Herbicide Intoxication: Still A Threat in Developing Countries

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https://doi.org/10.37275/jacr.v1i1.136

ABSTRACT
The critically ill patient has severe respiratory, cardiovascular or neurological disorder often in combination. The critically ill patient needs intensive care unit (ICU) admission and strict monitoring. Intoxication commonly experienced in a critically ill patient in ICU and can complicate management. In developing countries, poisoning of herbicide still common and used for suicide attempts. Herbicides such as paraquat and glyphosate are often used because of their availability. Paraquat and glyphosate have high mortality rate primarily as a suicide attempt agent in developing countries. The primary target for paraquat toxicity is in the lung and can cause lung fibrosis. Severe glyphosate intoxication can cause dehydration, hypotension, pneumonitis, oliguria, loss of consciousness, liver dysfunction, acidosis, hyperkalemia and dysrhythmia. Diagnosis for herbicide intoxication needs a history of herbicide ingestion, physical examination and laboratory examination. Stabilisation and supportive therapy is the only choice, and there is still no specific treatment for herbicide intoxication. The intoxication of herbicide particular critically ill patient because there is still no such specific treatment for these.

Keywords. Paraquat, Herbicides, Glyphosates, Attempted Suicide, Oliguria.
Introduction

Critically ill patient are patients with severe respiratory, cardiovascular or neurological disorder, often in combination, reflected in abnormal physiological observation.\textsuperscript{1} Intoxication from a specific substance is commonly experienced in patients in the intensive care unit (ICU) with the critically ill condition and can complicate management. The medical team needs to suspect the ingestion of a substance in critical patients.\textsuperscript{2}

In a large epidemiological study of more than 7000 inpatient in 8 inpatients the Netherlands who experienced acute intoxication, it was found that many patients died two years after hospitalisation. At first, the patient looked healthy, and there were no problems. ICU mortality was 1.2\% and hospital mortality was 2.1\%. The low mortality rate is not surprising because a young patient with low comorbidities experiences much intoxication. However, they still have a risk of death after discharge from the hospital, accounting for 9.2\% of the total population died within 24 months after release from the hospital.\textsuperscript{3} Acute intoxication varies between countries and changes over time. Attempted suicide by consuming poison is a standard method in developing countries. Pesticides and herbicides are toxic substances that are often used in developing countries compared to developed countries that regularly use drugs.\textsuperscript{8}

Intoxication management in the ICU requires more effort from doctors to quickly identify and evaluate patients to get focused therapy.\textsuperscript{4} The decision to move patients to the ICU should be facilitated with a multidisciplinary consultant team (clinical toxicology, intensivist and other doctors). Based on this approach, 83\% of patients coming from the emergency department (ER) had severe or moderate intoxication and were transferred to the ICU in less than an hour.\textsuperscript{5} Poisoning must be considered as life-threatening conditions and should be monitored closely, extraordinarily patient with comorbid, elderly or infants.\textsuperscript{6}

There may be a difficulty in obtaining ingestion history due to a decreased level of awareness and difficulty in getting a directed account from the family. Also, it is essential to consider the use of more than one substance in patients. Anamnesis must include the substance type, exposure time (acute or chronic), amount of ingestion, and route of administration (oral, inhalation, intravenous). Patients also need to be asked about previous medicines, vitamins and herbal treatments.\textsuperscript{2,7}

The most recent articles discussing herbicides intoxication are very few. This article will describe herbicide intoxication from the substance type, clinical manifestation and potential treatment.
Herbicide

Herbicides are part of pesticides which are chemical compounds that are used to kill or control pests that are considered to interfere or threaten the economy and health. A commercial pesticide formulation is not a single molecule but a mixture. According to a survey from Uthe K National Poison Information Service in 2005 stated that herbicides contributed to 29% of pesticide exposure.

Attempted suicide with herbicides is a significant health problem in developing countries with an estimated 300,000 deaths in the Asia Pacific each year. Sri Lanka has 3 to 400 per 100,000 populations committing suicide attempts with herbicides. Also, there is a possibility that herbicides suicide attempts are underreported due to difficulties in distinguishing them from other anticholinergic pesticides. The most common herbicides used are paraquat and glyphosate.

Paraquat

Paraquat (N'-dimethyl-4,4'-bipyridinium dichloride) made in 1882 is a non-selective herbicide that has been widely used in agriculture since 1955 because it works fast and does not settle in the environment. Paraquat is an organic and heterocyclic herbicide. The use of paraquat accounts for 20 deaths per one million people in the world. In Korea, there are 2000 cases of paraquat intoxication, and 60-70% of them die. In Europe paraquat sales have been banned since 2007.

Paraquat is very often used as a method of suicide in developing countries due to availability, low toxic dosages and relatively inexpensive. Paraquat intoxication had 50-90% mortality rate. Cases with a high fatality rate (> 50%) were reported from paraquat as the sole agent causing death from herbicide intoxication in several countries including Sri Lanka. Between 1986 and 1990, 63% of all suicide deaths in Trinidad and Tobago were caused by paraquat. Between 1945 and 1989, paraquat was also reported to cause most herbicide intoxication deaths in the countries of England and Wales. The American Association of Poison Control Centers' National Poison in 2008 reported more paraquat deaths than other herbicides. Paraquat mortality rates were caused by a variety of toxic symptoms as well as the lack of effective management. In addition to adults; cases are also found in children who accidentally or purposely ingest herbicide for suicide attempts.

Paraquat intoxication is a manifestation due to the redox cycle and the formation of reactive oxygen species (ROS). Paraquat is metabolised by several enzyme systems (NADPH-cytochrome P450 reductase, xanthine oxidase, NADH-ubiquinone oxidoreductase and nitric oxide synthesis). Metabolism through this system forms paraquat mono-cation radicals (PQ+). In cells, PQ+ is quickly oxidised to
PQ2+ and in the process is converted to superoxide (O$_2^-$). O2- acts as an electron acceptor and NADP as an electron donor for this reaction. Further, this condition will increase the formation of hydroxyl free radical (HO-) in the presence of iron via the Fenton reaction (Figure 1). NO- combined with O$_2^-$ forms peroxynitrite (ONOO-) which is a strong oxidant. NO- enzymatically produced through L-arginine with NO synthase, and paraquat also, directly and indirectly, induces NO synthase which is mediated by the production of nitric oxide. Formation of reactive oxygen and nitrite compounds results in toxicity in most organs, but severe toxicity will be experienced mostly by the lungs. The lung is an organ that is very susceptible to PQ intoxication. The concentration of paraquat in the stomach increases continuously during the first few hours after consumption of paraquat even though plasma levels decrease.

The most severe paraquat toxicity occurs in the lungs and results in acute alveolitis. The primary target of toxicity in the lungs is the alveolar epithelium. In the acute phase 'destructive phase' both types 1 and 2 pneumocytes experience swelling, vacuolation and disorders of the mitochondria and endoplasmic reticulum. This condition can also cause pulmo oedema. Damage to the pneumocytes is initiated by NADH which is converted to free radicals. The initial phase will be followed by a proliferation phase where the alveolar space is filled with mononuclear pro-fibroblasts which will mature into fibroblasts within a few days or weeks. This phase will result in pulmonary fibrosis. Kidneys which are exposed to paraquat show necrosis in the proximal tubule. Congestion and hepatocellular damage associated with degranulation and damage to the harsh and smooth mitochondria of the endoplasmic reticulum in the liver.

Paraquat is rapidly distributed to the lungs, liver, kidneys and muscles. Within 12-24 hours after drinking, 90% of the absorbed paraquat is quickly excreted without being changed in the urine. Elimination of the first half takes about 6 hours, but this lasts for four days after the first day.
Clinical manifestations of acute intoxication of paraquat are crystallised to high mortality, rapid deterioration, and lung and kidney damage. Acute poisoning of paraquat is generally asymptomatic. Clinical manifestations depend on the amount of paraquat taken. Drinking large amounts of liquid concentrates (> 50-100 ml of 20% ions) results in fulminant organ disorders including pulmonary oedema, heart, kidney and liver failure and impaired consciousness due to involvement of the central nervous system. Patients generally experience hypoxia, shock and metabolic acidosis during admission. Death results from multiple organ disorders within a few hours today. There are three degrees of severity of paraquat poisoning. Mild poisoning generally starts with oral irritation and gastrointestinal discomfort but generally can heal completely. Moderate to severe poisoning is usually accompanied by acute renal failure, acute hepatitis and severe pneumonitis or pulmonary fibrosis which can cause death within 2-3 weeks. Acute fulminant poisoning can cause death within a few weeks due to multiple organ failure and cardiovascular collapse.

Table 1. Sign and Symptom of Paraquat Intoxication

<table>
<thead>
<tr>
<th>Severity of Intoxication</th>
<th>Ingested amount (mL)</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt; 10</td>
<td>No specific symptom</td>
<td>No specific sign</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-40</td>
<td>Sore tongue</td>
<td>Tachypnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shortness of breath</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation</td>
<td>Increased serum creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal discomfort</td>
<td>Oral mucosa necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head lightness</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 40</td>
<td>Sore tongue</td>
<td>Tachypnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shortness of breath</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hiccup</td>
<td>Increased serum creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation</td>
<td>Oral mucosa necrosis</td>
</tr>
</tbody>
</table>
The diagnosis of paraquat intoxication is generally obtained directly from the history of exposure. However, sometimes the history of exposure is unclear, so there are difficulties due to clinical symptoms that are not specific.\textsuperscript{11} Urine dithionite test can be used as one diagnostic tool. Bicarbonate and sodium dithionite can be used as a bedside test in confirming systemic paraquat toxicity. In an alkaline medium, sodium dithionite reduces paraquat to blue radicals. If the urine has a paraquat concentration of more than 1 mg / L, the urine will turn blue, and this finding indicates the presence of paraquat in the urine.\textsuperscript{11,13,16} Measurement of plasma paraquat concentration is useful for diagnosis and prognosis prediction. Plasma concentration is only helpful for patient education and making clinical decisions because it will not affect intervention guidelines so that plasma concentration is not essential to do.\textsuperscript{16}

In addition to the plasma concentration of paraquat, biochemical tests (electrolytes, kidney and liver function) and haematology (complete blood) should be done at least once per day. A chest radiograph should be done to confirm pneumomediastinum, pneumothorax or pulmonary fibrosis. Chest x-rays are less sensitive and specific for evaluating lung damage due to paraquat intoxication. Chest CT scan can be used for the early detection of pulmonary fibrosis. Amylase and lipase can be used for acute diagnosis of pancreatitis. This condition must be suspected if the patient experienced abdominal pain and increased blood sugar levels\textsuperscript{16}.

Clinical and laboratory conditions can also provide prognosis predictor. Patients with systemic toxicity on the first day (hypotension, severe hypoxia, acidosis and low GCS) do not have a long life expectancy. Development of kidney failure, changes in chest X-rays and gastrointestinal lesions are signs of a poor prognosis\textsuperscript{16}. Patients with severe complaints generally do not have an excellent prognosis with
current management.

The patient's management is only supportive and palliative once the diagnosis is established. The principle of resuscitation includes assessment and management of airway, breathing and circulation. The airway can be disturbed due to mucosal toxicity or vomiting. Tachypnea and hypoxia can be caused by metabolic acidosis, aspiration and or alveolitis so that chest X-ray examination and blood gas analysis are needed.\textsuperscript{16} Hemoperfusion can reduce plasma PQ levels higher than hemodialysis. Doing hemoperfusion when the levels of plasma PQ reached peak levels is one of the most effective ways of eliminating PQ of the body. The faster the hemoperfusion is, the better the effect will be.\textsuperscript{13,16,18}

Table 2. Management of Paraquate Intoxication\textsuperscript{16}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous fluid</td>
<td>Inability to swallow, hypotension</td>
<td></td>
</tr>
<tr>
<td>Monitor fluid balance</td>
<td>All patients</td>
<td>Declining urine output- correct fluid balance and screen for acute renal failure</td>
</tr>
<tr>
<td>Intubation and ventilation</td>
<td>Acute stage</td>
<td>Avoid in acute pneumonitis due to large ingestions and lung fibrosis</td>
</tr>
<tr>
<td>Decontamination</td>
<td>The onset of intoxication within 2-4 h</td>
<td>Use activated charcoal or Fuller's earth</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>Pharyngeal/oesophageal burns PQ in urine</td>
<td>Insert prophylactically as early as possible as swallowing becomes difficult later</td>
</tr>
<tr>
<td>Monitor respiratory rate</td>
<td>All patients</td>
<td>Look for treatable causes (e.g. infection and pneumothorax). Acute pneumonitis (early) and fibrosis (late) indicate abysmal prognosis</td>
</tr>
<tr>
<td>and oxygen saturation</td>
<td>AVOID OXYGEN</td>
<td></td>
</tr>
<tr>
<td>Monitor cardiovascular status</td>
<td>All patients</td>
<td>Hypotension not responsive to fluid indicates an inferior prognosis.</td>
</tr>
<tr>
<td>Monitor level of consciousness</td>
<td>All patients</td>
<td>If CNS toxicity secondary hypoxia or acidosis, there is;</td>
</tr>
</tbody>
</table>
Glyphosate

Glyphosate is a widely used herbicide in agriculture to control industries pests. Glyphosate already used since 1971.\textsuperscript{19,20} Glyphosate is used as a non-selective herbicide. Herbicides contain carbon and phosphorus, but do not have anticholinesterase effects and do not have organophosphate effects (Figure 2).\textsuperscript{20} According to The US Environmental Protection Agency (EPA), glyphosate has relatively low oral and intradermal toxicity.\textsuperscript{10} This compound, when overexposed, can cause many clinical manifestations in humans such as skin and throat irritation, hypotension, oliguria and death.\textsuperscript{19,20} This glyphosate-containing herbicide has increased in frequency for the use of suicide attempts in Asia.\textsuperscript{21}

Glyphosate generally has three components, acids, salts and other property components such as surfactants and water. Formulations of the most commonly available products (Roundup) contain water, 41% glyphosate (isopropylamine salt) and 15% polyoxyethylene amine (POEA). POEA is a surfactant to penetrate plant tissue.\textsuperscript{10}

Glyphosate works by inhibiting enzymes that play a role in the synthesis of amino acids tyrosine, tryptophan and phenylalanine through the shikimic acid pathway.\textsuperscript{20} Glyphosate can also secondary impede the formation of tetrahydrofolate, ubiquinone, and vitamin K.\textsuperscript{22} In humans, the shikimic acid pathway does not exist, so glyphosate toxicity is not caused by disruption of the shikimic acid pathway.\textsuperscript{19,20,22} The mechanism of glyphosate surfactant herbicide (GlySH) in mammals is thought from termination from the incorporation of phosphorylation oxidation and cardiotoxicity mediated by glyphosate or POEA\textsuperscript{19,20}.

Ingesting massive glyphosate for suicide attempt or administering glyphosate intravenous can cause a significant toxic effect.\textsuperscript{22} The oral dose which is said to be lethal in the rat is > 4320 mg/kg in the skin, 2g/kg, and inhalation is >4.43 mg/L. Glyphosate exposure can be measured through blood or urine w
gas chromatography and high-performance liquid chromatography. After drinking, 30-36% of glyphosate is absorbed. The peak concentration occurs in the tissue 6 hours afterwards. Glyphosate undergoes metabolism and is excreted in faeces and urine.\textsuperscript{19}

Symptoms arising from intoxication itself are more due to surfactant than from glyphosate itself.\textsuperscript{22} Patients may appear asymptomatic for several hours before gradually becoming hypotensive. This non-hypovolemic shock can be dangerous.\textsuperscript{20} Gastrointestinal symptoms often found after oral ingestion. This will result in erosion of digestive tract, difficulty in swallowing and gastrointestinal bleeding. Eye and skin irritation is sometimes obtained when there is exposure to the skin. Inhalation from this herbicide can cause oral or nasal discomfort, itching, and throat irritation. Severe poisoning can cause dehydration, hypotension, pneumonitis, oliguria, loss of consciousness, liver dysfunction, acidosis, hyperkalemia and dysrhythmia.\textsuperscript{19}

Table 3. Glyphosate intoxication signs and symptoms (Bradberry)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sign and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>No sign and symptoms or laboratories abnormality</td>
</tr>
<tr>
<td>Mild</td>
<td>Buccal irritation and gastrointestinal symptom &lt; 24 hours</td>
</tr>
<tr>
<td>Moderate (minimal one sign or symptom)</td>
<td>Buccal ulceration&lt;br&gt;Esophagitis confirmed by endoscopy&lt;br&gt;Gastrointestinal symptom &gt; 24 hour&lt;br&gt;Gastrointestinal bleeding&lt;br&gt;Transient hypotension&lt;br&gt;Transient oliguria&lt;br&gt;Transient renal abnormalities&lt;br&gt;Transient acid-base abnormalities&lt;br&gt;Transient liver dysfunction</td>
</tr>
<tr>
<td>Severe (minimal one sign or symptom)</td>
<td>Hypotension and need for intervention&lt;br&gt;Loss of consciousness&lt;br&gt;Recurring seizure&lt;br&gt;Renal failure need for renal replacement therapy&lt;br&gt;Airway problem need for intubation</td>
</tr>
</tbody>
</table>
Cardiac arrest  
Death

Diagnosis of glyphosate intoxication is generally through anamnesis, physical examination and laboratory examination. History of glyphosate exposure, glyphosate intoxication signs and symptoms, blood or urine examination, gas chromatography and high-performance liquid chromatography are strengthening the glyphosate intoxication diagnosis.  

Until now there has been no antidote for glyphosate intoxication and management is generally still supportive. The objectives of management are stabilisation, decontamination and aggressive supportive therapy. Supportive management aims to maintain a patent airway, adequate ventilation and good circulation accompanied by close monitoring with electrocardiography and serum electrolytes.  

Gastric lavage or active charcoal can be given to patients if ingestion onset before 1 hour and have no evidence of buccal irritation or burns. Patient with hypotension or cardiac arrhythmias should be treated in ICU for close monitoring. Intravenous fluid administration can be useful in some patients with severe glyphosate cardiotoxicity. Hemodialysis or hemofiltration may be needed for patients with hyperkalemia or acute kidney injury (AKI). Early kidney replacement therapy can improve prognosis, but there is no reliable evidence.  

Intravenous fat emulsion (IFE) is used for the management of toxicity from local anaesthetics, calcium channel blockers, tricyclic antidepressants and beta-blockers. IFE can be useful in glyphosate intoxication with severe poisoning that is refractory to inotropic supportive therapy and increases safety without further sequels. The mechanism of action of IFE can be caused by reducing the serum concentration of free surfactant POEA component of GlySH (which is more lipophilic) by attracting the fat complemented by IFE thereby reducing its cardiovascular toxicity.  

Fatal conditions occur around 2-3% in patients who ingest large amounts of highly concentrate glyphosate, generally more than 75 ml or at least with 10% glyphosate concentration. Patients who experience AKI, hyperkalemia, pulmonary oedema and metabolic acidosis are more likely to have higher mortality rate. Metabolic acidosis, chest x-ray abnormalities, tachycardia and elevated creatinine, are important prognostic factors in the mortality of glyphosate intoxication patients.  

Conclusions
Herbicide intoxication is a common condition in ICU, especially in developing countries. An intensivist, especially in developing countries, must increase suspicion for herbicide intoxication in ICU settings because there is no specific sign and symptoms. This condition has a bad prognosis and does not have a particular treatment yet. Treatment for this intoxication is supportive, and there is still no specific treatment for herbicide intoxication. Future studies for particular treatment are needed because of high mortality and morbidity rate, especially in developing countries.

References


