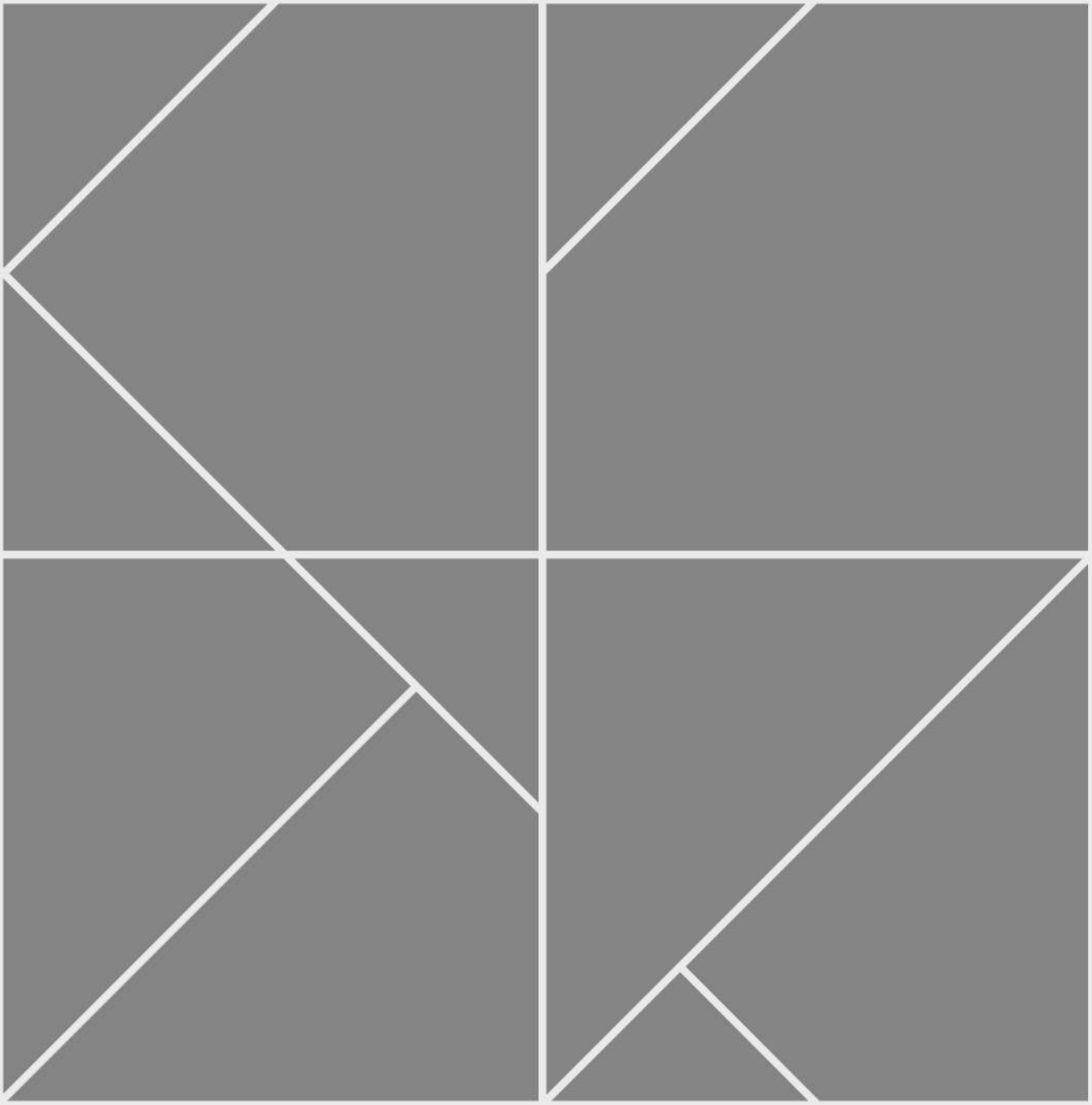
the poison®

Panamerican Toxicology Press

VOL.1|NO. 2|2024



ISSN 3008-8755

thepoisonjournal.com

The Poison® is a scientific journal aimed at the dissemination of Clinical Toxicology that is published biannually by Panamerican Toxicology® Press. It is an open journal, submitted to peer-to-peer review, and written in English. Entirely digital, it embodies our commitment to the environment and the protection of the resources. It can be accessed from The Poison®'s official website or by free subscription to the journal's newsletter.

The Poison® adheres to the *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* of the International Committee of Medical Journal Editors (ICMJE) and to the ethical guidelines established by the Committee on Publication Ethics (COPE). It is a member of Crossref, the world's leading registry of DOIs (Digital Object Identifiers) and metadata for academic research.

The journal is indexed in BASE (Bielefeld Academic Search Engine), LATINDEX DIRECTORIO (Sistema Regional de Información en línea para Revistas Científicas de América Latina, el Caribe, España y Portugal) and SCILIT (Scientific and Scholarly Research Database) by MDPI.

Published by Panamerican Toxicology® Press: 1737 Chivilcoy St. Castelar, Buenos Aires
(PO BOX 1712), Argentina

Editorial Board

Contents

the poison®

2024 | Vol. 1 | No. 2: 37-38

EDITORIAL

The Bhopal disaster (1984 – 2024): Reflections on the anniversary of a wound that does not heal

Ana M. Caresana*, MSc., Prof.

Chair of Toxicology, School of Exact and Natural Sciences, University of Morón, Buenos Aires, Argentina. Member of the Editorial Board of The Poison.
*anamcares@gmail.com

Published: 30/06/2024 - DOI: https://doi.org/10.62129/TZGD8946

Forty years have elapsed since that fateful 3 December 1984 in the city of Bhopal (India), where the tragedy triggered by the explosion of a container at the Union Carbide plant, devoted to the production of pesticides, would leave an indelible trace on the community. The leak from the containers provoked the release of methyl isocyanate (MIC), which was not only an irritant gas but also lethal. When the safety mechanisms failed, hazardous chemical substances in the gaseous state were released, including at least 27 tonnes of MIC, a highly toxic compound used as precursor in the production of carbaryl insecticide. In this plant. 8,000 people were killed and 500,000 suffered from systemic damage.[1,2] Fig. 1 shows the disaster area.

On this 40th anniversary, it is crucial to remember the devastating consequences of the exposure to toxic substances and the long-term impacts on human health

Figure 1. Union Carbide factory after the Bhopal accident (Credits: Nyča J).

and the environment. The MIC leak left a legacy of diseases, among them chronic respiratory diseases, eye injuries, immune system deficiencies, nerve and neuromuscular damage, and mental health problems persisting nowadays.[4] Behind each statistic, there are histories of pain, struggle and resilience.

The extent of the tragedy was largely due to the lack of efficiency in the safety systems, as well as to the lack of organisation and the neglect evident in the emergency response protocols, despite the high level of toxicity of the compound involved.[5] Although time can blur the memories, the tragedy is still a warning sign of the importance of industrial safety, responsibility and the protection of human rights. The Bhopal disaster epitomises the failure of governments to fulfil their responsibilities of preventing environmental catastrophes, tackling their consequences and stopping continuous environmental pollution.

Bhopal is a grim reminder of the critical need of properly assessing chemical hazards, implementing strict safety measures and enforcing effective emergency protocols in every industrial facility. Likewise, it emphasises the importance of transparency, of a clear risk communication and of the community participation in the management of chemical disasters. It is our responsibility to honour their memory and to heighten public awareness on the risks of negligence and lack of regulation. May the legacy of Bhopal inspire us to fight for a future where tragedies like this one are unthinkable and where justice and compassion prevail over indifference and oblivion.

REFERENCES

1 Teruel Levitski H. Terrorismo químico corporativo: la tragedia de Bhopal o la masacre de los inocentes. Acta Científica de la Sociedad Venezolana de Bioanalistas Españoles. 2005;8(2):89-93.

2 Raina V. Supervivientes del desastre gasístico de Bhopal. Veinticinco años después. Ecología política. 2009;(37):90-94. Available on: https://www.ecologiapolitica.info/wp-content/uploads/2009/06/037_Raina_2009.pdf

3 Nyča J. https://commons.wikimedia.org/wiki/File:Bhopal_Plant_13.JPG. On the site of Bhopal disaster [image]; 2011.

4 Secretariado internacional (Amnistía Internacional). Nubes de injusticia. El desastre de Bhopal 20 años después. London: Editorial de Amnistía Inernacional; 2004 November. 9 p. Resumen del informe de Amnistía Internacional ASA 20/015/2004. Available on: https://www.amnesty.org/es/wp-content/uploads/sites/4/2021/09/asa201042004es.pdf

5 Castro GD. Bhopal, un alerta al uso de sustancias químicas peligrosas en escala industrial. Centro de Investigaciones Toxicológicas, CEITOX (CITEFA-CONICET). N/d. Available on: https://www.carec.com.pe/biblioteca/biblio/4/81/Taller%20Bhopal.pdf

the poison®

2024 | Vol. 1 | No. 2: 39-49

REVIEW

Toxicological Chain of Survival (TCS): An integral approach to the intoxicated patient. Narrative review

Samantha De La Vega González[1]*, Ramsés Dorado García[2], Leslie D. Ramírez Luna[1], María V. Hernández Valencia[1], María E. Vásquez Sánchez[1] and Arlette B. Cardona Barco[1]

[1] Emergency Department, Zone 1 IMSS General Hospital "Dr. Rodolfo Antonio de Mucha Macías", Mexico City, Mexico.
[2] Clinical Toxicology Department, Zone 1 IMSS General Hospital "Dr. Rodolfo Antonio de Mucha Macías", Mexico City, Mexico.
*samovg@gmail.com

Submitted: 24/02/2024 - Accepted: 08/04/2024 - Published: 30/06/2024 - DOI: https://doi.org/10.62129/YCNP7473

Abstract. Intoxications are a frequent cause for consultation and admission in emergency medical services. Treating these patients is a challenge both diagnostically and therapeutically, where some critical circumstances may determine the prognosis. A structured search was conducted in the PubMed/Medline database, for articles discussing how intoxications were handled in emergency medical services published between March 2005 and December 2023. A combination of the following keywords was used to perform the search: "intoxication", "poisoning", "management", "emergency", and "patient". All reviews, clinical trials, observational studies, and case reports related to handling intoxicated patients were considered. Lastly, articles in the authors' databases were included, as well as reference books and gray literature. 42 articles that met the selection criteria were chosen. Upon review of the literature, a Toxicological Chain of Survival (TCS) was devised, a basic diagnostic and therapeutic algorithm that can be useful for the first responder.

Key words: *Intoxication; Poisoning; Management; Antidotes; Antagonists.*

Intoxications are a frequent cause for consultation in emergency medical services. Treating the intoxicated patient is a challenge both diagnostically and therapeutically, this approach is key to determine the prognosis. During 2022, in the United States (USA) alone, 2.064.875 cases of poisoning were reported. In Mexico the annual number is estimated to be around 13.600.[1-5] Mortality rates are varied and they depend on the causative agent, intentionality, age, and comorbidity.[1]

This review includes information regarding general treatment of the poisoned patient; emphasizing on the medical history, physical examination, toxidromes, and both general and specific treatment. A diagnostic and therapeutic algorithm within the framework of the Toxicological Chain of Survival or TCS (Fig. 1) is proposed.

MATERIALS AND METHODS

A structured search was conducted in the PubMed/Medline database, for articles discussing how intoxications were handled in emergency medical services published between March 2005 and December 2023. A combination of the following keywords was used to perform the search: "intoxication", "poisoning", "management", "emergency", and "patient". All reviews, clinical trials, observational studies, and case reports related to handling intoxicated patients were considered. Literature not related to human health, in a language other than English or Spanish, or which did not propose any relevant information for this study, was excluded.

The PubMed/Medline search returned 167 results, 130 f which were excluded and 37 articles meeting the selection criteria were considered. Lastly, 5 articles from the authors' personal databases were included, as well as reference books and gray literature.

DISCUSSION

Medical history

Even when there is only a suspicion that it may be a case

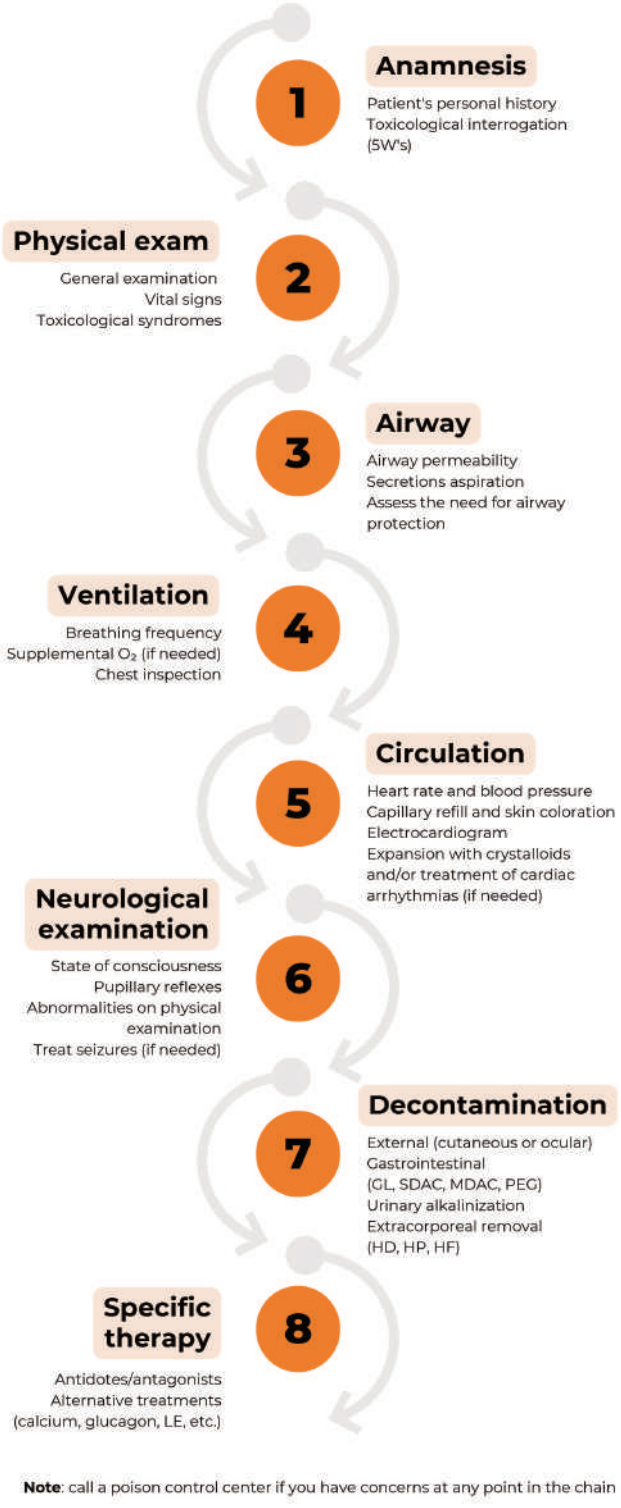


Figure 1. Toxicological Chain of Survival (TCS).

of poisoning, the diagnosis and therapy approaches must be simultaneous, as the patient's prognosis largely depends on these.[2,4] A detailed medical history must be included, where the patient is questioned not only regarding personal background, but also everything related to the intoxication, including motivation (accidental or voluntary), probable causative agents and their format, ingested dose and/or exposure time, as well as signs and symptoms.

The toxicological history can be summarized into five questions known as the "5W", which allow the physician to more easily determine the context of the intoxication (Table 1). When the patient cannot (or will not) cooperate, the person with them can provide valuable information on the medical background of the patient, where they were, which potentially toxic products were in the house, etc. The original package must always be requested (medicine tablets, chemical products, etc.). If unavailable, they must be retrieved from the place where the intoxication took place. This allows medical personnel to perform only the necessary studies.

A directed questioning must be conducted and, should it provide no relevant information, the physician will make use of the physical examination and complementary tests (general and specific) to conclude a suspected diagnosis.

Physical examination

It is vital to perform a comprehensive check of the patient, including a thorough physical examination, monitoring of the vital signs, measuring of pupillary responses, and neurological investigation. Therefore, allowing the physician to identify the commonly named "toxidromes": *sympathomimetic, anticholinergic, cholinergic, sedative-hypnotic, opiate*, *hallucinogenic, neuroleptic malignant*

TABLE 1. The 5Ws of the intoxicated patient's medical history.

Who	Patient's characteristics (sex, age, and personal background)
Whose	Check if the substance belonged to the patient or somebody else, so as to determine if exposure is acute, subacute, acute on chronic or chronic.
What	Determine which substance caused the intoxication, its dosage and format (solid, liquid or gaseous) and exposure route (cutaneous, intraocular, oral, parenteral or other)
When	Ask the date and time of day on which the exposure took place, and/or the last time the patient was acting normally
Why	Ask if the exposure was accidental or voluntary (malicious or suicide attempt)

syndrome, and *serotonin syndrome*. They may not always be present, and they frequently present themselves partially or simultaneously, as with cases of polysubstance use. The main characteristics of each toxidrome are summarized in Table 2.[6]

The inspection of the skin and mucosa is especially relevant in cases involving caustic substances (acid, alkaline and oxidizing substances), which produce chemical burns and hypoxia, such as methemoglobinemia, which causes the skin around the mouth, fingers or on the entire body to acquire a blueish tone due to a change in the way oxygen is transported and utilized. As detailed in Table 2, sweating and dry skin are typical for some intoxications. Lastly, the physical examination may reveal signs of violence (trauma), self-harm and sexual abuse.

Apprehensive patients pose a challenge when conducting a physical examination. Temporary physical restraint may be required to begin the examination, as well as sedation (benzodiazepines is the treatment of choice). It is recommended to approach these patients in a calm environment free of auditory stimulus, especially if the patient is suffering from hallucinations, so as to not trigger them. When dealing with children, the presence of their parents throughout the care process is vital.

Additional medical tests

Additional medical tests, both general (routine laboratory tests, ECG, imaging, among others) and specific (such as blood and urine toxicology screens) to be performed will depend on the nature of the toxic substance and the exposure to it.[1-3] In Table 3, the main toxicology screenings and the biological samples required to test for them are enumerated. A lack of availability of specialized laboratories that perform these screenings may be a limiting factor, but in these cases,

TABLE 2. Toxidromes.

Toxidrome	Clinical characteristics	Xenobiotics
Sympathomimetic	Agitation, mydriasis, tachycardia, high blood pressure, hyperthermia	Amphetamines, cocaine, ephedrine, phenylephrine, pseudoephedrine
Anticholinergic	Mydriasis, dry skin and mucous membranes, tachycardia, urinary retention, ileus, agitation, delusion	Antihistamines, tricyclic antidepressants, atropine, belladona, scopolamine
Cholinergic	Miosis, hypersalivation, bradycardia, bronchospasm, diarrhea, urinary incontinence, fasciculations, convulsions, coma, low blood pressure	Organophosphorus compounds, carbamates, pilocarpine, muscarine
Sedative-hypnotic	Somnolence, ataxia, dysarthria, obnubilation, coma	Benzodiazepines, barbiturates, alcohol, propofol, gamma-hydroxybutyric acid (GHB)
Opiate	Miosis, respiratory depression, bradycardia, constipation, sedation	Heroin, morphine, codeine, oxycodone, methadone, tramadol
Hallucinogenic	Visual and auditory hallucinations, sensory distortion, paranoia, anxiety, psychosis	Lysergic acid diethylamide (LSD), psilocybin, mescaline, N,N-dimethyltryptamine (DMT), phencyclidine (PCP)
Neuroleptic malignant syndrome	Fever, muscle rigidity ("lead pipe"), dysautonomia, delirium (hyperactive or hypoactive), elevated creatine kinase (CPK) levels	Antipsychotics (haloperidol, quetiapine, risperidone, etc.) and antiemetics
Serotonin syndrome	Clonus, agitation, diaphoresis, tremor, mydriasis, tachycardia, diarrhea, hyperthermia, convulsions, hyperreflexia	Antidepressants, tryptophan, amphetamine, cocaine, tramadol, fentanyl, LSD, lithium, mirtazapine, lamotrigine, ondansetron

www.thepoisonjournal.com | Cite as: Poison 2024; 1(2):39-49 | DOI: 10.62129/YCNP7473

it should be ensured that the samples are outsourced to a high complexity center.

The time of collection of the sample is not only relevant for the diagnostic, but also for the treatment. For example, when the presence of acetaminophen is determined, the sample should be collected between 4 to 24 hours after the exposure to be able to plot the results in the Rumack–Matthew nomogram, which will predict the risk of liver toxicity and, therefore, enable the physician to administer its antidote (N-acetylcysteine).

It is also a good practice to request the analysis of beta subunit (beta-hCG) in women of childbearing age, as well as to guarantee the chain of custody in cases where abuse or maliciousness are suspected.

Medical approach

Airway. Advanced airway management may be necessary for respiratory (ventilation/blood gas levels) and/or neurological reasons. For the latter, the Glasgow Coma Scale (GCS) is used, a score ≤ 8 signaling the need to secure the airway by means of intubation.[7] Nevertheless, in cases of poisoning, this procedure (stemming from the recommendations for patients with traumatic brain injury) may be wrong. In 2010, Kapur et al. found that out of all the patients that visited the emergency ward diagnosed with intoxication, 39% suffered inadequate care and up to 58% experienced improper airway management, which led to more adverse results or a worse prognosis.[8] For these reasons, two indications justify securing the airway:

a. Respiratory failure. Described as a failure in ventilation, oxygenation or both.

b. Imminent risk of bronchial aspiration. It may arise due to irregular airway protective reflexes, apnea or rostrocaudal deterioration that alters the breathing pattern.

If these indications are not present, intoxicated patients should not be intubated based solely on the GCS. Many xenobiotics produce alterations of consciousness without warranting advanced airway management. For certain patients, it is expected that once the toxicant has been metabolized, normal brain function is resumed. Conversely, when dealing with patients that sustained trauma, a GCS score ≤ 8 does warrant intubation.[8-10] In most cases, it suffices with keeping the airway clear by suctioning secretions. When the airway needs to be protected, it is important to determine which drugs will be used in the intubation procedure, taking into account the toxicants that caused the intoxication and the drug interaction.[8]

Ventilation. Assisted respiration should be performed with low-flow systems in order to maintain optimal oxygen saturation and arterial blood oxygen tension (PaO_2) levels. Other devices may be necessary in certain cases, such as carbon monoxide (CO) poisoning, where 100% oxygen is provided with a non-rebreather mask. For these cases, high-flow nasal cannula and continuous positive airway pressure (CPAP) have been tested, both being equally effective.[8,11-13] The administration of oxygen as a routine procedure without indications supporting it can also be detrimental in some cases. Such is the case of the herbicide paraquat, whose mechanism of toxicity is the production of oxygen free radicals, and therefore the supply of oxygen (above a certain threshold) may worsen the patient's medical condition by increasing the risk of pulmonary fibrosis.

Blood circulation and cardiotoxicity. In 2003 in the USA, cardiovascular drugs ranked 15th on the list of agents that caused most intoxications, and 5th in causes of death among these patients.[4] Electrocardiographic abnormalities caused by certain xenobiotics can be produced *directly* or *indirectly* by metabolic disorders. This requires different therapeutic approaches depending on the cause of the irregularity.[4,14,15]

TABLE 3. Main toxicology screenings and biological samples required to test for them.

Sample	Toxicology screenings
Urine	Cocaine metabolites, cannabinoids, amphetamines, benzodiazepines, opioids, barbiturates and hydrocarbons; heavy metals (mercury and chromium)
Serum/Plasma	Anticonvulsants (e.g.: diphenylhydantoin, valproic acid, phenobarbital and carbamazepine), tricyclic antidepressants, lithium, iron, methotrexate, alcohols (ethanol, methanol and glycol), salicylates, acetaminophen, butyrylcholinesterase (BuChE) and cyanide
Whole blood	Lead, erythrocyte acetylcholinesterase (AChE), carboxyhemoglobin (COHb), methemoglobin (MetaHb) and sulfhemoglobin (SulfHb)

Many cardiovascular effects are produced by drugs that are not prescribed for cardiopathies.[16-18]

The cardiotoxic mechanism of these drugs may be diverse, so in the interest of simplifying their investigation, they can be divided into 5 groups based on their effect on myocardial action potential: 1) K^{+1} channel blockers, 2) Na^{+1} channel blockers, 3) Na^{+1}/K^{+1}/ATPase pump blockers, 4) Ca^{+2} channel blockers and 5) β-adrenergic blockers. Another classification would be based on the electrocardiographic abnormalities they can cause, the most common being bradyarrhythmias or tachyarrhythmias, QRS complex and QT interval abnormalities, blocks, among others. It is important to mention that certain drugs can belong to more than one group. In Table 4 all the different groups are summarized based on their mechanism on the membrane action potential and electrocardiographic abnormalities.[4,14-19] Different xenobiotics can also cause myocardial ischemia, as detailed in Table 5.[1] QT interval prolongation poses a greater threat to life, since it can trigger lethal ventricular arrhythmias.[16,18,19]

TABLE 4. Main groups of xenobiotics that produce cardiac arrhythmias, their main characteristics and treatment.

Group	Mechanism	Electrocardiographic manifestation	Progression Risk	Treatment	Drugs
K^{+1} channel blockers	Action potential prolongation	Prolonged QT interval >440 ms in men >460 ms in women	Polymorphic ventricular tachycardia	2 - 4 gr Mg^{+2} sulfate bolus	Antihistamines Antipsychotics Chloroquine Cisapride Citalopram Class IA, IC, III antiarrhythmics Tricyclic antidepressants Fluoroquinolones Macrolides Tacrolimus Venlafaxine
Na^{+1} channel blockers	Slower phase 0 of the action potential	Wide QRS complex Nodal rhythm	Asystole Ventricular tachycardia Ventricular fibrillation	Sodium bicarbonate if QRS >100ms, 1 - 2 mEq/kg bolus (keep pH< 7.55)	Amantadine Carbamazepine Chloroquine Class IA, IC antiarrhythmics Citalopram Cocaine Tricyclic antidepressants Diltiazem Diphenhydramine Hydroxychloroquine Propranolol Verapamil
Na^{+1}/K^{+1}/AT Pase pump blockers	Positive inotropic (↑ intracellular Ca+2) ↓ AV conduction	Stimulating activity: supraventricular and ventricular extrasystole, tachyarrhythmia Suppressing activity: sinus bradycardia, bundle branch blocks, AV blocks	Combination of blocks and tachyarrhythmias	Symptomatic arrhythmias: digoxin-specific antibodies AV blocks: atropine; if patient does not respond to atropine: pacemaker	Digitalin and digitalis-derived drugs
Ca^{+2} channel blockers	↓ contractility ↓ conduction ↓ cardiac output	Sinus bradycardia AV Blocks Wide QRS complex	Asystole	Atropine Ca^{+2} gluconate 60 mg/kg/dose	Calcium antagonists
β-adrenergic blockers	β-receptor competitive antagonism: ↓contractility ↓ heart rate ↓ AV conduction	Sinus bradycardia AV blocks	Wide QRS complex (with propranolol a QRS >100ms is associated to a risk of convulsions)	Calcium (1 Ca^{+2} chloride ampoule or 3 Ca^{+2} gluconate ampoules) Glucagon (0.1mg/kg bolus + 0.1mg/k/h infusion) Pacemaker	β-adrenergic blockers

www.thepoisonjournal.com | Cite as: Poison 2024; 1(2):39-49 | DOI: 10.62129/YCNP7473

As detailed in Table 4, treatment will depend on the xenobiotic and the abnormality it produces. Over the past few years, lipid emulsions were used as a last line of treatment for cardiotoxicity. The toxicodynamic mechanism of lipid emulsion includes causing a "lipid sink" that traps lipophilic drugs, the adjustment of the drug tissue distribution, and the interaction with the cell membrane to antagonize toxic results. It is used to treat toxicity by calcium blockers, beta-blockers, cocaine, and tricyclic antidepressants, among others. Its administration is via a lipid emulsion bolus of 1.5ml/kg of weight at 20% followed by a 0.25-0.5 ml/k/min infusion.[15]

Neurological examination. The first approach to an intoxicated patient must include a neurological exam in order to determine the degree to which the central nervous system (CNS) and/or peripheral nervous system (PNS) are affected. This includes, among others, the assessment of the state of consciousness, the pupils, the presence of nystagmus, and the evaluation of osteotendinous reflexes.[20] Imaging, electroencephalograms and other tests may be necessary to complete the examination.

Decontamination procedures. External and/or gastrointestinal (GI) decontamination can prevent absorption and systemic effects produced by different substances.[20] The main route of exposure to toxic substances is oral, which forces all healthcare professionals to be familiar with the indications and contraindications of each emergency treatment.[21]

External decontamination. In cases of external contamination (skin or eyes), the removal of clothing and water wash is recommended. It should last 10-15 minutes, without filling the bathtub as that may cause the toxicant to come in contact with vulnerable areas previously unexposed, such as the eyelids and genitalia. The use of neutralizing solutions (such as acids or alkalis) is contraindicated, as they can produce reactions that may worsen the patient's medical condition.[22-24]

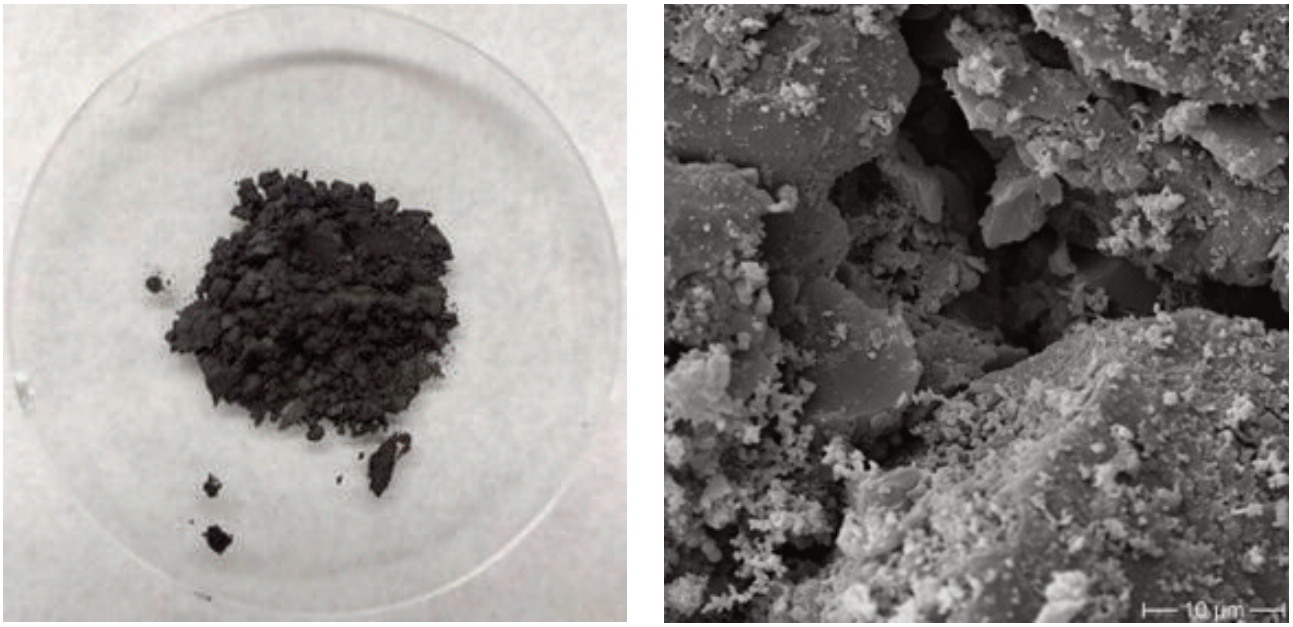
Gastrointestinal decontamination. The aim is to prevent the absorption of any toxins that were ingested by using activated charcoal (AC), gastric lavage (GL), cathartics, and whole bowel irrigation (WBI). As previously mentioned, the patient's state of consciousness must be assessed, given that any alteration may contraindicate using these therapeutic methods unless the airway is protected. This procedure for GI decontamination should only be performed under clinical prescription. Emesis is still indicated for veterinary patients, but contraindicated in humans due to the risk of pulmonary aspiration.[20,21]

a. Gastric lavage. Indications: There is no research backing up the use of GL over AC. Although it is usually performed within the first hour of exposure when the patient has ingested a "potentially lethal" substance, it should not be prescribed as a routine treatment. *Contraindications:* unprotected airway, caustic substances, hydrocarbons and patients with risk of bleeding or perforation (recent surgery, anatomic or pathological abnormality, coagulopathy, etc.). *Technique:* aspirate the GI contents and administer saline. Children 10 ml/kg, adults 150-250 ml per lavage, waiting for 1 minute before aspirating again and repeating the process until the fluid is clear. *Complications:* aspiration pneumonia, laryngospasm, hypoxia, arrhythmia, perforation of the digestive tract and electrolyte imbalance.[25]

b. Single-dose activated charcoal (SDAC). Indications: it is recommended to treat the ingestion of a "potentially toxic" substance within the first hour of exposure in most cases. The mechanism of action of AC is based on its ability to absorb substances on its surface, preventing GI tract absorption. It also prevents circulation of substances with enterohepatic metabolism. Nevertheless, not all substances can be absorbed by AC: e.g., alcohols, metals, hydrocarbons, and caustic substances.[26,27] Fig. 2 shows the macroscopic and microscopic characteristics of the AC.[28,29] *Contraindications:* unprotected airway, caustic substances, hydrocarbons, patients with intestinal obstruction (absolute contraindication) or decreased peristalsis (relative contraindication). *Technique:* AC can be diluted in any liquid (e.g. water, cola, etc.) and administered orally or via a nasogastric tube. It can be mixed with sorbitol (not recommended for children due to the elevated risk of electrolyte imbalance). *Dose:* 0.5-1 g/kg, maximum 25-50 g; teenagers and adults 1g/kg, maximum 100 g. C*omplications:* usually associated with inadequate use or technique of AC administration, tracheal pulmonary aspiration being the most relevant. Nausea and emesis have been reported in some cases after administration, especially when administered with sorbitol.[30,31]

TABLE 5. Substances that can cause myocardial ischemia.

Toxicant
Cocaine
Amphetamine
Nicotine
Carbon monoxide
Antipsychotics
Tricyclic antidepressant



(a) (b)

Figure 2. Activated charcoal. General appearance (a) and view from a scanning electron microscope – SEM (b) (Credits: Aariuser and Mydriasis respectively).

Multidose activated charcoal (MDAC). Indications: potentially lethal doses of carbamazepine, dapsone, quinine, theophylline, caffeine, aspirin, and diphenylhydantoin. Three mechanisms are involved in these cases: interruption of enterohepatic circulation, enabling of transluminal diffusion from the body to the intestinal lumen (gut dialysis), followed by excretion, and decrease of absorption of extended or delayed release drugs. *Contraindications:* similar to SDAC. *Technique:* administered in a similar way to SDAC, but its administration with cathartics like sorbitol is not recommended. *Dose:* there is no optimal dose accepted; generally, the same dose as SDAC is administered every 4 hours. Some treatment regimes suggest administering every 2 hours, but no method has been proven more effective than the other. *Complications:* similar to SDAC. Multidose administration may produce constipation and intestinal obstruction, therefore making frequent checks of the abdominal circumference and peristalsis crucial.[30,32]

c. Cathartics. There are two types of cathartics: saline or osmotic. *Indications:* nowadays they are not recommended, since while they can increase the rate at which the toxic is excreted, they do not prevent its absorption. In cases where its administration is deemed appropriate, it is recommended to use a single dose to prevent complications. The concomitant administration of AC and cathartics is also discouraged. *Contraindications:* patients lacking peristaltic sounds, recent abdominal trauma, intestinal obstruction, intestinal perforation, caustic substances, dehydration, low blood pressure and/or electrolyte imbalance. Cathartics with magnesium are contraindicated in patients suffering from nephropathy or heart block. *Technique:* administered orally or via a nasogastric tube. *Dose:* sorbitol (at 70%): 1-2 ml/kg of bodyweight in a single administration. Used at 35% for children. Magnesium hydroxide: 0.5 to 1 ml/kg/dose. *Complications:* nausea, abdominal pain, emesis, temporary low blood pressure and electrolyte imbalance.[33]

d. Whole bowel irrigation. WBI is the administration of polyethylene glycol (PEG). *Indications:* it should not be performed as a routine procedure; however, it can be adequate when the patient has ingested extended-release drugs, with an enteric coating or that cannot be absorbed by activated charcoal (lithium, potassium, iron), foreign bodies containing lead and body-packers/stuffers. *Contraindications:* ileus, intestinal obstruction, hemodynamic instability or intractable vomiting. *Technique:* with the patient in the semi-Fowler's position, the PEG is administered via a nasogastric tube. *Dose:* children between 9 months to 6 years of age: 500 ml/hr., children between 6-12: 1000 ml/hr. and adults: 1500 to 2000 ml/hr. If the patient develops emesis the administration rate should be decreased 50% for 30-60 minutes and then resumed. The treatment should persist until the effluent is clear. *Complications:* nausea, abdominal pain, emesis, angioedema, and anaphylactoid reaction.[34]

TABLE 6. Main antidotes and antagonists according to the xenobiotic consumed.

Antidote/antagonist	Xenobiotic
Fab fragments	Digitalin and digitalis-derived drugs
Atropine	OPCs (organophosphorus compounds) Carbamates Amitraz Physostigmine Mushrooms (Clitocybe, Inocybe)
Methylene blue	Methemoglobin
Calcium	Calcium blockers β-blockers Magnesium Hydrofluoric acid
D-penicillamine	Copper Lead Mercury
Deferoxamine	Iron
Dimercaprol/BAL (British anti-Lewisite)	Arsenic Lead Mercury Gold
EDTA (Edetate calcium disodium)	Lead
Ethanol	Methanol Glycols
Fomepizole	Methanol Glycols
Flumazenil	Benzodiazepines
Glucagon	β-blockers Calcium blockers Tricyclic antidepressants
Hydroxocobalamin	Cyanide
Sodium hyposulfite	Cyanide
N-acetylcysteine	Acetaminophen
Naloxone	Opioids
Amyl nitrite	Cyanide
Sodium nitrite	Cyanide
L-carnitine	Valproic acid
Leucovorin	Methotrexate
Pyridoxine	Isoniazid
Octreotide	Sulfonylurea
Vitamin K_1	Warfarin Superwarfarins

Enhanced elimination. *Alkalinization of urine. Mechanism of action and indications:* the creation of "ion traps", which based on the capacity of ionizing that some toxins have, helps prevent renal reabsorption which in turn eases their excretion. However, this process is more effective with certain substances such as weak acids, which are excreted faster with an alkaline pH (7.50). Salicylates are a classic example.[14,15] It is also used to treat long-acting barbiturate poisoning and methotrexate poisoning to prevent nephrotoxicity. *Precautions:* when this procedure is used, serum sodium levels must be closely monitored, with a maximum limit of 155 mEq/L, as well as serum pH to prevent alkalemia by exceeding a pH of 7.55. Likewise, serum potassium levels must be carefully observed, as there is a risk of hypokalemia.[35,36] *Dose:* the recommended dose of sodium bicarbonate for this procedure is a 1-2 mEq/kg of bodyweight bolus, followed by a 100-150 mEq infusion of sodium bicarbonate in a dextrose solution at 5%. The rate of infusion must be titrated until a urinary pH of 7.5-8 (monitoring every 6 hours) is reached, controlling serum pH and potassium levels.[36]

Extracorporeal techniques. In order to successfully eliminate a xenobiotic with extracorporeal therapy, certain quantities of it must be present in the interstitial fluid. To measure this, the volume of distribution (VD) is used: xenobiotics with a VD of less than 1-1.5 l/kg can be successfully eliminated with extracorporeal procedures, whereas if the VD is more than that, the efficacy of the treatment will be impaired. The plasma protein binding percentage also plays a significant role: if it is higher than 80% the therapeutic effect will be unsatisfactory.[37-39]

The best-known extracorporeal technique is hemodialysis (HD). Nevertheless, there are other procedures; for example, continuous renal replacement therapy, hemofiltration (HF), hemoperfusion (HP) and therapeutic plasma exchange.[37-39] The most common intoxications that respond well to extracorporeal therapy are those caused by salicylates, barbiturates, carbamazepine, lithium, metformin, phenytoin, thallium, theophylline, valproic acid and some toxic alcohols.[37,40] An accessible source of indications for these treatments are the recommendations of The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP), which can be found online.

Specific therapy. It pertains to those drugs that can counteract the effect of a toxin by bonding directly to it (antidotes) or by interacting with the receptors that the xenobiotic would bind to (and preventing said binding), or producing an effect opposed to the effect the toxin has (antagonist). Despite there being comprehensive lists of both antidotes and antagonists, their practical use is rather limited due to several reasons: lack of availability, contraindications, and their adverse effects. Nowadays, only few antidotes and antagonists are deemed useful in clinical practice, detailed below (Table 6).[41,42]

CONCLUSIONS

The approach of a poisoned patient poses a challenge regarding diagnosis and treatment, both to the general physician and the specialist. The TCS proposes a systematic sequence of steps that allow for an organized medical approach, prioritizing the safety of the patient. It is important to highlight that many procedures that used to be performed in clinical practice are nowadays found to lack supporting evidence and their routine use is discouraged. While possible, it is best to seek advice from a toxicology specialist in order to complement the poisoned patient's care.

Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES

1 Dorado García R, Soto Estrada M, & Ontiveros Holguín A. (2022). 10 Errores Graves en el Manejo del Paciente Intoxicado. *10 Errores en el Manejo del Paciente Intoxicado*, 1–7. Available from: https://doi.org/10.58281/ccme22191103
2 Thompson TM, Theobald J, Lu J, Erickson TB. The general approach to the poisoned patient. Dis Mon. 2014;60(11):509–24. Available from: http://dx.doi.org/10.1016/j.disamonth.2014.10.002
3 Erickson TB, Thompson TM, Lu JJ. The approach to the patient with an unknown overdose. Emerg Med Clin North Am. 2007;25(2):249–81; abstract vii. Available from: http://dx.doi.org/10.1016/j.emc.2007.02.004
4 Holstege CP, Eldridge DL, Rowden AK. ECG manifestations: the poisoned patient. Emerg Med Clin North Am. 2006;24(1):159–77, vii. Available from: http://dx.doi.org/10.1016/j.emc.2005.08.012
5 Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Rivers LJ, Feldman R, et al. 2022 annual report of the

national poison data system® (NPDS) from America's poison centers®: 40th annual report. Clin Toxicol (Phila). 2023;61(10):717–939. Available from: http://dx.doi.org/10.1080/15563650.2023.2268981

6 Holstege CP, Borek HA. Toxidromes. Crit Care Clin. 2012;28(4):479–98. Available from: http://dx.doi.org/10.1016/j.ccc.2012.07.008

7 Almarales JR, Saavedra MÁ, Salcedo Ó, Romano DW, Morales JF, Quijano CA, et al. Inducción de secuencia rápida para intubación orotraqueal en Urgencias. Rev Repert Med Cir. 2016;25(4):210–8. Available from: http://dx.doi.org/10.1016/j.reper.2016.11.009

8 Kapur N, Clements C, Bateman N, Foëx B, Mackway-Jones K, Hawton K, et al. Self-poisoning suicide deaths in England: could improved medical management contribute to suicide prevention? QJM. 2010;103(10):765–75. Available from: http://dx.doi.org/10.1093/qjmed/hcq128.

9 Burket GA, Horowitz BZ, Hendrickson RG, Beauchamp GA. Endotracheal intubation in the pharmaceutical-poisoned patient: A narrative review of the literature. J Med Toxicol. 2021;17(1):61–9. Available from: https://doi.org/10.1007/s13181-020-00779-3

10 Pellatt RA, Isoardi K, Keijzers G. Intubation for patients with overdose: Time to move on from the Glasgow Coma Scale. Emerg Med Australas. 2023;35(4):702–5. Available from: http://dx.doi.org/10.1111/1742-6723.14254.

11 Duncan R, Thakore S. Decreased Glasgow Coma Scale Score Does Not Mandate Endotracheal Intubation in the Emergency Department. J Emerg Med. 2009 Nov;37(4):451-5. Available from: https://doi.org/10.1016/j.jemermed.2008.11.026

12 Turgut K, Yavuz E. Comparison of non-invasive CPAP with mask use in carbon monoxide poisoning. Am J Emerg Med. 2020;38(7):1454–7. Available from: http://dx.doi.org/10.1016/j.ajem.2020.04.050.

13 Yesiloglu O, Gulen M, Satar S, Avci A, Acehan S, Akoglu H. Treatment of carbon monoxide poisoning: high-flow nasal cannula versus non-rebreather face mask. Clin Toxicol (Phila). 2021;59(5):386–91. Available from: http://dx.doi.org/10.1080/15563650.2020.1817477.

14 Menke NB, Walsh SJ, King AM. Cardiotoxicodinámica: Toxicidad de los xenobióticos cardiovasculares. Emerg Med Clin North Am. 2015;33(3):563–95. Available from: http://dx.doi.org/10.1016/j.emc.2015.04.007

15 Gunja N, Graudins A. Management of cardiac arrest following poisoning: Management of toxic cardiac arrest. Emerg Med Australas. 2011;23(1):16–22. Available from: https://doi.org/10.1111/j.1742-6723.2010.01369.x

16 Raj SR, Stein CM, Saavedra PJ, Roden DM. Efectos cardiovasculares de los fármacos no cardiovasculares. Circulación. 2009;120(12):1123–32. Available from: http://dx.doi.org/10.1161/CIRCULATIONAHA.107.728576.

17 Bradberry SM, Thanacoody HKR, Watt BE, Thomas SHL, Vale JA. Management of the cardiovascular complications of tricyclic antidepressant poisoning : role of sodium bicarbonate. Toxicol Rev. 2005;24(3):195–204. Available from: http://dx.doi.org/10.2165/00139709-200524030-00012.

18 Thanacoody HKR, Thomas SHL. Intoxicación por antidepresivos tricíclicos: toxicidad cardiovascular. Toxicol Rev. 2005;24(3):205–14. Available from: http://dx.doi.org/10.2165/00139709-200524030-000134

19 Tan HH, Hoppe J, Heard K. Una revisión sistemática de los efectos cardiovasculares después de una sobredosis de medicamentos antipsicóticos atípicos. Am J Emerg Med. 2009;27(5):607–16. Available from: http://dx.doi.org/10.1016/j.ajem.2008.04.020

20 Parris MA, Calello DP. Found down: Approach to the patient with an unknown poisoning. Emerg Med Clin North Am. 2022;40(2):193–222. Available from: http://dx.doi.org/10.1016/j.emc.2022.01.011.

21 Ornillo C, Harbord N. Fundaments of toxicology-approach to the poisoned patient. Adv Chronic Kidney Dis. 2020;27(1):5–10. Available from: http://dx.doi.org/10.1053/j.ackd.2019.12.001

22 Chiang C, Kashetsky N, Feschuk A, Burli A, Law RM, Maibach HI. Efficacy of water-only or soap and water skin decontamination of chemical warfare agents or simulants using in vitro human models: A systematic review. *J Appl Toxicol*. 2022;42(6):930-941. Available from: https://doi.org/10.1002/jat.4251

23 Zhu H, Jung EC, Phuong C, Hui X, Maibach H. Effects of soap-water wash on human epidermal penetration [published correction appears in J Appl Toxicol. 2016 Nov;36(11):1526]. *J Appl Toxicol*. 2016;36(8):997-1002. Available from: https://doi.org/10.1002/jat.3258

24 Procopio GL, Patel R, Gupta A. Clinical Pearls in Medical Toxicology: Updates Ranging From Decontamination to Elimination. *J Pharm Pract*. 2019;32(3):339-346. Available from: https://doi.org/10.1177/0897190019854565

25 Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman A, Höjer J, et al. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140–6. Available from: http://dx.doi.org/10.3109/15563650.2013.770154

26 Zellner T, Prasa D, Färber E, Hoffmann-Walbeck P, Genser D, Eyer F. The use of activated charcoal to treat intoxications. Dtsch Arztebl Int. 2019;116(18):311–7. Available from: http://dx.doi.org/10.3238/arztebl.2019.0311

27 Hoegberg LCG, Shepherd G, Wood DM, Johnson J, Hoffman RS, Caravati EM, et al. Systematic review on the use of activated charcoal for gastrointestinal decontamination following acute oral overdose. Clin Toxicol (Phila). 2021;59(12):1196–227. Available from: http://dx.doi.org/10.1080/15563650.2021.1961144.

28 File:Activated carbon A.jpg [Internet]. Wikimedia.org. Available from:

https://commons.wikimedia.org/wiki/File:Activated_carbon_A.jpg

29 Wikipedia contributors. Archivo:Activated Charcoal.jpg [Internet]. Wikipedia, The Free Encyclopedia. Available from: https://es.m.wikipedia.org/wiki/Archivo:Activated_Charcoal.jpg

30 Juurlink DN. Activated charcoal for acute overdose: a reappraisal. Br J Clin Pharmacol. 2015 Nov 9;81(3):482-7. Available from: https://doi.org/10.1111/bcp.12793

31 American Academy of Clinical Toxico, European Association of Poisons Cen. Position paper: Single-dose activated charcoal. Clin Toxicol (Phila). 2005;43(2):61–87. Available from: http://dx.doi.org/10.1081/clt-51867

32 American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. J Toxicol Clin Toxicol. 1999;37(6):731–51. Available from: http://dx.doi.org/10.1081/clt-100102451

33 Position statement: Cathartics: American academy of clinical toxicology; European association of poisons centres and clinical toxicologists. J Toxicol Clin Toxicol. 1997;35(7):743–52. Available from: http://dx.doi.org/10.3109/15563659709162570

34 Thanacoody R, Caravati EM, Troutman B, Höjer J, Benson B, Hoppu K, et al. Position paper update: Whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila). 2015;53(1):5–12. Available from: http://dx.doi.org/10.3109/15563650.2014.989326

35 Mégarbane B, Oberlin M, Alvarez J-C, Balen F, Beaune S, Bédry R, et al. Management of pharmaceutical and recreational drug poisoning. Ann Intensive Care. 2020;10(1):157. Available from: http://dx.doi.org/10.1186/s13613-020-00762-9

36 Boyer EW, Weibrecht KW. Salicylate (aspirin) poisoning in adults. In: Traub SJ, editor. UpToDate. Waltham: UpToDate; 2017

37 King JD, Kern MH, Jaar BG. Eliminación extracorpórea de venenos y toxinas. Clin J Am Soc Nephrol. 2019;14(9):1408–15. Available from: http://dx.doi.org/10.2215/CJN.02560319.

38 Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Uso de tratamientos extracorpóreos en el manejo de las intoxicaciones. Riñón Int. 2018;94(4):682–8. Available from: http://dx.doi.org/10.1016/j.kint.2018.03.026.

39 Jha VK, Padmaprakash KV. Extracorporeal treatment in the management of acute poisoning: What an intensivist should know? Indian J Crit Care Med. 2018;22(12):862–9. Available from: http://dx.doi.org/10.4103/ijccm.IJCCM_425_18

40 RECOMMENDATIONS [Internet]. extrip-workgroup. [cited 2024-03-25]. Available from: https://www.extrip-workgroup.org/recommendations

41 de Farmacia S. Guía de administración de Antídotos y Antagonistas [Internet]. [cited 2024-10-2023]. Available from: www.chospab.es.

42 Kaiser SK, Dart RC. The roles of antidotes in emergency situations. Emerg Med Clin North Am. 2022;40(2):381–94. Available from: http://dx.doi.org/10.1016/j.emc.2022.01.008.

the poison®

REVIEW

Poisoning due to ornamental plants belonging to the *Araceae* family: Review of botanical and toxicological aspects relevant for clinical practice

Ignacio M. Gallo* and Ana M. Caresana

Chair of Drug Toxicology, School of Exact and Natural Sciences, University of Morón, Buenos Aires, Argentina.
Centre for Scientific Research and Experiential Learning, University of Morón, Buenos Aires, Argentina.
**ignaciogallo@yahoo.com.ar*

Submitted: 15/04/2024 - Accepted: 19/05/2024 - Published: 30/06/2024 - DOI: https://doi.org/10.62129/NVKD2964

Abstract. Some genera of the *Araceae* botanical family used with ornamental purposes at home pose a risk to human beings and animals; therefore accidental or voluntary exposure becomes one of the most frequent causes of household poisoning, particularly among children. It is important to highlight that only a low percentage of those patients poisoned by these plants are accurately diagnosed. This is due to the following reasons: the difficulty establishing an early diagnosis due to the enormous diversity of species and the lack of botanical knowledge leading to difficulties identifying the plant, as well as its toxic potential. Therefore, the administration of a specific treatment is delayed. This evinces the multidisciplinary character of toxicology, which requires sciences such as anthropology, botany, agronomy, ethnobotany, mycology, chemistry, etc. to identify the material concerned, as well as its active principles and main uses. The aim of this article is to highlight those botanical, biochemical and medical aspects that are relevant to understand the mechanisms through which these vegetable substances may cause harm.

Key words: *Poisoning; Toxic plants; Araceae; Ethnobotany; Ornamental plants.*

Araceae constitute a cosmopolitan family with more than 3300 species of tropical origin in South America, even in Argentina, many of which are toxic or medicinal. This family encompasses specimens such as *Dieffenbachia*, *Philodendron*, *Caladium*, *Epipremnum*, *Colocasia*, *Monstera*, *Zantedeschia*, *Alocasia*, etc. (Fig.1).[1] Their good adaptation to indoor environments makes them suitable for their use as ornamental plants in gardens and homes in almost all cities.[2] Given the exuberance of their foliage and the colourful notes of their inflorescences, together with the high distribution of these species and the fact of being within children and pets' reach, poisonings by plants (phyto-poisonings) represent a frequent reason for toxicological consultation.

The most significant aspects to be considered in poisonings due to *Araceae*, as well as their diagnosis and treatment are described below.

MATERIALS AND METHODS

A bibliographic search was carried out in specialized literature in the botanical and toxicological field. Additionally, stems from adult plants of the genus *Philodendron* (grown under controlled greenhouse conditions) were selected. For fresh observation, the "tissue scraping" or "tissue imprint" method was used. This procedure consists of collecting superficial cells from plant tissue, which allows their immediate analysis under the microscope without the need for fixation or dehydration. Transverse and longitudinal cuts were made in the middle region of the stems to ensure the uniformity of the samples. Using a sterile slide, the surface of the plant tissue was gently scraped, causing the detached cells to adhere to the slide. Subsequently, a coverslip was placed over the sample to flatten the cells and facilitate their microscopic observation.

Figure 1. Some genera of the *Araceae* family. A. *Epipremnum* (Potos). B. *Syngonium* (Arrowhead plant). C-D. *Philodendron* (horsehead philodendron). E. *Zantedeschia* (Calla) (Credits: author's own).

Observation of the samples was performed immediately under the microscope, starting with low-power objectives and progressing to higher magnifications as necessary. This method is quick and simple, eliminating the need for long preparation processes and without requiring complex equipment or special reagents. However, limitations of the method include obtaining cells only from the surface of the tissue, which may not fully reflect the internal state of the tissue. Furthermore, the quality of the sample may vary depending on the technique used and the homogeneity of the tissue. Despite these limitations, the method is particularly useful for preliminary studies and for the observation of superficial cellular structures, such as calcium oxalate crystals present in the epidermis of plant tissues.

THE *ARACEAE* FAMILY

General characteristics

Table 1 describes the scientific and vulgar names, ethnobotany, active principles and post-exposure symptoms of the most important plants of the *Araceae* family from a toxicological point of view.

www.thepoisonjournal.com | Cite as: Poison 2024; 1(2):50-56 | DOI: 10.62129/NVKD2964

TABLE 1. Characteristics of the main species of clinical relevance.

Scientific name	Vulgar name	Ethnobotany	Active principle	Symptoms
Monstera deliciosa (Liebm.)	Swiss cheese, Adam's rib	Fruit (ripe) Leaves (wound healing ointments)	CaC_2O_4 Raphides (calcium oxalate)	Irritation of oral mucosa and gastrointestinal (GI) tract, vomiting
Dieffenbachia seguine (Jacq.)	Dieffenbachia, Leopard lily, Dumb cane	Ornamental	Raphides (calcium oxalate) Cyanogenic glycosides $C_4H_8N_2O_3$ (L-asparagine)	Intracellular crystals may cause mouth blisters and edema The eye condition includes crystalline lens damage Possible heart problems
Epipremnum pinnatum (L.)	Potos, Pothos, Devil's ivy	Ornamental	CaC_2O_4 crystals (calcium oxalate) Present in all the plant, particularly in the leaves	Ingestion: GI mucosa irritation, vomiting, diarrhoea Contact dermatitis
Zantedeschia aethiopica (L.)	Calla lily, Arum lily	Ornamental	Raphides (calcium oxalate) Cyanogenic heterosides Saponins Alkaloids	Local signs: skin,lips, mouth mucosa irritation General symptoms: vomiting, diarrhoea, mydriasis, drowsiness, coma and death
Colocasia esculenta (L.)	Elephant's ear, Taro	Rhizomes, petioles and inflorescences are consumed. Its tubers feature a high content of carbohydrates (flour) Folk medicine: treatment for abscesses, snakebitesand insect bites	CaC_2O_4 Raphides (calcium oxalate)	Serious irritation of oral and oesophageal mucosa caused by calcium oxalate crystals
Alocasia macrorrhizos (L.)	Giant elephant's ear	Ornamental Rhizomes are consumed in the Indo-Pacific region Starch-rich stem and leaves rich in minerals and vitamins A and C	CaC_2O_4 Raphides (calcium oxalate). Insoluble in water, distributed all over the plant L-asparagine	By ingestion, burning lips and mouth, glottis edema Less frequent: dysphonia and dysphagia, nausea and vomiting

Medicinal uses

In Southeast Asia, as well as in South America, *Araceae* are used for medicinal purposes. There are records of their use in propitiatory rites in the Amazon region. Contraceptive properties are often attributed to them. In the case of *Dieffenbachia* in particular, multiple medicinal uses encompassing the treatment of various diseases and conditions, such as gout, impotence, frigidity and hydropsy, among others, have been recorded. In the region of Guyana, specifically, the extract obtained from the stalks of this plant have traditionally been prescribed as part of the treatment for cutaneous leishmaniasis.[3]

Calcium oxalate crystals

The synthesis and accumulation of $Ca_2C_2O_4$ (calcium oxalate) crystals is common among some plants and is related to a biomineralization process. These crystals formed in the cytoplasm and which remain bound by a mucilaginous substance in a structure called *idioblast* (Fig. 2) may form raphides: needle-shaped crystals occurring in clusters within a cell; druses: aggregates of spherical crystals; styloids: elongated crystals with pointed or rough ends; prisms or rhombus: isolated or in groups by cell; and crystal sand: a mass of microscopic crystals.[4] In all the cases their role seems to be the elimination of excess calcium and the regulation of acidity in the cell.[5] Nevertheless, this does not seem to be their only role, since they also contribute to the way in which the plant absorbs sunlight and constitute a mechanism of defence against the threat posed by animals.

Toxicity

It is relevant to examine here the concepts of toxicity and toxic plant. As we know, a toxin is any substance that once introduced in a living organism is able to cause damage by altering its physiology, either perceptibly or not.[6] Plants can produce harm in humans, in cattle, in domestic or laboratory animals and/or in wild animals.[7] In Argentina there are few statistical records of poisoning by plants and all of them (about 0.1 to 1.3% of all toxicological consultations) generally underestimate the real number of poisoning cases.[8]

In the specific case of the genera of this family, calcium oxalate crystals act as needles, puncturing and injuring the tissues.[9] The concomitant release of vasodilator agents leads to a fast inflammatory reaction, characterised mainly by injuries:

- Mechanical in the digestive system: severe pain in the mouth and oropharyngeal region, open mouth and salivation which might be intense, congestive oral mucosa with areas of localised or generalised edema reaching the glottis, dysphagia, uneasiness, alterations in vocalisation; esophagitis, gastritis and enteritis if some sections of the plants were ingested;
- Inflammatory: some genera also have proteolytic enzymes (trypsin) featuring proinflammatory activity;
- In the skin and related structures: swollen lips, palpebral swelling, angioedema;
- In the respiratory system; larynx edema, dyspnoea;
- Eye injuries (exposure to sap): chemical conjunctivitis, corneal abrasion and, very seldom, permanent corneal opacifications.[10]

In general, chewing just one leave or any other part of the plant causes significant lesions in the mouth area, characterised by severe oropharyngeal irritation with sialorrhea which, in the most severe cases, may be followed by glottis edema, choking, dysphagia and even shock. If the plant or its content is ingested it may cause nausea, vomiting and diarrhoea. The most severe poisonings may cause peripheral paraesthesia, drowsiness, heart disturbances, hypocalcemia, renal failure, seizures, coma and death.[11, 12]

Damage mechanism

As mentioned above and according to the description in specialised literature, oxalic acid, its solutions or its alkaline salts such as CaC_2O_4, in fact widely present in this plant family, are caustic and highly irritating. Once they are in circulation they continue with kidney damage. They also produce effects on the nervous system. Alkaline oxalates, such as that of calcium, cause a rhythmical contraction of striated musculature isolated as a result of the Ca^{2+} ion sequestration from circulation, thus also depriving the blood of an essential element for coagulation and making it incoagulable.[13]

This highly irritating action may be due to the mechanical effect of calcium oxalate crystals, or in some cases to the free oxalic acid, present in the plant, as well as to the proteolytic activity added to histamine-like substances (similar to bradykinin). Furthermore, the acid absorbed when combined with calcium may precipitate forming insoluble salts and causing severe kidney and liver damage.[14]

www.thepoisonjournal.com | Cite as: Poison 2024; 1(2):50-56 | DOI: 10.62129/NVKD2964

Treatment of poisonings

After inadvertently ingesting or being exposed to this kind of plants, intense pain and irritation may appear in the oral cavity due to the mechanical action of their crystals, but they seldom cause systemic effects. Rinsing the mouth immediately is recommended to eliminate any plant residue. In the case of children, symptomatic treatment is also important by applying ice in the affected area to relieve pain and edema in the mildest cases. Oral pain relievers may be necessary in some cases. However, special attention should be given to the evolution of more serious symptoms, such as swelling or larynx oedema, which may require additional medical interventions.[15-19]

Due to the high release of histamine and inflammatory prostaglandins, antagonists of these mediators may be

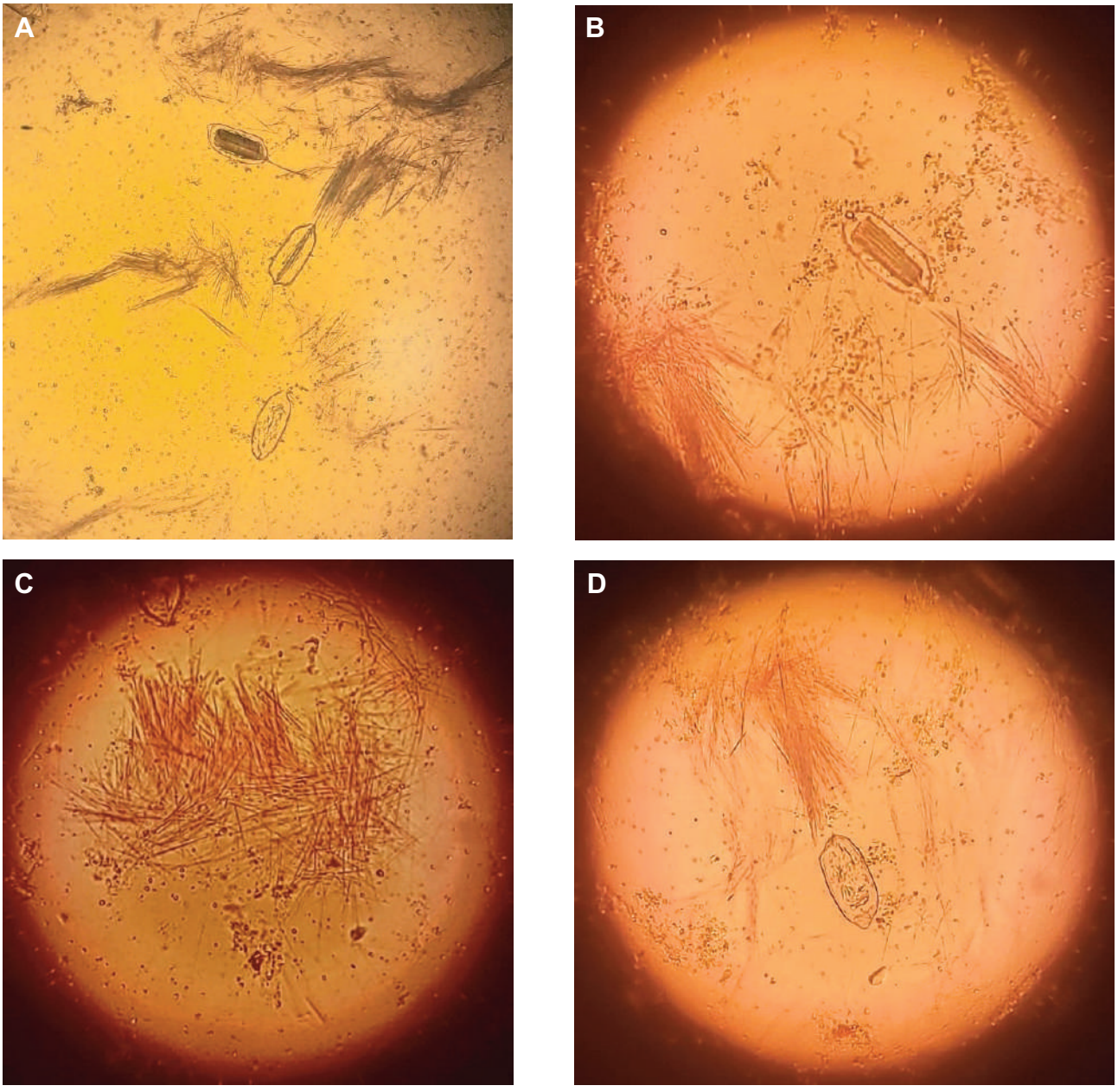


Figure 2. Crystallography. Microscopic observation (40X) of acicular crystals of calcium oxalate. Sample obtained from plant material (stalks from *Philodendron* genus), using the technique suggested by Fabré-Truhaut. A-B. Idioblasts with CaC_2O_4 crystals being released. C. Field covered by calcium oxalate crystals (raphides). D. Empty idioblast, after releasing the crystals contained inside it (Credits: author's own).

efficient at the beginning of the treatment. In particular, antihistamines are the most used. Pain relievers, parenteral opioids, corticosteroids and protection of the airways may be recommended.[20] Edema and pain usually start to decrease after 4-8 days.

In the case of eye exposure, eyes must be decontaminated by removing contact lenses and rinsing them thoroughly with saline 0.9% or water at room temperature for at least 15 minutes. Likewise, in order to clean the exposed skin, clothes and accessories should be removed, and the affected areas should be washed with abundant soap and water for 15 minutes, avoiding skin damage.[15]

Routine laboratory tests are not required. Nevertheless, in more critical situations a urine test is recommended to assess the presence of crystals in the urine, as well as to evaluate kidney function by the determination of the levels of serum urea and creatinine.[15]

DISCUSSION

The most common poisonings with plants from the *Araceae* family highlight the significance of botanical knowledge in the diagnosis and management of these cases. The difficulty in the precise identification of plant species may contribute to the lack of records of medical consultations related to poisonings by these plants. Their complex morphology and the variability in the toxicity of different species within that family emphasise the need of a close collaboration between botanists, toxicologists and healthcare providers to tackle these cases efficiently. Given the diversity of toxic compounds present in the plants, it is essential to have vast experience and specific knowledge of phytochemistry to diagnose and treat correctly those poisonings by plants. Failing to recognize the poisonings caused by specimens of this botanical family or underestimating their seriousness may have significant clinical consequences, thus the need of greater awareness and training in this field.

CONCLUSIONS

Although many plants in this family contain toxic compounds, not all of them pose a significant risk to human health due to the low chances of ingestion or contact. Therefore, it is essential to assess not only the intrinsic toxicity of the plants but also the incidence and the circumstances in which the poisonings occur. Furthermore, the relevance of the precise identification of the species of plants involved in the poisoning cases is highlighted, since different species within the *Araceae* family may have different toxicity profiles. This aspect emphasises the need of a multidisciplinary approach to guarantee a precise diagnosis and treatment for the poisonings by plants of this family.

Declaration of interest
The authors declare no conflicts of interest.

REFERENCES

1 Cabrera AL, Zuloaga FO. Araceae. En: Zuloaga FO, Belgrano MJ, Anton AM, editora(es). Flora Argentina: Flora Vascular de la República Argentina. Volumen 2. Córdoba: Instituto Multidisciplinario de Biología Vegetal (IMBIV), CONICET-UNC; 2023. p. 123-150.
2 Carretero EM, Martínez Ríos MB. Ecología Urbana. Plantas ornamentales tóxicas de Mendoza y San Juan. Guaymallén: Inca Editorial; 2018.
3 Bruneton J. Plantas Tóxicas. Vegetales peligrosos para el hombre y los animales. Zaragoza: Acribia, S.A.; 2001.
4 Galicia S, Velázquez O, Luna Monterrojo V, Vovides AP. Cristales de oxalato de calcio en plantas: morfología y función [Internet]; [cited 2024 May 4]. Available from: https://www.inecol.mx/inecol/index.php/es/ct-menu-item-25/ct-menu-item-27/17-ciencia-hoy/2092-cristales-de-oxalato-de-calcio-en-plantas-morfologia-y-funcion
5 Valla JJ. Botánica. Morfología de las plantas superiores. Buenos Aires: Hemisferio Sur; 2020.
6 Pérez Cuadra V. ¿Qué sabemos sobre las plantas "peligrosas" que conviven con nuestros niños? Rev Electron Sobre Ext Univ Fac Periodis Comun Soc UNLP. 2010;(2).
7 Herrera VF, Cano AN, Suárez ME. Etnobotánica de plantas tóxicas en el Partido de Vicente López (Buenos Aires, Argentina). Bonplandia. 2021;31(1):5-26.
8 Pérez Cuadra V. Plantas Medicinales y Ornamentales Tóxicas. Rev Asoc Medica Bahia Blanca. 2010; 20 (3).
9 Zeinsteger P. Abordaje terapéutico de las intoxicaciones en pequeños animales. Multimédica Ediciones Veterinarias; 2019.
10 Goldfrank's Toxicologic Emergencies. Eds. Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR. 11th ed. New York: McGraw-Hill Education; 2019.
11 Paccor AD. Plantas y malezas de la vía pública. El peligro a la vuelta de la esquina. Buenos Aires: Cátedra de Toxicología. Facultad de Medicina. Universidad de Buenos Aires; 2020. Apunte Carrera Médico Especialista en Toxicología.
12 Nogué Xarau S, Sanz Gallén P, Blanché Vergés C. El

médico en las situaciones urgentes. Intoxicaciones por plantas (I). Medicina Integral. 2000; 36 (10).

13 Fabré R, Truhaut R. Tratado de Toxicología. Vol. 2, Madrid: Paraninfo; 1977.

14 Laborde A, Pronczuk J. Plantas silvestres y de cultivo. Riesgo de intoxicación para el hombre. Div Publicaciones Ediciones Univ Republica. 1987.

15 Micromedex®. Drug Information [Internet database]. Greenwood Village (CO): Truven Health Analytics; 2017. Volume 172.

16 Curci OH. Toxicología. Buenos Aires: La Prensa Médica; 2005. Intoxicaciones por venenos de plantas; p. 299-305.

17 Mutti O. Intoxicaciones más frecuentes en pediatría. Buenos Aires: Héctor Macchi; 1992. Toxicología Vegetal; p. 217-23.

18 Dreisbach RH, Robertson WO. Manual de toxicología clínica: prevención, diagnóstico y tratamiento. 6a ed. México, DF: El Manual Moderno; 1988. Plantas; p. 446-58.

19 Crapanzano GA, Greco V, Talamoni MA. Guía de diagnóstico y tratamiento en toxicología. Buenos Aires: Eudeba; 2014. Plantas; p. 263-80.

20 Mutti OA. Intoxicación por plantas de la Medicina Popular. Enfoque multidisciplinario. Boletin Farmacoter Toxicol. 2002;9:16-22.

the poison®

2024 | Vol. 1 | No. 2: 57-61

CASE REPORT

Phenytoin-induced toxic epidermal necrolysis (TEN). Combined treatment with steroids and human intravenous immunoglobulin: Case report

María L. Melina[1]*, Antonella Milano Gil[1] and Patricia C. Docampo[2]

[1] Central Aeronautical Hospital, City of Buenos Aires, Argentina.
[2] National Poison Center (CNI) - Prof. Alejandro Posadas National Hospital, El Palomar, Buenos Aires, Argentina.
*laumelina@yahoo.com.ar

Submitted: 24/03/2024 - Accepted: 21/04/2024 - Published: 30/06/2024 - DOI: https://doi.org/10.62129/NBIK1402

ABSTRACT

Background. Toxic epidermal necrolysis (TEN) is a severe systemic disease that affects the skin and mucosa, with a mortality rate above 30%. Pharmaceutical drugs are the main causal agents of this reaction, with most cases being largely associated with phenytoin. There is no generally accepted treatment for TEN. The administration of systemic corticosteroids combined with human intravenous immunoglobulin (IVIG) may be a possible adjuvant therapy.

Case presentation. A 72-year-old patient who received phenytoin for four weeks as a prophylactic treatment after undergoing surgery to drain a chronic subdural hematoma developed TEN-compatible symptoms, which prompted treatment with methylprednisolone (1 g/day for 3 days) combined with IVIG (0.5 gr/kg/day for 5 days), with favorable response.

Conclusion. Our patient's response to the combination of corticosteroids and IVIG was favorable. However, due to the nature of this report, the function this combination of drugs has must be further researched.

Key words: *Toxic epidermal necrolysis; TEN; Toxicodermy; Phenytoin; Immunoglobulin.*

Toxic epidermal necrolysis (TEN) is a severe systemic disease that affects the skin and mucosa, with a mortality rate above 30%.[1] Its main symptoms are extended necrosis and epidermal detachment. Together with Stevens-Johnson syndrome (SJS) it forms a spectrum of disease, on which each case is classified according to the percentage of detached skin: <10% SJS, 10-30% SJS/TEN concurrence, and >30% TEN.

The exact mechanism of toxic epidermal necrolysis is unknown; however, one theory suggests that abnormalities in some patients' drug metabolism (e.g.: the lack of elimination of reactive metabolites) causes a T-cell-mediated cytotoxic reaction against keratinocyte-presented drug antigens. CD8+ T cells have been identified as a key agent in the formation of blisters.[2]

Pharmaceutical drugs are the main causal agents of this reaction,[2-5] with TEN being largely associated with phenytoin.[6] There is no generally accepted adjuvant pharmaceutical treatment for this disease, but various immunosuppressive or immunomodulating agents have been used to treat TEN based on varying levels of empirical evidence, such as systemic corticosteroids, intravenous immunoglobulin (IVIG),[7] ciclosporin,[8] plasmapheresis,[9] and anti-tumor necrosis factor (TNF).[10]

The case of a patient suffering from secondary TEN after being treated with phenytoin is presented. Her response was favorable after treatment with systemic corticosteroids and IVIG.

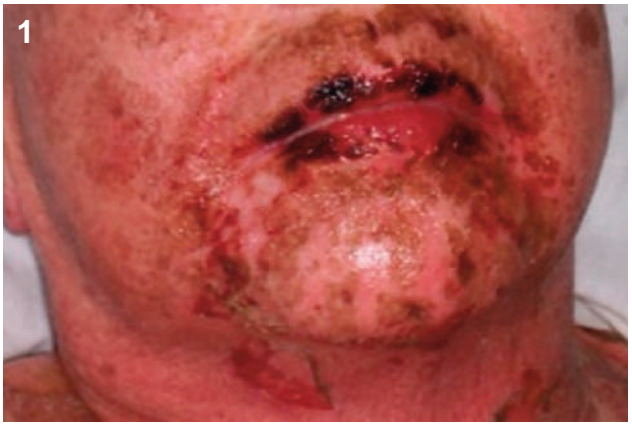
CLINICAL CASE

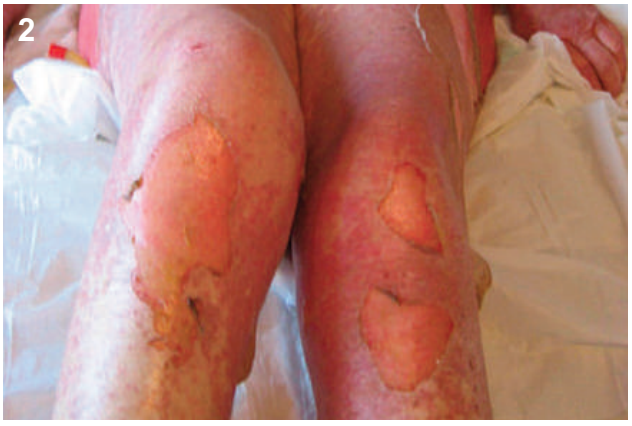
A 72-year-old female patient with a history of hypothyroidism, hypertension, myocardial ischemia and myelodysplasia was on phenytoin (100 mg every 6 hours) as

a prophylactic outpatient treatment after undergoing surgery to drain a chronic subdural hematoma one month prior. She came to the emergency ward after developing a pruritic maculopapular rash in her upper and lower limbs, which progressively spread, along with facial and mucosal edema accompanied by dysphonia and odynophagia in the previous 48 hours, which prompted her admission. During the physical examination, confluent lesions and blisters were observed, which caused erosions in her face, chest and limbs. Her mucosa was also affected, presenting blood-serum slough. She was also positive for Nikolsky's sign, with 30% of her superficial epidermal tissue being compromised (Fig. 1 and 2).

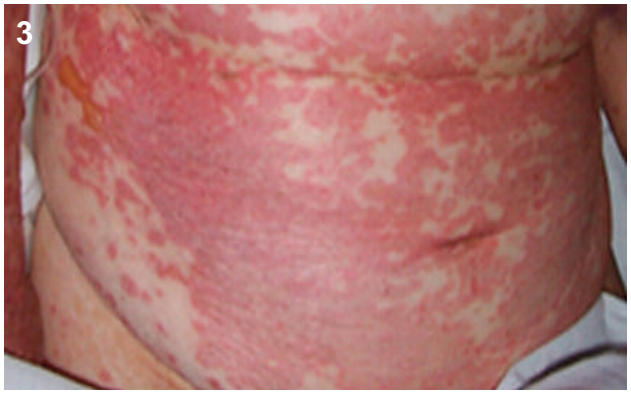
The case was initially diagnosed as phenytoin-induced angioedema, and the prescribed treatment was intravenous (IV) hydrocortisone (200 mg every 6 hours), diphenhydramine (50 mg every 8 hours) and parenteral hydration. Since the patient's condition did not improve, 1 mg/ml intradermal bolus adrenaline was administered. The ophthalmic exam was normal. The patient developed persistent fever; therefore, blood and urine samples were taken (no posterior bacterial growth), and vancomycin and cefepime were administered as an antibiotic empiric treatment. The skin biopsy showed evidence of keratinocyte necrosis, vacuolar degeneration of the basal layer and subepidermal blistering, which were compatible with TEN. Both the Naranjo algorithm and the TEN-specific drug causality algorithm (ALDEN) showed probable causality for phenytoin (7 "probable" and 6 "highly probable", respectively).

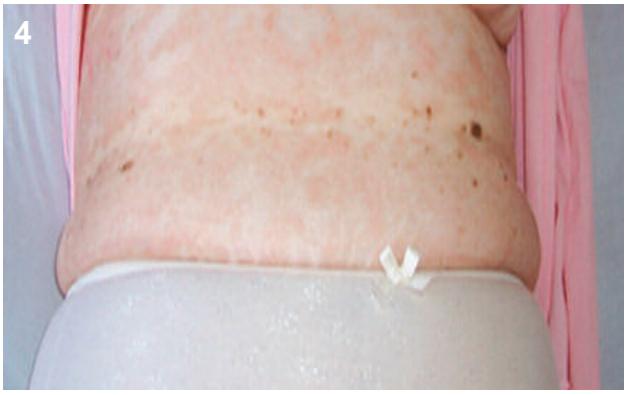
In view of the seriousness of the case, on the fourth day of hospitalization it was decided to administer IVIG (0.5 gr/kg/day for five consecutive days), and methylprednisolone (1 g/day IV for three days). The patient responded favorably, with lesion regression, no new tissue being compromised, and full mucosa recovery (Fig. 3 and 4). The National Administration of Drugs, Food and Medical Devices (ANMAT, as per the Spanish acronym) was informed of the adverse drug reaction and the patient was discharged after 30 days.





Figures 1 and 2. Day 1. Confluent erythema and blister sores combined with erosions and necrosis can be seen on face, torso, and limbs.





Figures 3 and 4. There is a noticeable improvement on the erythema and denudation.

DISCUSSION

While the case reported is an isolated one, it is a useful observational account regarding TEN treatment with systemic corticosteroids combined with IVIG. Despite that the route of administration (oral vs. IV), dosage, time, and duration of the treatment are not clear, and that immunoglobulin is not recommended as a monotherapy, the combination of IVIG and corticosteroids should be further studied.

TEN-suspected patients must be immediately examined in a medical facility in order to reach a definitive diagnosis, evaluate the seriousness of the case and its prognosis, determine a causal agent and implement the appropriate treatment. The prognosis can be improved by rapidly identifying and removing the causal agent. In a 10-year observational study of 113 TEN or SJS patients, the early discontinuation of the causal drugs with short half-lives reduced the risk of death by 30% for each day before the development of blisters and erosions (odds ratio [OR] 0.69; 95% CI: 0.53-0.89).[11] However, drugs with longer half-lives were linked to higher death risk, regardless of early or late discontinuation (OR 4.9; 95% CI: 1.3-18.9). This difference between drugs with short and long half-lives may be a result of the drug or the substrate that caused the reaction still being active, despite the discontinuation.

In our case at hand, the suspected causal drug was discontinued immediately while trying to determine the causal agent. As for the determination of causality, the timeline and suspected agent must be taken into account. Most treatments with TEN-inducing drugs are started 5 to 28 days (sometimes up to two months) before any symptoms develop.[2] This is consistent with our patient, who started her treatment 4 weeks prior. Furthermore, most TEN cases are triggered by a handful of high-risk medications,[3-5] phenytoin being one of them. A number of algorithms to determine drug causality have been created. The Naranjo algorithm is widely known in the field of pharmacovigilance, but to determine the causal drug of this adverse reaction, the ALDEN score has been specifically applied. In this case, both algorithms (Naranjo and ALDEN) have determined phenytoin as a probable or highly probable cause of TEN.

Regarding TEN-specific treatment, there is limited evidence that adjuvant treatments are beneficial, and none can be conclusively recommended. Nevertheless, the results of different meta-analysis suggest that treatment with ciclosporin, etanercept, systemic corticosteroids, and a combination of IVIG and systemic corticosteroids may be potentially beneficial. In our patient's case, due to a lack of availability of ciclosporin and etanercept, IVIG and systemic corticosteroids was the treatment of choice. This combination has been investigated in only a handful of studies, which are summarized in Table 1.

In Micheletti et al.'s research (2018) on SJS/TEN hospitalized patients, the standardized mortality ratio (SMR) of patients that were administered systemic corticosteroids (average daily dose of 148 mg of prednisone) and IVIG (average dosage of 1 g/kg/day for three days) was lower than the SMR of the populations who received corticosteroids alone, IVIG alone, or supportive care alone.[12]

In the propensity-matched study of Yang et al. (2022), there was no difference in the SMR of the two groups. Nevertheless, in contrast with corticosteroid monotherapy, the combined therapy was linked to shorter hospitalization times (-3.37 days) and a lower rate of skin infection.[13]

In Jagadeesan et al.'s non-randomized study (2013), all 36 TEN patients were administered small doses of IVIG (0.2 to 0.5 g/kg) and intravenous dexamethasone (0.1 to 0.3 mg/kg/day, gradually reduced within one or two weeks), or dexa-methasone alone. Differences in SMR were significant.[14]

In Schneck et al. (2008), 35 patients were treated with IVIG alone and 40 with IVIG combined with systemic corticosteroids.[15] The IVIG dose ranged between 0.7 and 2.3 g/kg and was administered during one to seven days. Gross mortality rate was 18% in the group treated with corticosteroids alone and 18% as well in the group treated with IVIG and corticosteroids.

In Zhu et al.'s research on TEN patients (2012), 39 patients were treated with 0.4 g/kg of IVIG for five days combined with 1.5 mg/kg methylprednisolone for three to five days, and 22 were administered methylprednisolone alone. Differences in SMR were not significant.[16]

Yang et al. (2009) compared 65 patients over a period of 14 years. 45 patients were treated with corticosteroids (1 to 1.5 mg/kg/day of methylprednisolone), and 20 were treated with IVIG (2 g/kg for five days) and corticosteroids (1 to 1.5 mg/kg/day of methylprednisolone). There was no statistical difference in mortality between the two groups.[17]

Chen et al. (2010) conducted a similar study, comparing patients treated with corticosteroids (n = 58) and patients treated with IVIG and corticosteroids (n = 24) and did not find any significant difference between the SMR of the two groups.[18]

By analyzing these studies, it is possible to conclude that a combination of corticosteroids and IVIG can be more effective than those two administered separately. However, given the nature of said studies, the small number of patients, their single-centered and retrospective nature, as well as the

TABLE 1. Summary of the main studies on TEN adjuvant treatment with corticosteroids alone versus treatment with corticosteroids + IVIG.

Study	Study type	Year	Total N	SMR	
				Corticosteroids	Corticosteroids + IVIG
Micheletti et al. (USA)	Multicenter retrospective observational	2018	377	0.72 [95% CI: 0.48-0.89]	0.52 [95% CI: 0.21-0.79]
Yang et al. (China)	Single-center retrospective observational	2022	145	0.75 [95% CI: 0.00-1.76]	0.38 [95% CI: 0.00-0.91]
Jagadeesan et al. (India)	Single-center prospective observational	2013	36	0.63 [95% CI: 0.00-1.34]	0.18 [95% CI: 0.00-0.54]
Schneck et al. (Germany and France)	Multicenter retrospective observational	2008	35	Authors report 18% gross mortality rate	Authors report 18% gross mortality rate
Zhu et al. (China)	Single-center retrospective observational	2012	55	0.93 [95% CI: 0.11-1.75]	0.54 [95% CI: 0.07-1.01]
Yang et al. (China)	Single-center retrospective observational	2009	65	1.16 [95% CI: 0.56-2.13]	0.85 [95% CI: 0.18-2.5]
Chen et al. (China)	Single-center retrospective observational	2010	82	0.48 [95% CI: 0.08-1.92]	0.57 [95% CI: 0.32-1.91]

diverse characteristics of the patients, the different corticoids used, and systemic dosages and duration of the treatments it is only possible to assign their findings a hypothetical status that needs to be confirmed by further randomized and controlled research.

Our patient's case is compliant with the treatment guidelines and serves as additional experience describing that the treatment combining corticosteroids + IVIG caused a favorable response and the patient's discharge.

CONCLUSION

Our patient's response to the combination of corticosteroids and IVIG was favorable. However, since this is a case report, the function this combination of drugs has must be further researched.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1 Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, Kardaun S, Sidoroff A, Liss Y, Schumacher M, Roujeau JC. Comprehensive Survival Analysis of a Cohort of Patients with Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis. J Investig Dermatol. 2013 May;133(5):1197-204. Available from: https://doi.org/10.1038/jid.2012.510

2 Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, Haustein UF, Vieluf D, Roujeau JC, Le Louet H. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010 Jul;88(1):60-8. Available from: https://doi.org/10.1038/clpt.2009.252

3 Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995 Dec 14;333(24):1600-7. Available from: ttps://doi.org/10.1056/NEJM199512143332404

4 Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008 Jan;128(1):35-44. Available from: https://doi.org/10.1038/sj.jid.5701033

5 Wang YH, Chen CB, Tassaneeyakul W, Saito Y, Aihara M, Choon SE, Lee HY, Chang MM, Roa FD, Wu CW, Zhang J, Nakkam N, Konyoung P, Okamoto-Uchida Y, Cheung CM, Huang JW, Ji C, Cheng B, Hui RC, Chu CY, Chen YJ, Wu CY, Hsu CK, Chiu TM, Huang YH, Lu CW, Yang CY, Lin YT, Chi MH, Ho HC, Lin JY, Yang CH, Chang YC, Su SC, Wang CW, Fan WL, Hung SI, Chung WH; Asian Severe Cutaneous Adverse Reaction Consortium. The Medication Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Asians: The Major Drug Causality and Comparison With the US FDA Label. Clin Pharmacol Ther. 2019 Jan;105(1):112-120. Available from: https://doi.org/10.1002/cpt.1071

6 The RegiSCAR Project. Available from: http://www.regiscar.org/index.html

7 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003 Jan;139(1):33-6. Available from: https://doi.org/10.1001/archderm.139.1.33

8 Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maître B, Revuz J, Bagot M, Roujeau JC. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010 Oct;163(4):847-53. Available from: https://doi.org/10.1111/j.1365-2133.2010.09863.x

9 Chaidemenos GC, Chrysomallis F, Sombolos K, Mourellou O, Ioannides D, Papakonstantinou M. Plasmapheresis in toxic epidermal necrolysis. Int J Dermatol. 1997 Mar;36(3):218-21. Available from: https://doi.org/10.1046/j.1365-4362.1997.00192.x

10 Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, Chang CJ, Su SC, Hui RC, Chin SW, Huang LF, Lin YY, Chang WY, Fan WL, Yang CY, Ho JC, Chang YC, Lu CW, Chung WH; the Taiwan Severe Cutaneous Adverse Reaction (TSCAR) Consortium. Randomized, controlled trial of TNF-α antagonist in CTL-mediated severe cutaneous adverse reactions. J Clin Invest. 2018 Mar 1;128(3):985-996. Available from: https://doi.org/10.1172/JCI93349

11 Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000 Mar;136(3):323-7. Available from: https://doi.org/10.1001/archderm.136.3.323

12 Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, Boggs J, Cardones AR, Chen JK, Cotliar J, Davis MDP, Dominguez A, Fox LP, Gordon S, Hamrick R, Ho B, Hughey LC, Jones LM, Kaffenberger BH, Kindley K, Kroshinsky D, Kwong BY, Miller DD, Mostaghimi A, Musiek A, Ortega-Loayza AG, Patel R, Posligua A, Rani M, Saluja S, Sharon VR, Shinkai K, John JS, Strickland N, Summers EM, Sun N, Wanat KA, Wetter DA, Worswick S, Yang C, Margolis DJ, Gelfand JM, Rosenbach M. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Multicenter Retrospective Study of 377 Adult Patients from the United States. J Invest Dermatol. 2018 Nov;138(11):2315-2321. Available from: https://doi.org/10.1016/j.jid.2018.04.027. Erratum in: J Invest Dermatol. 2019 Feb;139(2):495-496. Available from: https://doi.org/10.1016/j.jid.2018.11.013

13 Yang L, Shou YH, Li F, Zhu XH, Yang YS, Xu JH. Intravenous Immunoglobulin Combined With Corticosteroids for the Treatment of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Propensity-Matched Retrospective Study in China. Front Pharmacol. 2022 Jan 18;12:750173. Available from: https://doi.org/10.3389/fphar.2021.750173

14 Jagadeesan S, Sobhanakumari K, Sadanandan SM, Ravindran S, Divakaran MV, Skaria L, Kurien G. Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: a prospective comparative open-labelled study of 36 cases. Indian J Dermatol Venereol Leprol. 2013 Jul-Aug;79(4):506-11. Available from: https://doi.org/10.4103/0378-6323.113080

15 Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008 Jan;58(1):33-40. Available from: https://doi.org/10.1016/j.jaad.2007.08.039

16 Zhu QY, Ma L, Luo XQ, Huang HY. Toxic epidermal necrolysis: performance of SCORTEN and the score-based comparison of the efficacy of corticosteroid therapy and intravenous immunoglobulin combined therapy in China. J Burn Care Res. 2012 Nov-Dec;33(6):e295-308. Available from: https://doi.org/10.1097/BCR.0b013e318254d2ec

17 Yang Y, Xu J, Li F, Zhu X. Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China. Int J Dermatol. 2009 Oct;48(10):1122-8. Available from: https://doi.org/10.1111/j.1365-4632.2009.04166.x

18 Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. Eur J Dermatol. 2010 Nov-Dec;20(6):743-7. Available from: https://doi.org/10.1684/ejd.2010.1077

the poison®

IMAGES IN TOXICOLOGY

Paraquat poisoning with fatal outcome in a 56-year-old agricultural worker

María D. Montero*, Rodrigo A. Petter and Cinthia D. Gigliotti

National Poison Center (CNI) - Prof. Alejandro Posadas National Hospital, El Palomar, Buenos Aires, Argentina.
*monteromariadulce.md@gmail.com

Submitted: 18/04/2024 - Accepted: 19/05/2024 - Published: 30/06/2024 - DOI: https://doi.org/10.62129/MIAQ2963

Abstract. Paraquat is a highly toxic herbicide that can cause caustic lesions, acute kidney failure and delayed pulmonary fibrosis. We report a case of a 56-year-old male agricultural worker who intentionally ingested 20 ml of paraquat, leading to a fatal outcome. He presented with vomiting, diarrhea, dysphagia and sialorrhea. Despite prompt medical intervention with cyclophosphamide, methylprednisolone, and supportive care, the patient developed acute renal failure and progressive pulmonary fibrosis. His condition deteriorated rapidly, and he succumbed to refractory hypoxemia 31 days after hospital admission. This case highlights the lethal nature of paraquat poisoning and the importance of preventive measures to minimize exposure.

Key words: *Paraquat; Herbicides; Pyridinium compounds; Caustics; Tongue; Pulmonary fibrosis.*

Paraquat is a non-selective herbicide that is widely used in agriculture. It is a highly toxic substance that can cause caustic lesions, acute renal failure (usually reversible) and delayed oxygen-dependent pulmonary fibrosis (after 7 to 14 days). Paraquat poisoning is a medical emergency that requires immediate treatment due to its high mortality. We present the case of a 56-year-old male agricultural worker who presented to a low-complexity health center with vomiting and diarrhea, immediately after intentional ingestion of 20 ml of paraquat of unknown concentration.

After 48 hours, due to persistence of symptoms and appearance of dysphagia and sialorrhea, he went to a more complex center. On hospital admission, a whitish depapillated tongue was observed, a sign known as "paraquat tongue" (Fig. 1). Complementary studies were carried out, including chest X-ray and laboratory tests. Analyses showed an elevated white blood cell count (16500/mm3), elevated urea (96 mg/dl) and creatinine (4.3 mg/dl), and alterations in liver enzymes (alanine aminotransferase/ALAT 34 IU/ml and aspartate aminotransferase/ASAT 94 IU/ml). Arterial blood gas was as follow: pH: 7.44, pCO2: 32 mmHg, pO2: 79 mmHg, bicarbonate: 20.8 mEq/l, base excess: -2.1 and Sat O2: 96% (FiO2 at 0.21). The sodium dithionite test in urine was positive, confirming the presence of paraquat in the body (Fig. 2).

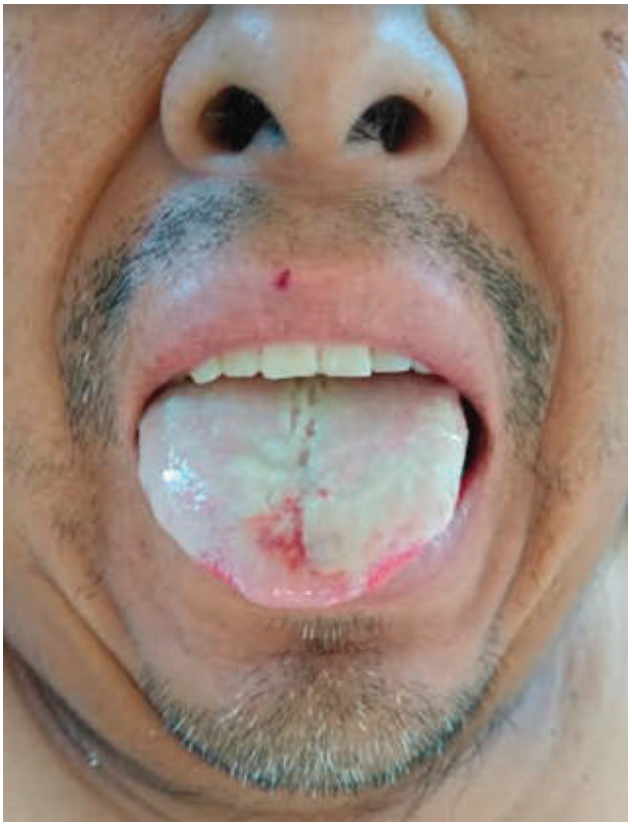


Figure 1. 48 hours after ingestion. We can appreciate the "paraquat tongue": depapilated and whitish tongue.

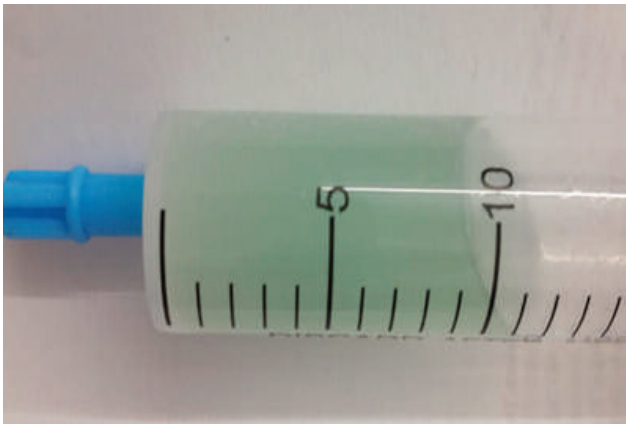


Figure 2. Dithionite test 48 hours after ingestion. Positive result for paraquat: bluish staining of urine.

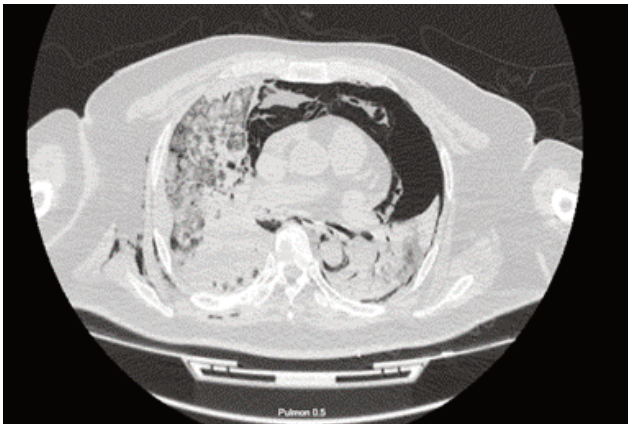


Figure 3. 30 days after ingestion: pneumomediastinum, pneumothorax, pulmonary fibrosis, images of consolidation and subcutaneous emphysema.

Based on the anamnesis, physical examination and complementary studies, it was decided to start immunomodulatory treatment with cyclophosphamide (1 g/day) for 48 hours and methylprednisolone (1 g/day) for 72 hours. The Nephrology Unit opted for a wait-and-see approach to renal replacement therapy. Upper gastrointestinal endoscopy was not performed due to the time elapsed since ingestion.

During hospitalization, the patient presented a deepening of renal injury, with uremia of 287 mg/dl and creatinemia of 8.2 mg/dl, but maintained an adequate diuretic rhythm. From the seventh day after ingestion, he progressed to respiratory failure secondary to progressive pulmonary fibrosis, documented by computed axial tomography (Fig. 3). He required different modalities of ventilatory support, from high-flow nasal cannula to non-invasive ventilation and finally orotracheal intubation. He died from refractory hypoxemia 31 days after hospital admission.

Conflicts of interest

The authors declare no conflicts of interest.

www.thepoisonjournal.com | Cite as: Poison 2024; 1(2):62-63 | DOI: 10.62129/MIAQ2963

Published by Panamerican Toxicology® Press: 1737 Chivilcoy St. Castelar, Buenos Aires
(PO BOX 1712), Argentina