

Glyphosate Poisoning with Acute Fulminant Hepatic Failure

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Abstract

Background: Glyphosate containing herbicides are widely used the world over. They are marketed as nontoxic to humans, but numerous studies have showed that these glyphosate-based herbicides (GlySH) can cause multiorgan damage.¹ Recent reports of animal studies on rats have raised a doubt of liver damage after long term exposure to GlySH.

Case Presentation: a young male had chronic exposure to Glyphosate for 5 years in the form of spraying GlySH in farm and eating cereals sprayed with GlySH. He developed fulminant liver failure after accidental consumption of glyphosate containing herbicide. His liver function deteriorated in spite of supportive treatment. He developed hepatorenal syndrome later and died.

Discussion: Studies done on rats have showed that chronic consumption of extremely low levels of a GlySH formulation (Roundup), at admissible glyphosate-equivalent concentrations, is associated with marked alterations of the liver proteome and metabolome.² It has been reported that chronic exposure to Glyphosate of more than 5 years' duration due to consumption of food grains sprayed with this herbicide or inhalation of particles results in development of Fatty Liver, i.e., non-alcoholic fatty liver disease. Any acute insult can result in decompensation and development of fulminant liver failure. Although this herbicide is relatively safe, other complications like Acute renal failure, Acute pulmonary edema with respiratory distress and shock can also occur.

Conclusion: Chronic as well as acute exposure to GlySH can lead to NAFLD and fulminant liver failure. As there is no antidote to glyphosate, clinicians must depend only on intensive supportive management which might not always be fruitful as in our case. It is important to be aware of systemic complications of this commonly used herbicide so that appropriate preventive measures can be taken.

Keywords: Cumulative Effect; Glyphosate Poisoning; Hepatic Failure; NAFLD

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INTRODUCTION

Glyphosate-surfactant herbicide (GlySH) is a general-purpose herbicide with no anticholinesterase effect and no organophosphate-like central nervous system effects (1, 2). GlySH intoxication has a case fatality rate of between 3.2% and 29.3% (3). GlySH, commercially known as 'Roundup', 'Glycel' or 'Lagaam' is used by farmers in Vidarbha region of Central India. Recently, there have been many reports in the regional newspapers about the systemic complications causing morbidity and mortality in farmers of this region, who were chronically exposed to the harmful effects of the insecticides and pesticides, which were hitherto undetected. There exists a rampant off-label pesticide and herbicide use and poor regulatory oversight in India. Now, the cases must be notified to the health authority. Chronic liver damage caused by GlySH has been reported in rats and fish, but no such toxicity has been reported in humans.

CASE REPORT

A 20-year-old male patient was referred to our hospital from a private hospital after 5 days of treatment for alcohol

drinker with increased risk of alcohol accidental ingestion of Lagaam, a GlySH herbicide (Figure 1). (The use of trade names is for product identification purposes only and does not



Figure 1. Glyphosate 41% Pesticide

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imply endorsement.). He had ingested about 25 ml of the liquid when trying to open the lid of the bottle, by holding it between his teeth. He was routinely spraying it in his farm for the last 5 years. Not only that, he also used to consume the grains from his farm which were sprayed by this herbicide. He was a non-alcoholic. Based on this history, we postulated that he had a chronic exposure to GlySH. He had severe anorexia and recurrent vomiting. On admission to our hospital, patient was conscious, well oriented and his vitals were stable. On examination of oral cavity, he had stomatitis, glossitis and multiple mucosal ulcers. He also had icterus (Figure 2). There were no signs of hepatic encephalopathy. There were no petechiae or bleeding tendencies. Systemic examination revealed a liver which was just palpable and tender.

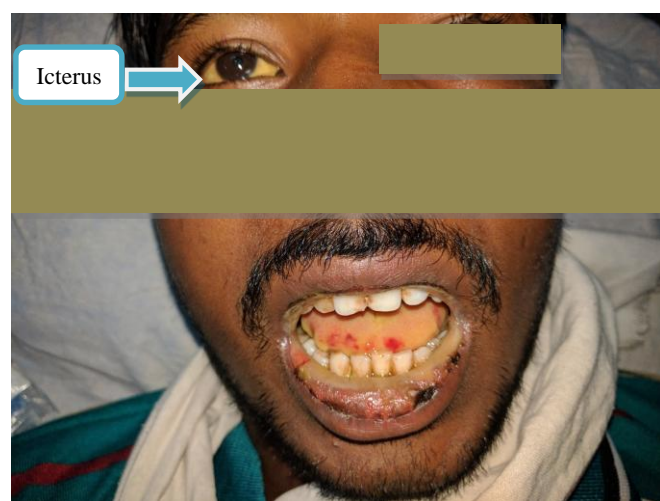


Figure 2. Icterus and Oral ulcers due to GlySH

On investigations, hemogram and complete blood counts were normal. Serum Bilirubin was elevated; 6.3 mg/dl with direct bilirubin of 4.4 mg/dl and indirect of 1.9 mg/dl, and Serum AST was 1021 IU/L and ALT was 1311 IU/L. Serum Alkaline phosphatase was only marginally elevated, i.e., 70 KAU. Patient's serum creatinine was 8.6 mg/dl, blood urea was 179 mg/dl and urine proteins were in traces. Patient's urine output was around 1000 ml/day. Serological markers for infective hepatitis were negative and Elisa for HIV was also negative. Ultrasonography of the abdomen revealed mild hepatosplenomegaly. The echotexture of liver was altered with minimal ascites. There was a layered Gall bladder oedema. Ascitic fluid was aspirated under sonographic guidance and it was transudative on analysis. Slit lamp examination of the eye did not reveal any Kayser Fleisher ring. Sickling test was negative and other investigations for any other cause for liver damage were also normal.

He was started on supportive treatment comprising of intravenous fluids, anti-emetics, proton pump inhibitors, Ursodeoxycholic acid, multivitamins, and Rifaximin. Patient showed initial improvement with treatment as his serum

creatinine and blood urea levels reduced to 3.0 mg/dl and 80 mg/dl, respectively; AST and ALT also decreased to 75 IU/L and 104 IU/L, respectively. But his serum bilirubin increased to 8.9 mg/dl and serum albumin dropped to 2.9 gm/dl. He was given fresh frozen plasma and intravenous albumin. Two days later, patient's condition deteriorated. He developed mucosal bleeding and his ascites increased. He also developed bilateral pleural effusion. His counts were normal and repeat aspiration of ascitic fluid did not reveal any infection. Serum electrolytes were normal. A guarded therapeutic tapping was also done. Next day, he developed gastrointestinal bleed. He developed hepatic encephalopathy and urine output also decreased. He was transfused with 1 unit of compatible blood. He was shifted to intensive care unit. Upper GI endoscopy was done which showed erosive gastritis but no varices. His Prothrombin time and PTTK were elevated suggestive of coagulopathy due to deterioration of liver function. He was given fresh frozen plasma. But his condition continued to worsen. His repeat liver function tests revealed an increased AST and ALT of 234 IU/L and 1271 IU/L respectively, and serum bilirubin of 20 mg/dl. Renal parameters also worsened; serum creatinine was 7 mg/dl and blood urea level increased to 130 mg/dl. Arterial blood gas analysis showed pH of 7.3 and serum bicarbonate level of 16.0 mg, suggestive of uncompensated metabolic acidosis. He was given slow haemodialysis after which his creatinine came down to 1.8 mg/dl. His liver function failed to improve and in next 3 days he became comatose. He developed a massive bout of GI bleed and succumbed despite all supportive and resuscitative measures.

DISCUSSION

Glyphosate based herbicide is one of the most advanced herbicides as the crops have been genetically modified to increase their tolerance to it. Dr. Henri Martin, who is a Swiss scientist working for a pharmaceutical organization, found glyphosate [N-(phosphonomethyl) glycine] in 1950 (4). In 1970, the herbicidal function of glyphosate was recognized by Dr. John Franz, and he was the one who defined an end-use item called Roundup first marketed industrially by Monsanto in 1974 (5). "Roundup Ready," hereditarily designed herbicide-tolerant soybean, maize, and cotton assortments were endorsed for being planted in the United States in 1996. This innovative leap forward made it conceivable to use glyphosate as a broadcast, post-rise herbicide, in this way drastically broadening the course of time amid which glyphosate-based herbicides could be utilized. Since glyphosate is reasonably steady and motile, levels in surface and groundwater will probably ascend parallel with use, and this will expand the variety of potential paths for animal and human exposures (6). In India also GlySH is widely used as an herbicide.

Most people are exposed to glyphosate through water and through residues in foods, in particular cereals and pulses. Its use on farms has increased exponentially over the last 20 years since the introduction of genetically modified crops, which are engineered to withstand repeated sprayings with GlySH and not die. Round up, it is presently the most ubiquitous herbicide used across the country; it has permeated

our food supply indefinitely. Traces of this toxic substance have even been found in rainwater and air samples.

After oral ingestion of GlySH, 30–36% is absorbed and peak concentrations occur in tissues 6 hours following dosing, undergoes little metabolism, and is excreted mostly unchanged in the faeces and secondarily in the urine. The spectrum of GlySH poisoning includes minimal irritation of eyes to severe as shock and death (3). Severe poisoning causes dehydration, hypotension, pneumonitis, oliguria, altered level of consciousness, hepatic dysfunction, acidosis, hyperkalaemia, and dysrhythmias (7). A recent detailed review on GlySH reported that adverse human impacts include acute poisoning, kidney and liver damage, imbalances in the intestinal microbiome and intestinal functioning, cancer, genotoxicity, endocrine disruption, reproductive and developmental reduction, neurological damage, and immune system dysfunction. The ingestion of products containing glyphosate isopropylamine or ammonium salts, and polyoxyethyleneamine (POEA) as a surfactant can cause severe organ injury (8).

A number of toxicity studies have demonstrated that glyphosate and its business details have non-target impacts on mammalian digestion and incite poisonous impacts, particularly as for liver and kidney structure and capacity. Potential unfavorable hepatic impacts of glyphosate were first seen during the 1980s, including its capacity to upset liver mitochondrial oxidative phosphorylation. As glyphosate can go about as a protonophore expanding mitochondrial membrane penetrability to protons and Ca^{2+} , it can trigger the creation of responsive oxygen species caused in oxidative stress observed. Studies demonstrate that glyphosate changes liver chemical trends, disturbs mitochondrial oxidative phosphorylation, harms liver cells, harms DNA, and can lead to tumors. A portion of these impacts (enzymes, cell harm) happen at low dimensions of exposure. Some impacts are more grounded with definitions than specialized glyphosate (9).

Robin Mesnage et al in their study on rats found that consumption of far lower levels of a GlySH formulation, at admissible glyphosate-equivalent concentrations, is associated with wide-scale alterations of the liver and kidney transcriptome that correlate with the observed signs of hepatic and kidney damage as a result of anatomorphological and biochemical pathological changes in these organs. They reported the first in vivo multiomic analysis combining the proteome and metabolome profiles of the livers from rats following long-term (2-year) exposure to a GlySH (Roundup) at an environmentally relevant dose (50 ng/L glyphosate equivalent concentration; 4 ng/kg bw/day). Their integrated analysis of these molecular profiles was clearly reflective of features of non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH) (10). Our patient also had a low dose long term exposure of 5 years to GlySH. He might have had underlying NAFLD and acute decompensation of liver

function must have occurred following accidental ingestion of GlySH.

CONCLUSION

There is no specific antidote for GlySH or its surfactant poisoning. The treatment is usually supportive. Gastric lavage, activated charcoal administration, intravenous fluids and vasopressors are helpful when used early. Continuous veno-venous hemodiafiltration can be beneficial in Acute kidney injury and intravenous (IV) lipid emulsion (20% intralipid 100 ml) has been useful in some cases of multiorgan involvement. Our patient improved with slow hemodialysis, but he succumbed to fulminant hepatic failure.

This case report is to emphasize on the hepatotoxicity of glyphosate containing herbicide which can be lethal even with aggressive supportive treatment. Those farmers who are using it chronically should be screened for presence of NAFLD.

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