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Review Article

Therapeutic Dilemma of Wheat Pill Poisoning: A Narrative Review and Management Proposal

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A B S T R A C T

Background: The ingestion of wheat or rice pills poses a significant challenge in medical management due to their aggressive course and high mortality rate. In countries like Pakistan, factors such as easy accessibility, inadequate safety regulations, low literacy rates, and a large population living below the poverty line contribute to both unintentional and intentional overdoses. The main toxic compounds found in wheat pills, zinc or aluminium phosphide, are extremely harmful to the human body. The absence of an antidote or established treatment protocols further complicates the management of patients who present to emergency departments after ingestion.

Objective: This review aims to investigate existing literature on therapeutic interventions for individuals experiencing wheat pill poisoning. By synthesizing this information, it seeks to offer a summary that could serve as a basis for future research endeavours aimed at establishing standardized guidelines and management protocols for acute toxicity from wheat pill ingestion.

Methodology: A review was conducted across four databases (Google scholar, PubMed, Cochrane Library and up-to-date) to identify various therapeutic modalities used for the treatment of patients presenting with wheat pill poisoning.

Results: We identified 57 publications, consisting of case reports, case series, clinical trials and literature reviews highlighting various aspects of management, complications, and outcomes.

Conclusion: While there is no specific antidote for wheat pill toxicity, supportive measures yield positive outcome. The authors have compiled and organised the findings from the limited available evidence to serve as an initial guide for the development of a more comprehensive, evidence-based, and rigorously tested clinical guideline. The purpose is to guide the management of such patients presenting to the ED until more robust guidelines can be established through research and clinical testing.

Keywords: Rice pills; Therapeutic dilemma; Wheat pill toxicity

Introduction

Wheat pill, also known as rice pill, is a cost-effective rodenticide frequently employed in developing nations to safeguard food crops like rice and wheat from infestation. In Pakistan, an agricultural country producing approximately 27 million metric tonnes of wheat and 8 million metric tonnes of rice annually, the use of wheat pill, containing aluminium phosphide (ALP), is extensive[1]. To combat rodent damage, a considerable quantity of wheat pill is required, with an average recommendation ranging from 2 to 5 pills per ton of crop[1].

The active ingredient in wheat pill is either zinc or aluminium phosphide (ALP), typically constituting around 56% of the formulation. This primary component remains inert until it meets moisture, at which point it undergoes a chemical reaction, converting into phosphine gas[2]. Phosphine gas is colourless, highly inflammable, and has a garlicy odour. It is a potent enzyme inhibitor that generates free radicals in the human body. This results in high cellular toxicity and adverse effects manifest within hours of inhalation, with rapid deterioration and death within the first 24 to 72 hours[3]. The ingestion of the wheat pill produces phosphine intoxication when the solid phosphide reacts with the gastric contents causing necrosis of the gastrointestinal tract, kidney, and liver. The phosphine gas produced also causes pulmonary damage as it is inhaled. The multiorgan involvement can culminate in rapid death[4].

The wheat pill is widely used in developing countries for deliberate self-harm (DSH) and suicide due to its easy availability, coupled with factors such as low literacy rates, lack of awareness, and socio-economic disparities. The incidence of poisoning resulting from the ingestion of wheat pills has been reported to be around 2.7%[5]. However, the lack of a centralised reporting and data collection system, combined with social stigmata associated with DSH may contribute to under-reporting, suggesting thereby suggesting the actual incidence of wheat pill poisoning is much higher than reported. This underscores the necessity for preventive vigilance at a national level, through a series of effective public awareness campaigns, enforcing stringent regulatory oversight and establishing governance mechanisms for the distribution, usage, and toxicity of wheat pills.

Despite ample literature on the epidemiology, aetiology, mechanism of action, and outcomes associated with wheat-pill poisoning, there remains a notable dearth of information concerning its management. Currently, there is no antidote available for wheat pill poisoning. Consequently, treatment primarily revolves around supportive measures aimed at addressing the systemic effects of phosphine gas and preventing associated complications[3]. There are several case reports of successful and unsuccessful treatment, but very little consolidated evidence that may be used as guidance for better outcomes. This review aims to consolidate various therapeutic options, albeit primarily supportive, to generate a comprehensive summary. The goal is to propose a skeletal management outline with potential for further research and development of evidence-based standardizes guidelines for the management of patients presenting to the emergency department (ED) with acute toxicity following wheat pill ingestion.

Materials & Methods

A broad-based literature review was conducted to include four electronic databases (Google scholar, PubMed, Cochrane Library, Up-to-Date), grey literature, reference lists and bibliographies. Using the keywords [wheat pill + management + treatment], literature in the English language from the last decade (2014 - 2024) was examined for various therapeutic options, complications, and outcomes. Autopsy reports, opinions, comments, polypharmacy, mass exposure with multiple victims, letters to the editor, and studies on animals were excluded. Patients whose initial ED management was not mentioned or died within minutes of arrival, were also excluded as they would not have had sufficient time for management beyond cardiopulmonary resuscitation (CPR). Case reports, case series, clinical trials and studies, and literature reviews were all included to gather a broad spectrum of knowledge.

Results

The initial search showed 17,700 publications, titles of which were populated on Microsoft Excel (version 16.82) spreadsheet to identify and exclude duplicates. Following this, above-mentioned exclusion criteria were applied to the titles and screened for relevance, leaving 111 publications for thorough scrutiny. Two independent reviewers carefully examined the abstracts of these remaining articles and after applying exclusion criteria, 57 publications were deemed suitable for thorough exploration for this narrative review. These included eighteen case reports/series[6-24], twenty-three clinical studies[25-46] and sixteen literature reviews[47-62].

Discussion

Clinical Course

The clinical course of wheat pill poisoning mimics a roller coaster ride. In the initial 24 hours, the patients may experience a dramatic progression from mild symptoms like tachycardia to multiorgan involvement and potential cardiorespiratory arrest[7,11,13]. Subsequently, over several days, the condition fluctuates between periods of improvement and deterioration before gradually showing signs of improvement, typically by the end of the first week. Full recovery can take days to months[7,13,15,20].

The severity of toxicity and the onset time of initial symptoms may or may not be directly related to the dose of the toxin, as insufficient evidence exists in the literature to establish a clear correlation. In general, the effects of toxicity can start manifesting from as early as 30 minutes[6]. The most common presenting complaints in acute phase are vague abdominal cramps, nausea, and vomiting[6-20]. The earliest clinical finding is tachycardia (110 -140 beats/min), followed by a sudden rapid fall in blood pressure (BP), increase in respiratory rate (RR) and a drop in the oxygen saturations (SpO_2), in this order[6-24]. The commonly noted biochemical abnormalities are metabolic acidosis within the first 6 -12 hours, deranged liver function tests (LFTs) over 1-3 days and raised creatinine levels (acute kidney injury AKI secondary to renal excretion of phosphine). Refractory shock and cardiac rhythm problems, ventricular tachycardia (VT) being most common, ischemic changes on ECG, global hypokinesia and transient reduction in left ventricular ejection fraction (LVEF) are reported in most cases, requiring aggressive intervention[6,10]. Most of the cardiac complications occur within the first 24 hours and myocardial injury is not irreversible[10]. Severe metabolic acidosis and cardiotoxicity are the earliest to manifest and most common causes of early mortality if left unaddressed within 24 hours of ingestion[23,27].

Diagnosis is mostly clinical with relevant history and garlic odour-of breath. Several diagnostic tests are available. The most valuable diagnostic and prognostic tools in these patients in the ED are point-of-care blood gas analysis (metabolic acidosis), ECG (anterolateral ischemia and arrythmias), blood lactate levels, and bedside echocardiography (global hypokinesia and LVEF measurement)[6-23,34].

Therapeutic Conundrum

This review highlights the challenges posed by the lack of a specific antidote for phosphine poisoning, coupled with its high cellular toxicity and rapid progression, which limit the window for effective treatment. Nonetheless, there are promising supportive treatment options that have demonstrated the potential to significantly reduce mortality[17]. For instance, in eighteen of

the case reports, consisting of ninteen patients, varied supportive therapeutic measures in the acute phase showed a promising survival rate of nearly 80%[6-24]. The conventional supportive therapy commonly found in most literature typically includes a combination of some or all the following measures: gastric lavage (GL), Oxygen (O_2), sodium bicarbonate ($NaHCO_3$), intubation and mechanical ventilation, intravenous (IV) fluids, inotropes, antiarrhythmic agents, N-acetylcysteine (NAC) and magnesium sulphate ($MgSO_4$). Additional interventions such as haemodialysis, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP) and lipid emulsion therapy are showing promising results[15,19-21].

Gastric Lavage (GL)

GL is the mainstay of treatment in the acute phase as it helps decontamination of the gastrointestinal tract (GIT). It should be performed as soon as possible, as it is most effective during the first two hours of exposure. The choice of agent for GL has been a topic of interest with many clinical trials focusing on this aspect of management[22]. Oil-based GL is recommended as it creates a protective mechanical barrier over the GIT mucosa, reducing breakdown of ALP to phosphine as well as slowing systemic absorption of phosphine gas. Both saturated (paraffin oil) and unsaturated (coconut, vegetable) oils may be used. The addition of 8.4% $NaHCO_3$ to the lavage oil has the added benefit of further inhibiting the release of phosphine by neutralising the gastric acid. Another popular GL cocktail is a combination of potassium permanganate and activated charcoal. Here, the phosphine gas released from the breakdown of the wheat-pill is oxidised to potassium phosphate and aluminium permanganate, which adhere to the activated charcoal, reducing absorption into the GIT. Water-based and saline GL are strongly discouraged as phosphine is highly water- soluble resulting in adverse outcome[26,30,48, 51].

Intravenous Fluid Therapy

Patients with wheat pill poisoning tend to develop a sudden dramatic drop in their BP prompting rapid infusion of large volumes of IV fluids. While, early cautionary use of IV fluids should be initiated, aggressive fluid therapy must be avoided as it can be counterproductive. After initial fluid replacement with one litre of crystalloids, further fluid therapy should be judicious, guided by clinical parameters such as urine output, CVP measurement, invasive BP monitoring (arterial line) and bedside assessment of the inferior vena cava (IVC) using point-of-care ultrasound (POCUS). Overenthusiastic fluid resuscitation carries the risk of developing refractory shock[10-15].

Oxygenation, Intubation & Mechanical Ventilation

Respiratory features in case of ingestion are often a late sign and so low-dose prophylactic O_2 (1 – 4 L/min) therapy should be started in all patients. It is crucial to monitor specifically for hypotension and tachypnoea in these patients, as these are often rapidly followed by hypoxia necessitating intubation and mechanical ventilation.

Sodium bicarbonate ($NaHCO_3$)

One of the main features of wheat pill toxicity is resistant metabolic acidosis. It is one of the first biochemical changes seen in these patients. Repeat doses of 8.4% $NaHCO_3$ are usually required and may need to be continued for 24 hours or beyond.

Ionotropic support

In case of refractory shock and persistent metabolic acidosis, ionotropic support should be started early and may need to be continued for several days. While any combination of noradrenaline, dobutamine and vasopressin may be required, given the pathophysiology of this toxicity, noradrenaline is preferred in the ED[6,11].

Dopamine

Low-dose dopamine (4-6 mg/kg/min) should be considered for adequate hydration and renal perfusion in refractory shock.

Magnesium Sulphate ($MgSO_4$)

Over the last decade, $MgSO_4$ has surfaced as an important therapeutic agent in various life-threatening conditions. In the case of phosphine intoxication, early administration of IV $MgSO_4$ plays a significant role in preventing fatal arrythmias. Its membrane stabilizing and antioxidant properties reducing the oxidative stress level of the myocardium, rendering it cardioprotective, subsequently reduce mortality by up to 50%[15]. The exact dose remains to be determined, However, a stat dose followed by 12 -20 G in divided doses in the first 24 hours is likely to be beneficial[22,23,27].

N-acetylcysteine (NAC)

Over the recent years, NAC has emerged as an important adjunct to supportive management in wheat pill poisoning[33,50,58]. NAC prevents hepatic necrosis. High dose of NAC (300mg/Kg for 20 hrs) is associated with reduced myocardial oxidative stress, thereby reducing the risk of cardiac arrythmias. Lower doses (140mg/Kg loading dose, followed by 70 mg/Kg IV every four hours) has been shown to reduce duration of mechanical ventilation and hospital length of stay.

Haemodialysis, ECMO, IABP

Once multiorgan involvement sets in, persistent refractory shock, low LVEF, severe metabolic acidosis, AKI and other complications occur, placing the patient on a downhill path. Timely intervention with a combination of renal replacement therapy (RRT), haemodialysis, ECMO, and IABP has also shown good outcomes. Recent studies have reported better outcomes with the use of ECMO[7,13,20,23,24]. Early institution of ECMO, before significant decline in LEVF is likely to give the best outcome. In a case report, Daliri et al reports a patient with phosphine toxicity on whom ECMO was initiated after a prolonged CPR. The patient's EF improved from less than 5% to 55% over the course of a few days[13]. Where advanced technology is not available, IABP should be considered as this has also shown good outcomes[15,21,24].

Novel Therapies

Several novel therapies have been reported in recent literature with promising results, but a significant amount of research work needs to be done before they may be considered safe and efficient. One of these such novel therapies is lipid emulsion. The potential role of lipid emulsion is being explored to see its utility in wheat pill / phosphine gas poisoning. Taalab Y et al 2022, and ELabdeen S et al 202, have conducted clinical trials with promising results in increasing survival time[32,35]. The administration of 20% lipid emulsion infused at the rate of 10ml/hr is considered safe. Further studies are required to establish the full benefits of lipid emulsion therapy. Insulin is another drug under the spotlight[22,36] to assess its role in management of wheat pill toxicity. Two studies conducted by Sedaghattalab M et al 2022, Adel B et al 2023 have shown that insulin-euglycemic therapy is safe and effective in the first six hours after ingestion.

Overall mortality and need for mechanical ventilation are also lower in these patients.

Miscellaneous

Several other supportive modalities have been used such as exchange transfusions, diuretics to prevent fluid overload, L-carnitine, and other anti-oxidants such as melatonin and Vitamins E &C. Further studies are required to determine the extent of benefit these additional therapies might provide.

Proposed Management Approach

Although the evidence is weak and inadequate to generate a standardized guideline, the authors propose the following comprehensive management plan for consideration when dealing with patients suffering from acute wheat pill poisoning. However, this proposed approach needs to be validated through robust clinical trials. The authors recommend that all patients who have ingested wheat pills should be promptly managed in the critical area of the ED, eg. the resuscitation room. This recommendation is made because of the aggressive nature of wheat pill toxicity, necessitating immediate initiation of treatment to mitigate its lethal toxic effects. (**Table 1**) summaries the proposed management approach to patients presenting to the ED with acute wheat pill poisoning.

Table 1: Proposed approach to wheat pill toxicity in the ED.

ACUTE WHEAT PILL POISONING (ED)	
Preferably within 2 hours Of ingestion	Triage to high acuity area such as the Resuscitation Room
	Focused history, establish time of ingestion
	Continuous monitoring Maintain observation chart (eg. NEWS)
	Oxygen Therapy
	IV access (2 large bore cannula)
	Point-of-care tests: (Blood gas analysis, ECG, Random Blood glucose)
	Oil-based Gastric Lavage (Paraffin / Coconut / Vegetable) with 8.4% $NaHCO_3$ Repeat Gl every few minutes until lavage fluid is clear
	IV Fluids (Isotonic Saline or Ringer's Lactate) – Caution: after the first liter, further judicious use is advised.
	Laboratory Investigations: Complete blood picture, Renal profile, Liver profile, S Electrolytes, Blood Lactate Levels
Metabolic Acidosis	Intravenous $NaHCO_3$ (8.4%)
Tachycardia (unresponsive to IV fluids therapy	IV $MgSO_4$ (Loading dose 4g)
	IV NAC (Loading dose: 140 mg/Kg)
	Adjuvant antioxidants (if available): Vitamin C & Vitamin E
	Process for ICU admission
Hypotension / Refractory Shock	Noradrenaline / Norepinephrine infusion Dopamine infusion Consider Lipid Emulsion Therapy (20% @ 10ml/hr
Hypoxia	Intubate and Ventilate (Sedation: Midazolam; Paralysis: Rocuronium)
Monitoring	Non-invasive BP (arterial line) Volume assessment: POCUS to assess IVC CVP monitoring Intake/Output monitoring: Foley's catheter, I/O chart
Prepare for ICU admission as soon as possible	
Consider further Management of Complications (In ED or ICU) (with expert multidisciplinary input)	
Cardiopulmonary arrest	Cardiopulmonary resuscitation as per ACLS/ALS guidelines
Cardiogenic shock with severe LVF dysfunction	IABP ECMO Euglycemic-Insulin Therapy
Broad-complex tachycardia	Cardioversion +/- antiarrhythmics depending on hemodynamic status of the patient
Heart Block	Pacemaker
Deranged Liver Function Tests	No intervention required, will resolve spontaneously as the patient starts to recover
Acute Kidney Injury	Haemodialysis, RRT
TTP	Consider: Prednisolone, Therapeutic plasma exchange, PRBCs

Conclusion

Wheat pill poisoning represents a grim reality, characterized by a high mortality rate ranging from 40% to 91%. Despite the absence of a specific antidote, various supportive therapeutic interventions are available. Timely initiation of these treatments holds the potential to reduce mortality rates[17]. However, to devise a comprehensive and effective treatment strategy, there is a pressing need for multicentre, large-scale studies. Such studies are essential for synthesizing evidence-based, time-specific, and aggressive treatment protocols aimed at enhancing patient care and outcomes.

Limitations

The literature on wheat pill poisoning is diverse and often lacks crucial information, particularly regarding medication doses and treatment timelines. This dearth of comprehensive data poses challenges in reaching solid, evidence-based conclusions.

Ethical Approval

This research does not contain any human subjects.

Disclaimer

The views expressed in this narrative review are those of the authors and do not reflect the official policy of affiliated institutes.

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