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RESEARCH ARTICLE

FIRST CASE REPORT ON METRIBUZINE, AN HERBICIDE SUICIDAL POISONING, PRESENTED WITH FATAL METABOLIC ACIDOSIS, ACUTE RENAL FAILURE, AND HYPOKALEMIA.

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Abstract

Background: A 27 years female patient presented within 21 hours of alleged history of suicidal ingestion of Metribuzine, an herbicide, in a drowsy state and with acute renal failure.

Clinical Presentation: Patient's arterial blood gas revelaed severe fatal metabolic acidosis and hypokalemia. Inspite of aggressive resuscitation with early invasive positive pressure ventilation, intravenous crystalloid, intravenous potassium and sodium bicarbonate, patient went into cardiac arrest and after 1 hour of high quality cardiopulmonary resuscitation patient died. During resuscitation clinical signs of pulmonary oedema and hemorrhage also noticed.

Discussion and Conclusion: Metribuzine, inspite of being an widely used herbicide, no case has been reported so far, specially with fatal outcome. No data available in human. Animal studies concluded that it is a non acutely toxic herbicide in mammals. Though we differ seeing the fatal outcome in our case and suggest more extensive studies in human.

Introduction:-

Herbicide is considered most detected pollutant chemical in water and besides synthetic fertilizers it also leads to disturbance in the biodiversity of the ecosystem and its residues enter food chain and finally ingested by human. So environmental risk of herbicides and protection from it become a global worry.

Metribuzine is a synthetic organic compound used as a selective triazinone pre- and post-emergent weed control herbicide, launched in 1970[1, 2]. Metribuzin is presently sold in more than 75 countries, with the top five being the United States, Brazil, Canada[3], China, and Germany[4]. In India it is sold under various trade names, used as broad spectrum herbicide to control of grasses and broad-leaf weeds sugar-cane, potato, tomato, wheat, soy-bean. It effectively controls Phalaris minor, which has developed resistance to most of the herbicides in addition to many other grasses and broad leaf weeds.

Microbial degradation is the principal route of removal of metribuzin from the soil. Metribuzin is reported to be rapidly detoxified by deamination by the soil fungus Cunninghamella echinulata[6], also moderately adsorbs to soil with high clay and/or organic matter content[5, 7, 8].

Table 1:-

Common Name	Metribuzine
IUPAC Name	4-amino-6-tert-4,5-dihydro-3-methylthio-1,2,4-triazin-5-

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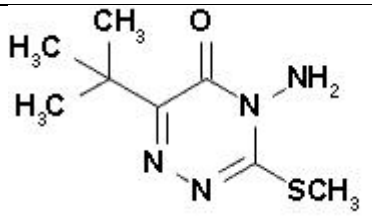
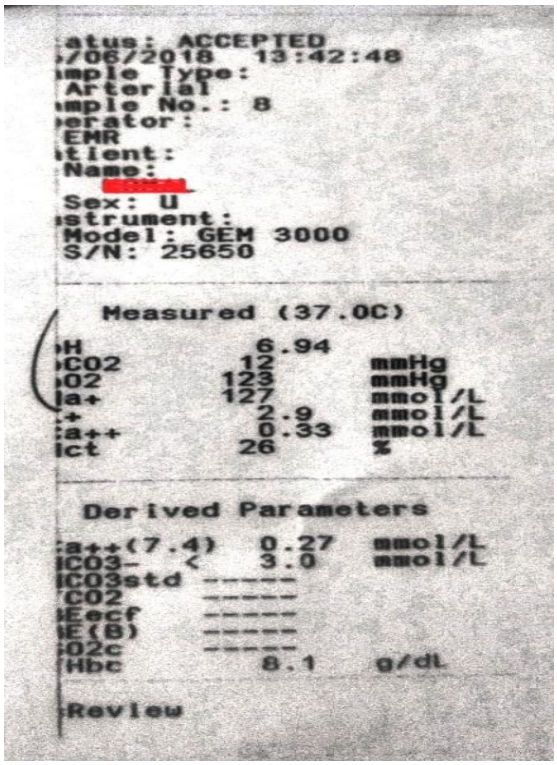
	one
Chemical Abstracts Services Registry Number	21087-64-9
Molecular Weight	214.3
Molecular Formula	
Appearance	White to offwhite crystalline powder
Formulations	70% WP

Case presentation:

We are reporting a case of acute suicidal ingestion of aprox. 500mg Metribuzine, by a 26 years old female, who presented in emergency room after 21 hours of ingestion, in a state of altered mental status, very agitated and anuria for last 6 hours. On presentation, she was tachycardic, hyperventilating; blood pressure was not recordable, maintaining oxygen saturation of 89% in room air, capillary blood glucose of 100 mg/dl. Patient received gastric lavage and atropine i.v. from outside hospital.

12 lead ECG done which was suggestive of sinus tachycardia. Arteiral blood gas done in ER which revealed severe fatal metabolic acidosis: pH=6.94, Pco_2=12, PO_2=123, Potassium=2.9, Sodium=127, Bicarbonate < 3.



We intubated the patient; advanced airway was secured, and ventilated. Almost 2Litre of intravenous crystalloid fluid was rushed via 2 large bore peripheral intravenous accesses. Intravenous 200ml 8.4% sodabicarbonate and potassium were given and 200ml sodabicarbonate intravenous infusion was started. Shortly, after 30 minutes of arrival in ER patient went into cariac arrest. Cardiopulmonary resuscitation was started immediately as per ACLS protocol but after almost one hour of high quality of CPR patient could not be revived. During resuscitation copious

pink frothy secretions with fresh blood were noticed to come out from endotracheal tube, suggestive of pulmonary oedema and also pulmonary hemorrhage.

Discussion:-

No reports on the effects of exposure of humans to metribuzin were identified in the literature. Hazard characterization has therefore been accomplished in animal toxicity studies. Metribuzin is considered to be relatively non-acutely toxic to mammals[9].

Studies in rats reported to eliminate about 80% in the first day following administration, and 95% by the second day after intragastric administration of Metribuzine. Almost equal amounts were found in the urine and faeces. The major urinary metabolite was deaminometribuzin mercapturate[10]. Metabolites identified in the tissues included the deaminated metabolite, the diketo metabolite and the deaminated 1 diketo metabolite, the diketo metabolite is 2 to 3 times more toxic in rats than the parent compound, whereas the deaminated and deaminated diketo metabolites are of equivalent toxicity[11].

Kimmerle et al. (1969) showed that metribuzin was not an eye irritant in a primary eye irritation test in rabbits. Another study also conducted by Kimmerle et al. in 1969, metribuzin exposure produced very slight irritation of rabbit skin. However, it has not been shown to produce sensitization effects in guinea pigs (ACGIH, 1986).

Table 2:-Acute Toxic Effects of Metribuzine

Species	Active Ingredient	Route of Exposure	Results	Reference
Rat	Not specified	Oral	LD50: Males 2,300 mg/kg Females 2,200 mg/kg	Kimmerle et al.,1969
Rabbit	Not Specified	Dermal	LD50: > 20,000 mg/kg	Crawford and Anderson, 1972
Rat	Not Specified	Oral	LD50: Males 1,090 mg/kg Females 1,206 mg/kg	Crawford and Anderson, 1974
Guinea Pig	Not Specified	Oral	LD50: Males 245 mg/kg Females 274 mg/kg	Crawford and Anderson, 1974
Rat	Not Specified	Oral	LD50: Males 2,379 mg/kg Females 2,794 mg/kg	Mobay Chemical, 1978a
Rat	Not Specified	Dermal	LD50: > 5,000 mg/kg	Mobay Chemical, 1978a
Rat	Not Specified	Inhalation	LC50: > 20,000 mg/m3	Mobay Chemical, 1978a
Rat	Not Specified	Oral	LD50: 1,100 mg/kg	Morgan, 1982
Mouse	Not Specified	Intraperitoneal	LD50: 210 mg/kg	PCBPBS, 1984
Rat and Rabbit	Not Specified	Dermal	LD50: > 2,000 mg/kg	ACGIH, 1986
Mouse	Not Specified	Inhalation	LC50: > 860 mg/m3	ACGIH, 1986
Rat	92.6%	Inhalation	LC50:> 648 mg/m3	Shiotsuka, 1986
Mouse	Not Specified	Oral	LD50: 698- 711 mg/kg	Hartley and Kidd, 1987
Cat	Not Specified	Oral	LD50: > 500 mg/kg	Hartley and Kidd, 1987
Guinea Pig	Not Specified	Oral	LD50: 250 mg/kg	Hartley and Kidd, 1987
Rat	Not Specified	Percutaneous	LD50: > 20,000 mg/kg	Hartley and Kidd, 1987

Mahmoud M Elalfy et al (2017), found in his study in rats, Metribuzine to caused decrease in weight gain ratio of albino rats, proportional with increase in dose level, increased liver enzymes (ALT and AST), significant elevation of LDH, urea and creatinine, decreased glucose, cholesterol, total protein and albumin level. Histopathological changes in liver, kidney and spleen and testes were documented. Significant normocytic normochromic anemia and leukocytosis noticed. Additionally, at a dose of 440 mg/kg metribuzin induce anomalies in both head and tail of sperm and reduced level of IL-2 expression in liver and level of globulin[12].

In a two-year feeding study in beagle dogs reviewed by the Food Directorate of the Department of National Health and Welfare, food consumption and body weight gain were reduced in the highest dose group (55.5 mg/kg bw per day); thyroid weight in males and females and liver, spleen and kidney weights in males were increased relative to body weights. At 3.5 mg/kg body weight per day, there was an increase in the incidence of necrobiosis of the liver, mucopolysaccharide droplets in the lobular periphery of the liver weres also noted. No-observed adverse-effect level (NOAEL) [13] concluded as 0.83 mg/kg body weight per day,

In accordance with current cancer guidelines (U.S. EPA, 1986a), it is a Class D carcinogen in humans and animals. Metribuzin was not found to be mutagenic or teratogenic in several bacterial assays or microbial point mutation assays[14, 15,16,17,18].

Conclusion:-

No previous case was reported either in India or globally in any past literature, the reason can be due to mostly non fatal outcome. Though in our case report the patient, with acute Metribuzine toxicity had died from severe metabolic acidosis, pulmonary oedema and pulmonary hemorrhage within 24 hours of ingestion, neither of which was mentioned in any previous literature. More so, it is mostly mentioned as having mild to moderate acute toxicity. The reson of severe metabolic acidosis, pulmonary oedema and pulmonary hemorrhage leading to death in our case remains inconclusive. We, the authors suggest further study of toxic effects of Metribuzine in human, especially effects on coagulation profile, vascular system and lung. Also possibility of fatal outcome needs to be studied further, as use of Metribuzine as an herbicide is widespread not only in India but worldwide.

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