Short Communication

Combination of Cardiac, Hepatic and Nephrotoxicity in Atrazine Poisoning: A Case Report and Literature Survey

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ABSTRACT

Not only due to its action but also due to its effectiveness and affordability atrazine is still used as a herbicide in agriculture. Atrazine passes the most stringent, up-to-date safety requirements in the world. In 2006, the United States Environmental Protection Agency (EPA) re-registered atrazine based on the overwhelming evidence of safety from nearly 6,000 studies. However its use is controversial due to widespread contamination in drinking water and its association with birth defects, menstrual problems and cancer when consumed by humans at concentrations below government standards. Although it has been excluded from a re-registration process in the European Union, it is still one of the most widely used herbicides in the world. No information was found on the acute toxicity of products containing atrazine alone in human subjects.

This is a case report of suicide by atrazine resulting in cardiac, hepatic and nephrotoxicity. It is important to note that atrazine can cause such trio-toxicity following ingestion which can result in mortality.

Key Words: 2-chloro-4-ethylamino-6-isopropylamino-s-triazine; Atrazine; 2,3-diamino-6-chloro-s-triazine; DACT; Herbicide; Weedicide

Introduction

For decades farmers around the world have relied on the chemical atrazine as a genuine herbicide which fights effectively in controlling a broad range of yield-robbing weeds in corn, grain sorghum, sugar cane and other crops. Not only due to its action but also due to its effectiveness and affordability atrazine is used in agriculture even today. It is safe to the crop and fits to a variety of farming systems and favours yield. Atrazine passes the most stringent, up-to-date safety requirements. In 2006, the United States Environmental Protection Agency (EPA) re-registered atrazine based on the overwhelming evidence of safety from nearly 6,000 studies.[1]

However its use is controversial due to widespread contamination of drinking water and its association with birth defects, menstrual problems and cancer when consumed by humans at concentrations below government standards.[2] Although it has been excluded from a re-registration process in the European Union,[3] it is still widely used. There is scarce information on the acute toxicity of products containing atrazine alone in human subjects.[4]

Aside from above mentioned health hazards, in order to create awareness among medical practitioners treating atrazine poisoning, we present a case of suicide by ingestion of atrazine which resulted in cardiac, hepatic and nephrotoxicity. Literature survey reveals minimal information regarding the fatality associated with this trio-toxicity of atrazine.

The Case: An apparently healthy 35-year old farmer, moderately built, and averagely nourished consumed a herbicide (weedicide) containing atrazine, and was brought to the emergency department after a time lapse of six and half hours with altered sensorium, and passing red coloured urine. The relatives produced the container of the consumed compound.

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Examination of the patient revealed the following: afebrile, pulse 156/ min, regular, low volume, character and condition of vessel wall normal, blood pressure 140/90 mmHg, respiratory rate 38/min and oxygen saturation 70%. Renal parameters: blood urea 185mg%, serum creatinine 5.5. Liver function revealed total bilirubin 2.9, direct bilirubin 0.43, total protein 6.5, serum albumin 2.9, albumin/globulin ratio 0.8, SGOT 2599 and SGPT 449. Serum electrolytes: Na^+ 162 mEq/L, K^+ 6.9mEq/L, HCO^-_3 16mEq/L, Cl^- 123mEq/L. Patient had low platelet count of 36,000 and was administered 3 pints of platelet-rich transfusion.

A high performance liquid chromatography (HPLC) method revealed the presence of atrazine in gastric aspirate sample, which correlated with that of the container. The test was negative for other common compounds such as organophosphorus, organochlorine, carbamates and pyrethroids. Haemodialysis was performed in an effort to eliminate the toxic substance and stabilize the renal parameters. The patient expired after a survival period of 20 hours.

On autopsy, most of the the organs were congested. Tissue samples weighing approximately 10g were taken from the kidneys, liver and heart, and were homogenized, and the concentration of atrazine was estimated. The highest concentration of atrazine was found to be in the kidneys with lesser concentration in liver, and least in the heart.

Discussion

Atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine), an organic compound consisting of s-triazine ring, belongs to the chemical class triazine, and is a colourless crystalline powder with molecular weight 216, sparingly soluble in water, and readily soluble in ether, chloroform and methanol. It is available in the form of odourless grayish-brown granules. Toxicity can result from ingestion and inhalation; there can be mild to moderate irritation when it comes in contact with skin or eye.

In circumstances of poisoning there is no specific antidote, and the treatment is based on symptomatic and supportive care.[4] The United States Department of Health and Human Services, and Public Health Service Agency for Toxic Substances and Disease Registry reveal that damage to liver, kidneys, and heart has been observed in animals exposed to atrazine; it is not clear if this would also occur in humans.[5] In the case being reported, aside from hepatic and nephrotoxicity, cardiotoxicity was also noted. Features included acute renal failure and haematuria with severe thrombocytopenia, associated with sinus tachycardia, ventricular fibrillation, altered liver function and electrolyte imbalance.

In experimental animals, cardiac toxicity seen with high doses of atrazine was doubtfully attributed due to the metabolite of atrazine, 2,3-diamino-6-chloro-s-triazine (DACT).[6] Significant fatal arrhythmia was determined as the clinical cause of death. Chemical toxicity rapidly changes the cyto-architecture of liver and kidney due to the stress of metabolism and excretion. Even though acute clinically significant disturbances in hepatic and renal parameters were noted, histo-pathological studies revealed only congestion. This can be probably attributed to the short survival period. Histopathologically there was no change in the heart.

Arakawa stated that chemical injury causes denudation of vascular endothelium which results in alteration in endothelial cell integrity and function.[7] This induces pro- and anti-inflammatory molecular adhesion which releases hypoxia-inducible factor-1 alpha (HIF-1alpha), and causes damage to the intima with thrombus formation. Vessel occlusion occurs leading to tissue ischaemia and necrosis.[7] In toxic acute renal injury, extensive necrosis is present along the proximal convoluted tubule segments and necrosis of distal tubule, particularly ascending Henle's loop occurs. Vis-à-vis ischaemic acute renal injury, tubular necrosis is patchy, and a relatively short length of tubules are affected, while straight segments of Henle's loop are most vulnerable.[8] The loss of polarity in tubule cell injury increases distal sodium delivery.

Pommery et al reported hepatic necrosis and acute renal failure in one case of ingestion of an atrazine-containing herbicide formulation. However, the formulation also contained amitrole, ethylene glycol and formaldehyde, and the exact causative agent is uncertain.[9] In an animal study, Gammon et al revealed cardiotoxicity and oncogenecity on chronic exposure and developmental toxicity on acute exposure to atrazine.[10] Quantitative analysis was unable to establish the fatal dose in this case. The material safety data sheet of Sipcam Agro USA claims that atrazine is only a moderate health hazard, and it has very low acute toxicity, with oral lethal dose (LD) of >3000 mg/kg in Sprague–Dawley rats (SD rats). The LD by dermal route is more than 3,100mg/kg among rats.[11] Meaningful extrapolation of animal data to humans is difficult, but it

would be wise to assume ~100 mg/kg (1/20 of the rat LD) could be an acute toxic dose in human subjects.[4]

As per the World Health Organization, animal acute toxicity LD data of individual compounds are assigned to one of four groups, in decreasing order of toxicity as laid out in **Table 1**.[12]

Table 1

Class	LD50 (Rat – mg/kg body weight)			
	Oral		Dermal	
	Solid	Liquid	Solid	Liquid
Ia	<5	<20	<10	<40
Ib	5–50	20–200	10–100	40–400
II	50–500	200–2000	100–1000	400–4000
III	>500	>2000	>1000	>4000

The metabolites of atrazine which are excreted in the urine are claimed to be responsible for some of the toxic effects. Extractive electrospray ionization mass spectrometry (EESI-MS) method detects atrazine and its metabolites in undiluted raw urine. Zhou et al detected 4.3×10^{-14} g atrazine in spiked raw urine, identified by EESI-MS. A single sample analysis was completed using tandem EESI-MS within 1 min, providing a practical convenient method for rapid analysis of trace amounts of targeted metabolites present in complex matrices.[13]

Conclusion

Atrazine poisoning can be the cause of sudden death following ingestion. Clinicians as well as forensic toxicologists should be aware of the fact that atrazine poisoning can present as trio-toxicity comprising cardiac, hepatic and nephrotoxicity, and hence this should be given due importance in antemortem as well as postmortem diagnosis.

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