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Systematic Review Protocol

Characteristics and Outcomes in Acute Propanil Poisoning: a Scoping Review Protocol.

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Abstract

Background: Propanil is a widely used weedicide for rice cultivation in Sri Lanka and other paddy-cultivating countries. Agrochemical ingestion as a mode of deliberate self-harm commonly occurs in farming communities. Acute propanil poisoning (APP) is frequent due to its availability and lethality. The clinical presentation of APP may vary, and there are many treatment modalities for the cases of propanil poisoning. The available literature on characteristics and outcomes of propanil poisoning is limited to case reports, case series, and limited retrospective and cohort studies.

Methods: We will search for published and grey literature without a language restriction. MEDLINE (PubMed), CINAHL, and TRIP databases will be used to find studies on APP by browsing keywords. Studies that will not appear online but are published in key journals in Sri Lanka will also be included after searching in library archives. Identified sources relevant to the study will be retrieved in toto, and their citation details will be imported into the Joanna Briggs Institute (JBI) System for the Unified Management, Assessment, and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia). The study results will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.

Discussion: There are no specific clinical manifestations following APP. There may be several commonly shared clinical presentations in this context, but they are not described well. Biochemical evaluation of the propanil levels is costly and not readily available in most centres worldwide. There may be cheaper and more readily available tests that may help diagnose and assess the clinical severity of APP. Though methemoglobinemia is the most described complication following APP, this study aims to identify other complications. There are several treatment modalities for the management of propanil poisoning, and the outcomes of each treatment modality may vary. Therefore, this scoping review will be done on accessible and available literature to assess the characteristics and consequences of APP.

Keywords: Acute, poisoning, propanil, toxicity

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Introduction

Propanil (3,4-dichloropropionanilide) is a commonly used herbicide in Sri Lanka and worldwide in paddy farming. Propanil poisoning has a case fatality of 8.2%-10.7% [1,2]. This makes it the third most lethal herbicide in Sri Lanka, behind paraquat and quinclorac [1,2]. Propanil is an acylanilide group herbicide primarily used in paddy cultivation [2,3].

Agrochemical self-poisoning is considered one of the most common methods of attempted suicide worldwide, according to the World Health Organization [4]. It is also considered the most preventable way of suicide by the implementation of strict pesticide regulations [1,5].

Following exposure, propanil is readily absorbed via the skin, gastrointestinal tract following ingestion and respiratory tract following inhalation [3,6]. Once absorbed, propanil is hydrolysed by acylamidase in the liver into 3,4 dichloroaniline, which is later oxidised to a potent methemoglobin inducer 3,4 dichlorophenylhydroxylamine. This can lead to severe and treatment-resistant methemoglobinemia, ultimately resulting in death [2,3,6]. Propanil poisoning is similar to dapsone toxicity. These metabolites are responsible for methemoglobinemia and later hemolysis due to prolonged stay in the systemic circulation [2,6,7].

Propanil poisoning is considered an acquired cause of methemoglobinemia. Other common causes of acquired methemoglobinemia are local anaesthetic agents injected subcutaneously and therapeutic doses of dapsone [8,9].

The clinical manifestations of propanil poisoning can vary depending on the entry site of the poison and the dose. Following exposure, patients may experience local effects such as a burning sensation in the nose and mouth and irritation of the upper gastrointestinal tract. Despite enough arterial oxygen saturation, there is relative tissue hypoxia, as methemoglobin cannot bind and transport oxygen. Organ dysfunction occurs due to this relative tissue hypoxia, leading to depression of the central nervous system, low blood pressure and acidosis [2,3,7]. This leads to the manifestation of typical clinical features, including an altered level of consciousness, confusion, and respiratory depression [7,10,11]. Immunotoxic effects of propanil are also described, leading to impaired development of T and B cells in the thymus and bone marrow. Further, it can result in thymic atrophy and splenomegaly [3,6].

The severity of propanil poisoning is determined primarily by the clinical features or methemoglobin levels. Patients are considered asymptomatic if there are no physical or laboratory abnormalities. Mild, severe patients are the ones who have mild clinical features such as nausea and abdominal pain with no organ involvement. Poisonings requiring an intervention (commencement of methylene blue treatment, exchange transfusion, oxygen therapy, or intubation) are considered moderate or severe [2]. Clinical features with methemoglobin levels less than 20% with or without associated acidosis and initial hypotension responding to fluid therapy are considered moderately severe propanil poisoning. Raised methemoglobin levels of more than 20% with associated acidosis (pH <7.2), hypotension and target organ damage are regarded as severe poisoning [2,12].

A rise of more than 3% in methemoglobin levels is defined as methemoglobinemia [2,7]. It can be regarded as clinically significant methemoglobinemia if the pulse oximetry value is less than 90% or methemoglobin levels are more than 20% [7]. Patients are usually asymptomatic if methemoglobin levels are less than 20%. Clinical features may appear if methemoglobin levels are greater than 20%. Reduced consciousness to convulsions may occur when methemoglobin levels rise to around 50-70% and, ultimately, death if the methemoglobin level goes to more than 70% [10,11].

Various methods are used to determine propanil-induced methemoglobinemia, which includes the presence of saturation gap, biochemical measurement of methemoglobin and colour chart [2,7,13]. Laboratory facilities for detecting methemoglobin levels are not readily available in Sri Lanka and worldwide [2,7]. Therefore, the gap between arterial oxygen saturation and pulse oximetry reading and desaturation that does not improve with oxygen supplementation is also considered reliable in diagnosing methemoglobinemia. Due to a lack of access to advanced laboratory diagnosis, a validated colour chart as a bedside tool was introduced in 2008 in Sri Lanka [13]. This colour chart estimates methemoglobin levels, enabling diagnosis, categorising severity, and monitoring response to treatment. Treatment is recommended when the methemoglobin levels exceed 20% [13].

Patients who arrive in the hospital within one to two hours of propanil ingestion and can maintain airway

may be considered for gastric lavage [3,11]. However, forced emesis is currently not recommended in propanil poisoning [3]. Another emergency management option is the administration of activated charcoal. This can be administered as a single dose of 1g/kg or repeated over the first 24 hours as multiple dose activated charcoal [2,3]. Oxygen is administrated to patients with cyanosis or respiratory depression [3,11].

There are several targeted therapies for propanil-induced methemoglobinemia. Treatment following propanil poisoning is considered in patients with moderate to severe poisoning depending on the clinical features, saturation gap and colour chart or laboratory measurement of methemoglobin levels [2,11,13]. The most widely practised and recommended treatment is administering methylene blue in doses of 1-2mg/kg (0.1 ml/kg) intravenously over 5 minutes. A repeat bolus may be considered after one hour if there is no clinical improvement. Methemoglobinemia can reappear following initial treatment in large volume propanil poisoning. Thus, multiple doses of methylene blue are required [2,7,8,11]. Oral methylene blue is considered if intravenous preparations are unavailable in a dose of 300mg daily or 3-5mg/kg [10,11]. If none of the preparations of methylene blue is available, ascorbic acid 1g intravenously twice daily or oral ascorbic acid 1g two to three times daily can be given [2,11]. A combination of methylene blue and ascorbic acid therapy has also been attempted successfully [7]. Repeated doses of methylene blue can worsen Heinz's body formation and hemolytic anaemia, thus necessitating caution during management. Also, ascorbic has a slow onset of action, which may make it less useful in acute methemoglobinemia [8,10].

The other important treatment modality in severe propanil poisoning is exchange transfusion (ET). ET can be used as a lifesaving measure for patients not responding to initial therapy with methylene blue (11). The theory behind exchange transfusion is that it replaces methemoglobin and removes the poison in circulation. The effectiveness of ET can vary as propanil and its metabolites are primarily lipophilic. The effectiveness of ET is doubted based on the above, but it is still considered the treatment of choice in treatment-resistant cases. ET also carries all the risks of blood transfusions [14,15]. ET is often not practised, possibly due to a lack of resources. However, several patients received multiple blood transfusions due to low haemoglobin with hemolysis following propanil poisoning with good clinical outcomes [7,10]. In one case report, venesection and replacement with blood transfusion have also shown survival advantages [16].

Apart from methemoglobinemia, other complications of propanil poisoning are not discussed adequately in the available literature. The most described complication is hemolysis [7]. There is a wide variety of clinical presentations in propanil poisoning. So, certain clinical features following an unknown toxicity or poisoning may alert the clinician to the possibility of propanil poisoning. It is crucial to identify such clinical features through the available literature.

As mentioned above, the biochemical analysis for methemoglobin levels is expensive and rarely carried out in the diagnosis. Though modern arterial blood gas machines can give methemoglobin values, those are not available in Sri Lankan hospitals. Therefore, there should be other laboratory measurements that can successfully predict the possibility of methemoglobinemia in propanil poisoning.

According to available literature, methylene blue has been the treatment of choice for acquired methemoglobinemia. ET has been used in a few instances, especially in treatment-refractory or severe cases [9,11,12]. The currently available literature does not assess the efficacy of each treatment modality compared with others. This mainly includes using methylene blue versus ET in severe propanil poisoning.

Objectives

1. To produce evidence on sociodemographic factors, clinical manifestations, and laboratory evaluation in acute propanil poisoning.

2. Different treatment modalities have different outcomes in acute propanil poisoning.

Methods

Following the initial search, all the identified citations will be uploaded into a citation management system to remove duplicates. The titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Identified sources that are relevant to the study will be retrieved in total, and their citation details will be imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia) [17]. Two independent reviewers will do a detailed assessment of the imported full-text citations per inclusion criteria. Reasons for excluding sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process will be

resolved through discussion. The study results will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram [18]. The Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (PRISMA-P) checklist is in Annexure 1.

Eligibility criteria

Full manuscripts and abstracts published in peer-reviewed journals, including case reports, case series, and prospective and retrospective cohort studies, will be included, with no restriction in language, study design, or year of publication.

The concepts examined by this scoping review include various sociodemographic, clinical, and laboratory manifestations of propanil poisoning. Outcomes in currently used treatment modalities will also be explored with special attention on evaluating whether ET has a better outcome than methylene blue.

Information Sources

We will search for published and grey studies without a language restriction. MEDLINE (PubMed), CINAHL, and TRIP databases will be used to find studies on propanil poisoning by browsing keywords. Reference lists of all included studies will be searched again to see the possibility of additional applicable studies. Studies that will not appear online but are published in key journals in Sri Lanka will also be included after searching in library archives.

Search strategy (Table 1)

Two independent investigators will extract data from the studies selected according to the inclusion criteria for this scoping review. Two independent reviewers will look for duplicates using Rayyan software. This will further help us to identify articles for the scoping review. A third investigator's opinion will be taken if a discrepancy arises between the two investigators.

Data items

Specific data to be extracted from the included studies will include:

1. Study type, author/s, year of publication and geographic distribution.
2. Sociodemographic data, including age, gender, and background of recorded cases and studies.
3. Common clinical presentations following propanil poisoning.
4. The severity of poisoning- mild or moderate to severe.
5. Measurement of methemoglobin levels and method of measurement (colourimetric/ laboratory measurement)
6. Initial management modality followed- either gastric decontamination or activated charcoal.
7. Time taken to peak the concentration of methemoglobin levels from the time of poisoning.
8. The treatment method used in propanil poisoning and outcome.
9. Time consumed to drop methemoglobin levels to a safe level following administration of methylene blue.
10. Complications of propanil poisoning.
11. Outcome and mortality following propanil poisoning.

Table 1- Initial search strategy

Participants	**Cases of acute propanil poisonings- including all ages and regardless of gender**
Keywords – to be searched	"acute" AND "propanil" or "3,4-dichloropropionanilide" AND "Toxicity" or "poisoning"
Context	All healthcare facilities, laboratories
Study types	Any available articles

Two independent authors will extract the data using the JBI SUMARI data extraction template. The initially grafted data extraction form will be modified depending on the variations in individualised studies while extracting data. The extracted data will be entered into Excel sheets, and the missing or unclear data will be coded as missing/unclear. Only the authors of the study will have permission to access the data. The data will be saved in JBI SURMARI servers. The flow of information along the review process will be graphically depicted using a PRISMA flow diagram. The scoping review will be conducted per the Joanna Briggs Institute methodology for a scoping review. Changes that will be done to this scoping review protocol will be detailed in the final scoping review report.

Quality appraisal

Quality appraisal tools will be used extensively on all selected articles. This will be done using JBI Revised Critical Appraisal Tools [19].

Synthesis and presentation of results

Depending on availability, the extracted data will be analysed manually or using NVIVO and presented as diagrams, tables, or charts. Once the review process advances, the approach to synthesis and presentation of results might change. The final report will discuss gaps in the current knowledge of outcomes and management of propanil poisoning. We will try to use "Grades of Recommendation, Assessment, Development, and Evaluation" (GRADE) recommendations as much as possible in study selection and in preparing the final report to assess the body of evidence. A narrative summary will accompany the tabulated and charted results. The final scoping review report will summarise the authors' conclusions and suggestions. The study results will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.

Conclusion

This review aims to gather evidence on sociodemographic factors, clinical manifestations, and laboratory evaluation in acute propanil poisoning and to see whether different treatment modalities have different outcomes in treating acute propanil poisoning. This review will enable us to identify gaps in existing knowledge on acute propanil poisoning. The study's results will be vital for the clinicians who manage those patients, future researchers, and governing bodies involved in policymaking.

Ethics approval

Ethical approval was obtained from the Ethics Review Committee, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka (ERC/2023/06).

Conflict of Interests

The authors declare that they have no competing interests.

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Authors' contributions

PPBH, SS, MW and KW were involved in developing the concept, planning the study, and writing the manuscript. PPBH prepared the draft protocol under the supervision of SS and KW. SS was the supervisory author, guiding all research areas and the guarantor for the review. KW and MW provided edits to the manuscript. All authors approved the final manuscript.

Data availability

After the scoping review, the raw data will be available as a supplementary file upon request from the corresponding author.

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