of alphachloralose is most commonly reported in children, often due to ingesting baited food prepared for rodent control (Birich et al., 2021). Despite its neurotoxic profile being well-documented, reports of alphachloralose-induced cardiotoxicity remain rare and poorly understood. Few studies have explored this association, and the underlying mechanisms of cardiac involvement are not fully elucidated.

In this context, the present case study reports a rare instance of cardiac toxicity following alphachloralose ingestion in a child. Additionally, we employ an *in silico* investigation to explore the potential molecular mechanisms linking alphachloralose to cardiotoxicity. This integrated approach aims to shed light on this uncommon complication and highlight the need for systematic cardiac assessment in cases of severe poisoning.

2. Materials and Methods

2.1. *In silico* study

2.1.1. Potential Targets of AlphaChloralose

Identifying potential targets for alphachloralose was carried out using the ChEMBL database (https://www.ebi.ac.uk/chembl/) and the SwissTarget Prediction tool (http://www.swisstargetprediction.ch/). SwissTarget Prediction predicts compound targets by analyzing chemical structure similarities, whereas ChEMBL offers broader coverage with its larger collection of compounds and associated targets. The results from both databases were consolidated, and duplicates were removed. To standardize the data, the identified targets were mapped to gene symbols using the UniProt database (https://www.uniprot.org/) (Xian et al., 2021).

Potential Targets of CardiotoxicityThe GeneCards database (https://www.genecards.org/) was used to identify cardiotoxicity-associated targets by querying the term "cardiotoxicity." GeneCards provides an extensive resource of genomic, proteomic, and disease-related annotations. Higher GeneCards scores indicate a stronger correlation between a target and the associated disease (Xian et al., 2021).

2.1.2. Protein-Protein Interaction (PPI) Network for AlphaChloralose Cardiotoxicity

To explore the interaction between targets associated with alphachloralose and cardiotoxicity, a Venn diagram was generated to identify shared targets. These overlapping targets were analyzed using the STRING database (https://string-db.org/) to construct a protein-protein interaction (PPI) network, highlighting their interrelationships. Cytoscape software was employed to prioritize key targets based on the degree values of the interaction nodes within the network (Xian et al., 2021).

3. Results

3.1. Clinical Observation

We report the case of a 5-year-old female patient with no significant medical history who was admitted to the pediatric emergency department following accidental ingestion of alphachloralose in July 2024. The incident occurred 40 minutes before admission when the child consumed a piece of cake containing the rodenticide, which a family member had placed on the floor as bait. Concerned, the family sought medical attention at the Pediatric Emergency Unit of Hassan II University Hospital in Fez.

Upon admission, the child presented with nausea as the sole symptom. Clinical examination revealed no abnormalities. The patient was fully conscious with a Glasgow Coma Scale score of 15, normal oxygen saturation on ambient air, a heart rate of 98 beats per minute, a respiratory rate of 16 breaths per minute, and blood pressure of 110/60 mmHg. Neurological examination was initially expected, with no seizures, altered consciousness, or neurological deficits. The electrocardiogram (ECG) showed harmful T waves in the anteroseptal leads (Figure 1).

The therapeutic decision was to administer a dose of activated charcoal at 1 g/kg and to keep the child under observation in a calm environment, avoiding any physical or auditory stimulation. Thirty minutes later, the child experienced a single myoclonic seizure affecting one side of the body, accompanied by bronchorrhea, which resolved with midazolam administration.

Biological tests were normal except for CPK-MB levels at 78 U/L and troponin at 80 ng/mL. Toxicological analysis of the aspirated gastric content was positive for alphachloralose (Fujiwara-Ross technique).

The child remained under observation without incident for 48 hours, during which troponin levels decreased. Discharge was granted due to the favorable clinical course, and parents were educated on the importance of keeping baits and pesticides out of children's reach.

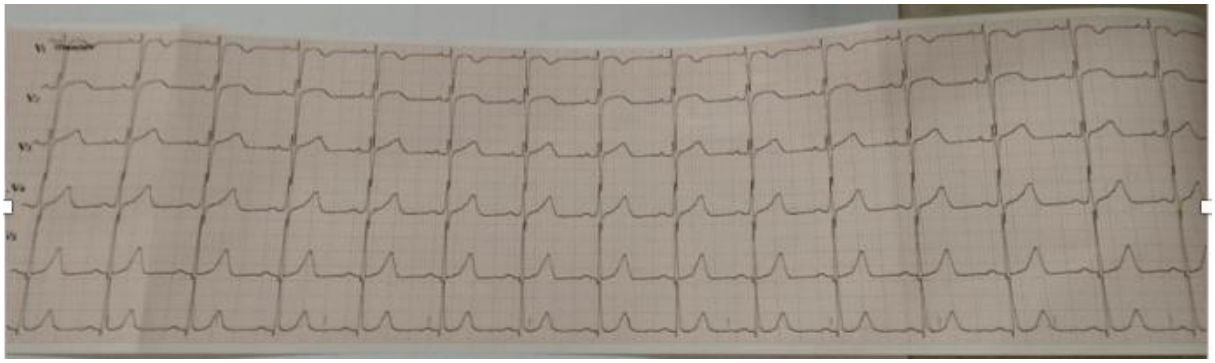

Figure 1: ECG showing the presence of negative T waves in the antero-septal leads

3.2. *In silico* study

Following standardization in UniProt and elimination of duplicate entries, 100 potential targets for alphachloralose were identified using SwissTarget Prediction and ChEMBL databases. Meanwhile, 513 cardiotoxicity-related targets were extracted from the GeneCards database. As depicted in Figure 2, 15 overlapping targets were identified between the alphachloralose-associated targets and the cardiotoxicity-related genes. These shared targets are likely pivotal in the cardiotoxic effects of alphachloralose.

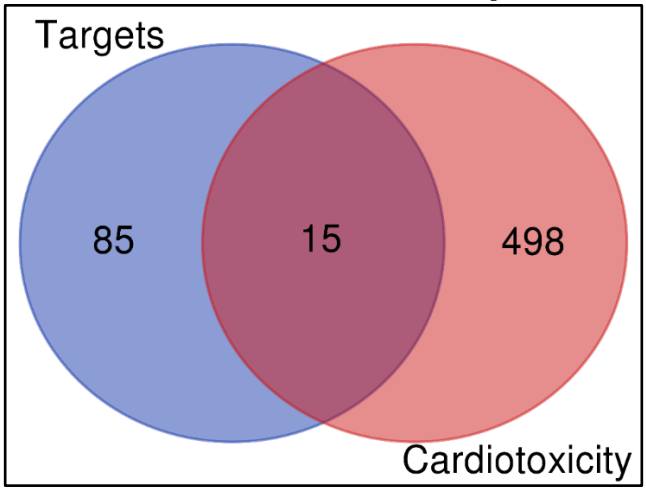

Figure 2: Screening analysis of overlapping genetic symbols between alphachloralose and cardiotoxicity.

The correlation analysis demonstrated a strong interrelation among the shared targets (Figure 3). Cytoscape software further evaluated these to compute their correlation degree values (Table 1). Among the identified targets, STAT3, MMP2, CASP3, and others exhibited notably higher degree values, indicating their potential as critical contributors to alphachloralose-induced cardiotoxicity.

4. Discussion

Rodenticides are biocides used against harmful rodents and, by extension, moles. Controlling harmful rodents involves many commonly used substances readily available in domestic environments. As a result, these products are often responsible for accidental or intentional poisonings. Rodenticides include several chemically diverse families (Gamelin and Harry, 2005). Alphachloralose belongs to the family of convulsant rodenticides.

Alphachloralose, also known as glucochloral or chloralose, is a synthetic organic compound discovered in 1889, formed by combining one molecule of chloral with one molecule of glucose (Gamelin and Harry, 2005). Initially used in human medicine for years as a hypnotic and anesthetic, this therapeutic application ceased entirely in 1989 due to its side effects. However, its α-isomer is now used as a pesticide, typically in powder or bait form, with concentrations ranging from 10% to 100%. It is used to control rodents, moles (causing death), and crows (causing sedation) (Foster, 1995).

Acute poisoning is frequent due to its common use as a rodenticide and over-the-counter availability. Toxic effects primarily target the nervous system, causing paradoxical central depression and motor hyperexcitability, as well as the respiratory system. The toxic dose is estimated at 20 mg/kg for children and 16 g to 1 g for adults (Thomas et al., 1988). The triad of coma, myoclonus, and bronchorrhea is highly suggestive of alphachloralose poisoning (Leveau, 2016).

Consciousness disturbances range from pseudo-drunken states to delirious excitement, confusion, drowsiness, and coma. Motor hyperexcitability manifests as spontaneous or stimulus-induced involuntary muscle movements, ranging from fasciculations to choreiform movements and convulsions. Myoclonus (myoclonic encephalopathy) is constant, and hypertonia may also occur. Bronchial hypersecretion causes pulmonary congestion. Respiratory complications in comatose patients are exacerbated by bronchial and salivary hypersecretion. Hypothermia may also be observed. Rhabdomyolysis is rare. Electrocardiographic or hemodynamic abnormalities are not typically observed, although shock has been reported in massive poisonings (Thomas et al., 1988). Alphachloralose can even induce a state of apparent death.

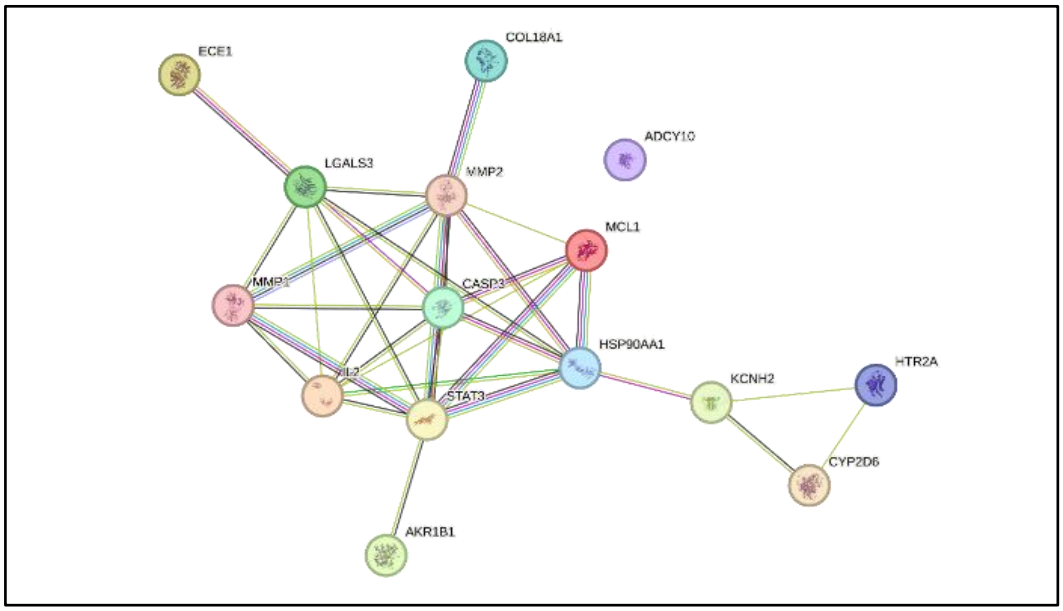

Figure 3: Protein-protein interaction (PPI) network analysis

Treatment is symptomatic, focusing on maintaining vital functions. This includes artificial ventilation in cases of respiratory distress and the use of short-acting benzodiazepines or barbiturates for convulsions. Alphachloralose is well-absorbed in the gastrointestinal tract and undergoes partial glucuronidation in the liver, with an apparent half-life of 4-5 hours. It is primarily excreted in the urine as glucuronide derivatives (Thomas et al., 1988).

Signal Transducer and Activator of Transcription 3 (STAT3), Matrix Metallopeptidase 2 (MMP2), and Caspase-3 (CASP3) are pivotal mediators in cardiotoxicity, each contributing through distinct yet interconnected pathways. STAT3 plays a dual role in cardiac health, with its activation via the JAK/STAT pathway promoting cardiomyocyte survival and reducing oxidative stress by upregulating anti-apoptotic proteins like Bcl-2. However, aberrant STAT3 activation can exacerbate inflammation and fibrosis, contributing to cardiomyopathies(Anjos et al., 2021; Madamanchi et al., 2001; Paulin and Michelakis, 2014).

Table 1: correlation degree values using Cytoscape software

Gene name	Degree	Gene name	Degree
STAT3	8	MCL1	5
MMP2	8	KCNH2	3
CASP3	7	CYP2D6	2
IL2	7	HTR2A	2
LGALS3	7	AKR1B1	1
HSP90AA1	7	COL18A1	1
MMP1	5	ECE1	1

MMP2, a crucial enzyme in extracellular matrix (ECM) remodeling, becomes pathogenic when overactivated, leading to excessive ECM degradation. This destabilizes myocardial structure, promoting adverse remodeling, dilated cardiomyopathy, and heart failure, as observed in chemotherapy-induced cardiotoxicity (Chan et al., 2021; Siwik et al., 2001). CASP3, a key executor of apoptosis, is heavily implicated in cardiomyocyte death through both intrinsic and extrinsic pathways. Its overactivation, triggered by oxidative stress and mitochondrial dysfunction, is a hallmark of conditions like anthracycline-induced cardiotoxicity (Wang et al., 2021; Zhang et al., 2020). The dysregulation of STAT3, MMP2, and CASP3 collectively underscores their critical roles in cardiotoxicity, making them potential targets for therapeutic intervention to mitigate cardiac damage in pathological conditions. Furthermore, the potential role of alphachloralose in modulating these pathways highlights its capacity to disrupt the delicate balance of protective and pathological processes in the heart. Dysregulation of STAT3, MMP2, and CASP3 by alphachloralose could synergistically contribute to its cardiotoxic effects, making these genes critical targets for further investigation into the molecular mechanisms underlying alphachloralose-induced cardiac toxicity.

5. Conclusion

This report presents a case of cardiac involvement discovered incidentally following alphachloralose poisoning, which resolved favorably with early symptomatic treatment. Clinicians should systematically assess cardiac function, especially in severe or massive poisonings, to ensure appropriate management and avoid missing potentially life-threatening complications. This includes conducting electrocardiographic and biological tests,

particularly troponin measurements, a sensitive and specific biomarker for myocardial injury.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Funding

The author(s) declare that no financial support was received for this article's research, authorship, and/or publication.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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