RESEARCH ARTICLE

A CASE REPORT ON NEAR FATAL PRESENTAION WITH SULFAMETURON-METHYL (NON UREA SYNTHETIC SULFONYLUREA) HERBICIDE POISONING.

Dr. Sayani Banerjee, Dr. Sujoy Das Thakur and Dr. Santosh Kumar Singh.

Abstract

**Background:** We present a case of sulfonylurea herbicide poisoning of a 65 year containing Sulfometuron methyl (75%).

**Clinical Presentation:** Though the literature suggests they are less toxic to human in acute poisoning, in our case report patient presented with acute respiratory failure, ARDS, metabolic and respiratory acidosis.

**Conclusion:** self-poisoning with these newer non-urea synthetic organic herbicides including metsulfuron-methyl is a newly emerging phenomenon in India. Limited information regarding their toxic effects in human poses several clinical challenges to the treating physician. Literature suggests they are less toxic to human in acute poisoning, which is contradictory to the presentation in our case. There is no specific antidote available for sulfometuron methyl poisoning. Thus further documentation and research are needed to contrive more organized understanding in the clinical presentation, fatal possible outcomes of these herbicides’ poisoning, thereby formulate a consensus regarding approach in the management.

Introduction:-

Despite widespread availability and use of herbicides of different kinds, relatively little has been published on acute poisoning with herbicides and their effect on human in acute toxicity, other than paraquat and glyphosate. We are reporting a case of self-poisoning with herbicide containing sulfometuron methyl 75%, which is a broad spectrum sulfonylurea herbicide without EU regulatory approval for use. General population exposure to sulfonylurea herbicides is still not well known in India, while the use of it is steadily increasing in modern agriculture. This was first marketed in the early 1982 for control of nuisance broadleaf weeds and grasses. Sulfonylurea herbicides are about 100 times more toxic to plants than older herbicides, and sulfometuron methyl is “one of the most potent” herbicide in this family. It inhibits the acetolactate synthase (ALS) enzyme (also known as acetohydroxyacid synthase, or AHAS) which acts on the first step in the synthesis of the branched-chain amino acids (valine, leucine, and isoleucine). Sulfonylurea herbicides slowly starve affected plants of these amino acids, which eventually leads to inhibition of DNA synthesis. They affect grasses and dicots alike both in pre and post emergence phase. Used in non-crop sites. In mammals, following oral administration, metsulfuron-methyl is excreted predominantly unchanged. The methoxycarbonyl and sulfonylurea groups are only partly degraded, by O-demethylation and hydroxylation.

Corresponding Author:- Dr. Sayani Banerjee.
Molecular Structure

IUPAC Name
2-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]-oxomethyl]sulfamoyl]benzoic acid methyl ester

CAS Registry Number
74223-64-6

Chemical formula
C14H15N5O6S

Case Presentation:
We present a case of a 65 year old male presented in our emergency in an intubated, ventilated and unconscious state with alleged history of suicidal ingestion of approximate 40 ml of poison named "Spyder" containing Sulfometuron methyl (75%) 7 days ago, denied any co-ingestion of pesticides or organophosphate or carbamate compound., admitted outside at 5th hour of ingestion where he was received in a gasping condition, intubated and ventilated, gastric lavage was done and then managed conservatively with intravenous infusion of atropine, PAM, prophylactic antibiotic and other supportive treatment. On day 5 he was extubated and then again intubated on Day 7 due to progressively increasing dyspnea, tachypnea and drowsiness and referred to higher center to our hospital.

On presentation in ER patient had following findings:

CNS - unconscious and unresponsive, GCS being E1V1M1, Pupils bilaterally 3.5mm & reactive to light. BP=130/80mmHg, HR=130/min, SpO2=98% (Endotracheal Tube in situ, FiO2=0.6, RR=22/min on pressure control ventilation, Capillary blood glucose 108mg/dl. CVS= S1 & S2 audible, No murmur. Chest on auscultation = bilateral crepitation +

Blood investigations revealed:
Hemoglobin=13.7gm/dl,
Total Leukocyte Count=10400/cumm (N86L09)
Platelet count=2,24,000/microliter
Renal & Liver function tests were within normal limits.

On presentation to our ER, his chest x-ray antero-posterior view & arterial blood gas was suggestive of adult respiratory distress syndrome secondary to chemical pneumonitis. In due course, patient was managed by lung protective ventilation, intravenous broad spectrum antibiotics and other supportive treatment. Atropine and PAM infusions were omitted. Patient was extubated after 20 days of ventilator support. Patient was also having persisting hypernatremia, which was managed with replacing intravenous normal saline with intravenous dextrose containing solution. On day 22, he started having febrile spikes and his total leukocyte count went up to 24,000/cumm with neutrophilic leukocytosis, intravenous antibiotic was escalated to meropenem from piperacillin+tazobactum and he responded to the treatment. Patient was discharged on 32nd day.

Arterial blood gas on Day1 vs Day2 are:

| Arterial blood gas parameter | Day7 | Day1 |
|------------------------------|------|------|
| pH                           | 7.365| 7.00 |
| P02 (mmHg)                   | 56.8 | 83   |
| Pco2 (mmHg)                  | 45.2 | 50   |
| HCO3 (mmol/L)                | 25.3 | 12   |
| Na+ (mmol/L)                 | 151.9| 145  |
| K+ (mmol/L)                  | 4.60 | 4.3  |
| MetHb                        | 0.7% |      |
| COHb                         | 1.2% |      |
| Lactate (mmol/L)             | 1.15 |      |
| SO2                          | 88%  | 85%  |
| FiO2                         | 1.0  | 1.0  |
| PaO2/FiO2 Ratio              | 56.8 | 83   |
Discussion:
Self-poisoning with pesticides is a major public health problem across the Asia Pacific Region. It is estimated that globally 250-370,000 people die from pesticide poisoning each year. According to the extension toxicology network and toxnet database, Metsulfuron-methyl is classified by EPA in acute Toxicity Category III, and must bear the signal word "Caution" on commercial products. These agents have low systemic toxicity. Eye exposure may result in ocular irritation. Irritation of the respiratory mucous membranes may be observed following prolonged heavy contact. Irritation of skin has been noted upon exposure. Severe toxicity has only been reported after deliberate ingestion. Nausea, vomiting, abdominal pain, and diarrhea have been reported. Methemoglobinemia may rarely occur following large ingestions, and may be delayed in onset. Patients that have methemoglobin concentrations greater than 30% are more likely to develop severe symptoms. Patients may develop headache, fatigue, weakness, dizziness, syncope, and tachycardia with methemoglobin concentrations 20% to 40%. With methemoglobin concentrations 40% to 60%, dyspnea and increasing respiratory distress may occur. Patients with methemoglobin concentrations greater than 60% may develop coma, seizures, cardiac dysrhythmias, and cardiorespiratory arrest. Hemolysis has also been reported.

| Acute toxicity | This chemical has very low toxicity in mammals. Based on laboratory tests, the oral dose of metsulfuron-methyl that causes mortality in half of the test animals (LD50) is > 5,000 mg/kg in rats. It has low dermal toxicity in tests with rabbits, with an LD50 > 2,000 mg/kg, and low inhalation toxicity in rats, with a median lethal concentration in air of greater than 5 mg/liter air. Moderate but reversible eye irritation has been seen in rabbits, and mild skin irritation has been observed in guinea pigs. No skin sensitization has been observed in guinea pigs. Systemic poisoning by sulfonylurea based compounds is unlikely, unless large quantities have been ingested. No accounts of poisoning by metsulfuron- methyl are currently available. |
| Chronic toxicity | A 2-year feeding study in rats resulted in a No Observable Effects Level (NOEL) of 25.0 mg/kg/day (or 500 ppm in feed), based on decreased body weights seen at 250 |
mg/kg/day (5,000 ppm) which was the highest dose tested. EPA has based its reference dose (0.25 mg/kg/day) on this study<sup>9</sup>.

| 1) Reproductive Effects | Multigeneration studies in rats did not result in any reproductive effects at the highest doses tested of 250 mg/kg/day<sup>9</sup>. |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 2) Teratogenic Effects  | Metsulfuron-methyl did not cause developmental abnormalities to offspring of rats and rabbits fed 1000 mg/kg/day and 700 mg/kg/day respectively during gestation. These doses represent the highest dose tested for each experiment<sup>9</sup>. |
| Mutagenic effect        | The weight of evidence presented by a battery of tests to measure mutagenicity and other adverse effects on DNA indicates that metsulfuron- methyl is neither mutagenic nor genotoxic<sup>10</sup>. |
| Carcinogenic effect     | Negative for rats and mice in laboratory tests, but studies may not have been at maximum tolerated dose<sup>10</sup>. |
| 3) Organ Toxicity       | Metsulfuron-methyl is a moderate eye irritant<sup>10</sup>. |
| 4) Fate in Humans and Other Animals | The chemical is broken down quickly and eliminated from the body. In tests with radiolabeled metsulfuron-methyl in rats, the excretion half-lives ranged from 9 to 16 hours and 23 to 29 hours for rats administered low and high doses, respectively. It did not bio accumulate in fish<sup>10</sup>. |

Following oral exposure, in mild to moderate toxicity of sulfometuron methyl, management is supportive. Decontamination by washing exposed skin and irrigate exposed eyes thoroughly. Consider activated charcoal only after large, recent ingestions in patients who are alert and can protect the airway. Obtain a methemoglobin concentration in cyanotic patients. Treat symptomatic methemoglobinemia (usually at methemoglobin concentrations above 20% to 30%) with methylene blue and oxygen therapy. Patients with severe hemolysis may require transfusion.

**Conclusion:-**

In conclusion, self-poisoning with these newer non-urea synthetic organic herbicides including metsulfuron-methyl are a newly emerging phenomenon in India. Limited information regarding their toxic effects in human poses several clinical challenges to the treating physician. Though the literature suggests they are less toxic to human in acute poisoning, in our case report patient presented with acute respiratory failure, ARDS, metabolic and respiratory acidosis. Symptoms are non-specific and high clinical suspicion and a good clinical history is key to the diagnosis. There is no specific antidote available for sulfometuron methyl poisoning. Methemoglobinemia and severe hemolysis are rare but dreaded complications of these herbicides. Further research is needed for metsulfuron-methyl and other sulfonylurea herbicides to contrive a holistic approach to the potential life threatening acute poisoning of these herbicides.

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