

Amitraz Poisoning: A Case Report of an Insufficient Acknowledged Poison in Nigeria

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Abstract

Amitraz is a pharmacological product widely used in the veterinary setting, in the control of ectoparasites (e.g., ticks and mites), in the treatment of demodicosis in dogs, cattle etc, and in the agricultural setting as a pesticide. There have been a limited number of cases of amitraz poisoning published in the literature, as it is often under-recognised and mistaken for organophosphate poisoning (OPP). So far, there has been no specific antidote for its management. However, case reports on successfully managed patients are available and may assist doctors and other medical practitioners in the management of such cases. This index case is that of an 18-year-old male secondary school leaver who ingested an unknown quantity of an amitraz containing insecticide in a suicidal attempt and was brought to Enugu State University Teaching Hospital about 3.5 hours later, following a prior visit to a clinic close to his home. He received both symptomatic and supportive treatment, recovered fully within 3 days and was discharged on the sixth day and referred to psychiatric department for further supportive management. It is pertinent to avoid misdiagnosis as it may lead to respiratory failure, necessitating the use of ventilators which are not available in a significant number of hospitals in Nigeria.

Keywords: Amitraz, poisoning

1. Introduction

Amitraz is a member of the formamidine family of pesticides. It is chemically known as 1, 5-Di (2, 4-Dimethylphenyl)-3-methyl-1,3,5-Triaza-Penta-1,4-Diene. It has emerged as an established cause of poisoning in humans and animals. It is commercially available in formulations generally containing 12.5-20% of the compound dissolved in organic solvents like xylene, acetone and toluene. Amitraz poisoning in humans as against animals is fairly uncommon. In humans, majority of cases are among children and depressed patient as a suicidal attempt. Of the 137 cases reported in journals, 119 were in children. Eizadi-Mood, Sabzghabae, Gheshlaghi, Yaraghi (2011) reported one case of Amitraz poisoning in humans in Iran as a result of suicidal attempt. Further report in 2011 reveals that 69 cases were reported in South Africa and two cases in Kenya as at 2016. In Nigeria, no case of Amitraz poisoning in humans have been reported, despite its use in the agricultural and veterinary settings. This may be as a result of this poisoning being under-recognised and mistaken for organophosphate poisoning. However, there have been cases of amitraz poisoning reported in animals in Nigeria. We present the case of an 18years old male with Amitraz poisoning.

2. Case Presentation

An 18-year-old male secondary school leaver who resides with his parents was brought to the Enugu State University Teaching Hospital emergency room with a 3 hour history of loss of consciousness. He was found by his mother after he consumed an unknown quantity of an amitraz containing insecticide, following a domestic dispute. He was taken to a nearby clinic where he was administered activated charcoal. However, symptoms persisted, necessitating presentation to the above centre. He had a background history of depression but has not been adherent of clinic visits. There was no history of seizures, vomiting, and diarrhoea, copious secretions from the mouth or nose, or diaphoresis.

On examination, he was unconscious with a Glasgow Coma Scale (GCS) score of 4/15 (M-I, V-2, E-I). Pupils were pin point bilaterally. The patient's vitals were; temperature- 35°C, pulse- not palpable, blood pressure- non-recordable, oxygen saturation- 89% on room air, and there was no respiratory effort. Abdomen was not distended. Cardiopulmonary resuscitation was commenced with the vitals being monitored concurrently. About 3 minutes into the resuscitation, the vital signs improved; pulse-57bpm, blood pressure- 120/70mmHg, respiratory rate- 9cycles/minutes (shallow breaths). He was administered intravenous Atropine sulphate and other supportive measures like, use of warming blanket to counter hypothermia, administration of activated charcoal, oxygen supplementation, fluid replacement with warm normal saline and intravenous hydrocortisone, were instituted. He was subsequently admitted in to the intensive care unit (ICU). An initial diagnosis of organophosphate poisoning (OPP) was made, but following a review by the clinical pharmacological unit, a definitive diagnosis of Alpha 2 adrenergic agonist poisoning was made.

On the second day of admission, he remained unconscious. However, there was a slight improvement in the level of consciousness, evidenced by a GCS score of 8/15 (M- 4, V- 2, E- 2). Pupils were dilated and fixed bilaterally. Available investigation showed elevated creatinine level (252umol/L).

He regained full consciousness on the third day with a GCS score of 15/15. He had significant clinical and laboratory improvement and was subsequently transferred from the ICU to the general ward. In the general ward, he was being seen by the physicians, psychiatrists and clinical psychologists. After six days in the general wards, he was discharged to out-patients clinic to continue his medical, psychiatric and psychological treatment.

3. Discussion

3.1 General

For a patient presenting with pharmacological poisoning, two important issues are relevant to the successful management of the case. The first is emergency treatment of the acute poisoning in order to save the life of the patient. The second is to determine whether the poisoning was intentional or unintentional as intentional poisoning means attempted suicide, which is a more complicated problem than accidental pharmacological poisoning. In attempted suicide by intentional pharmacological poisoning, (just like attempted suicide by any other method), there is a likelihood of recurrence either by the same method or by a more lethal method if the risk factors for suicide persist. Therefore, any neuropsychiatric disorder which will continue to predispose the patient to suicidal ideation should be identified and treated. Also, the clinical psychologists should try to identify other risk factors for suicide in the patient and also plan and institute the necessary psychological intervention. The overall aim will be to improve the quality of life of the patient and also significantly reduce suicidal ideation in the patient. And that way, recurrent attempts at suicide will be minimised or may even become eradicated in the patient. The index patient was suffering from depression and also he attempted suicide by intentionally ingesting amitraz. Therefore, it is important to discuss the medical treatment of amitraz poisoning as well as the psychiatric and psychological aspects of the management.

3.2 Medical Management of Amitraz Poisoning

Amitraz poisoning can be described as an onslaught of acute symptoms resulting from intentional or unintentional exposure to a significant dose of an Amitraz containing substance through inhalational, oral or dermal routes. According to Yilmaz et al (Yilmaz & Yildizdas, 2003), the minimum toxic dose is 3.57mg/kg². It is not common in the human population as against animals. Amitraz is an Alpha 2 adrenergic agonist which effects its actions by stimulating alpha 2 receptors in the central nervous system and alpha 1 & 2 receptors peripherally. In the CNS, its alpha 2 agonistic actions are both on the pre- and post-synaptic receptors. In the pre-synaptic receptors, it causes inhibition of noradrenaline discharge, while in the post-synaptic receptors, it leads to effects similar to alpha 1 stimulation. Its action peripherally in both alpha 1 and 2 adrenergic receptors result in the inhibition of the liver monoamine oxidase enzyme activity, inhibition of prostaglandin E2 synthesis, suppression of insulin secretion and stimulation of glucagon secretion. Studies have also shown it has an inhibitory effect on antidiuretic hormone and renin.

The clinical manifestations of Amitraz poisoning are as a result of its pharmacological properties as well as that of the organic solvent used in the preparation. For instance, xylene may additionally cause acute toxic signs like

central nervous system (CNS) depression, ataxia, nystagmus, coma and episodes of neuro-irritability. Following presentation, even in emergency settings, a brief history is essential for proper management, as most features seen in Amitraz poisoning can be easily misconstrued to be those of organophosphate poisoning. Added attention should be paid to the following aspects of the history;

- a) Time of exposure: The relevance of this is mostly in predicting the time of onset of symptoms. In a research involving 9 children with accidental amitraz poisoning, the estimated time from ingestion to onset of symptoms is 30-120 minutes.
- b) Route and quantity of exposure: Most cases of poisoning are via the oral route. And poisoning through this route has a more acute presentation as against that via the dermal or inhalational route. Ingestion of large amounts of amitraz usually predicts worse symptoms and outcomes. Mydriasis is usually seen in poisoning with large amounts, while miosis occurs with lesser amounts.
- c) Circumstance of exposure: The commonest circumstance of exposure is accidental ingestion, which mostly occurs in children. Ingestion due to suicidal ideation is also common, as in the index case, and patients in this setting usually ingest more quantities as against those who ingest amitraz accidentally.
- d) Psychiatric history: Knowing the patient's past history can also help ascertain the purpose and circumstance of ingestion. As in the case of our patient, the history of psychiatric illness in the form of depression predisposed him to suicidal ideation.

Other aspects of the history worthy of note are; the severity of symptoms, as severe cases would benefit from management in an ICU. The time and type of first aid administered is also relevant in preventing atropine overdose if it had been previously administered.

Clinical features are mainly as a result of CNS depression. Patient may present in altered consciousness or with loss of consciousness, as in our patient, drowsiness, disorientation or seizures. GCS score is usually less than 9/15 in patients with altered consciousness. Hypothermia seen may be due to its inhibitory effect on prostaglandin E2. Vomiting, abdominal pain and diarrhoea are as a result of decreased gastro-intestinal motility. Amitraz poisoning is an unusual cause of Ogilvie syndrome. Polyuria is consequent on its effect on ADH and renin.

On examination, patient may have a solvent or mothball like smell as a result of the organic solvent e.g. xylene. There may be bradycardia or tachycardia, hypertension or hypotension. Usually, there is a short-lived tachycardia with or without a raise in blood pressure, which then gives way to sustained bradycardia and hypotension. Bradypnea as a result of respiratory depression can be observed. Pupillary eye reflex is usually delayed or absent. Miosis is a common feature. As stated above, it is usually seen in cases of ingestion of small amounts and is as a result of the pre-synaptic effect, dominant in the early phase. While mydriasis is seen with ingestion of larger amounts and is as a result of both pre- and post-synaptic effect dominant in the late phase.

Differential diagnosis of amitraz poisoning include OPP, opioid, clonidine and benzodiazepine overdose. Excessive sweating and copious oral/nasal secretions seen in OPP are not usual features of amitraz poisoning. Pralidoxime is an antidote in OPP but does not reverse the effect of amitraz. Opioid overdose has similar features with amitraz poisoning. However, mydriasis seen in the late phase of amitraz intoxication is usually absent in opioid poisoning. OPP can also be reversed by administration of naloxone. Clonidine is an alpha 2 adrenergic agonist with similar CNS effects as amitraz. However, its overdose can be reversed by Naloxone through poorly understood mechanisms. The classic presentation of benzodiazepine overdose consists of CNS depression with normal vital signs and its antidote is Flumazenil.

Awaiting investigation results should not delay intervention, as there may be no significant abnormalities seen upon investigations. Some studies have shown that mild to moderate hyponatraemia may be seen in amitraz poisoning, probably due to excessive diuresis. This was not so in the index case. However, he had elevated creatinine level. Few studies have reported this but its significance is yet to be determined. Elevation of liver enzymes, especially the transaminases, has been documented. Amitraz is a potent hepatotoxic drug that decreases hepatic glutathione activity, but liver function tests return to normal within 48 hours. Electrocardiography may show sinus bradycardia, as was seen in our patient, ST segment changes, ventricular arrhythmias and torsade des pointes. The usual metabolic derangement seen in amitraz poisoning is respiratory acidosis. This is as a result of respiratory depression with subsequent accumulation of carbon dioxide. Blood glucose may also be elevated, with resultant glycosuria on urinalysis.

Currently, there is no antidote for amitraz poisoning. Yohimbine and Atimprazole have been successfully used in experimental studies in animals but there is insufficient evidence concerning their use in humans. Atropine can be used in reversing symptomatic bradycardia.

Management of amitraz poisoning has been mainly supportive and symptomatic. This entails; airway protection, oxygenation/ventilation, especially in patients with severe respiratory depression, as the index patient. Such

cases should be managed in an ICU. Haemodynamic support with intravenous fluid, with or without vasopressors may be commenced in patients with hypotension. Seizures can be aborted with Diazepam.

Other supportive measures include; correction of temperature abnormalities and metabolic derangement, prevention of secondary complications like prevention of pressure sores in unconscious patients. Activated charcoal and cathartics have not been studied extensively, however, they may still be considered. Gastric lavage may not be advised, as the solvents are usually oil-based, connoting a high risk of aspiration. Although in cases of ingestion of large volumes, gastric lavage may be carried out following precautionary measures.

3.3 Psychiatric and Psychological Interventions in Intentional Pharmacological Poisoning

As stated earlier on, it is important to determine whether a pharmacological poisoning is accidental or a suicide attempt when evaluating a patient. Completed (or successful) suicides as well as attempted suicides are seen among males and females (Kalyoncu et al, 2002). In a year, about 700,000 persons die by suicide, globally (WHO, 2021). There are several known suicide methods. Among these, pharmacological poisoning was shown in a study in Korea to be the most common method seen in suicide attempts (Lim et al, 2014). The reason for this is that pharmacological poisoning is considered to be a less lethal suicide method than hanging. Suicide attempt by hanging invariably leads to death while a victim of pharmacological poisoning can be saved if medical intervention is timely.

Several psychiatric disorders, including depression, are associated with suicide thoughts and suicide attempts (Orsolini, et al). It is therefore important that every case of attempted suicide by pharmacological poisoning be thoroughly evaluated by a psychiatrist in order to identify and treat any underlying neuropsychiatric disorder. That was the case with the index patient who suffered from depression and which was what predisposed him to suicide ideation and suicide attempt using amitraz. There is a notable prevalence of suicide ideation, suicide plan and suicide attempt among persons suffering from major depressive disorder (Cai et al, 2021) Such persons suffering from major depression should be treated and followed up by the psychiatrist.

Intervention by clinical psychologists is also important in the management of a case of attempted suicide by pharmacological poisoning. The clinical psychologist should identify all the risk factors for suicide in the patient. The clinical psychologist should also enhance preventions to re-exposure to those risk factors, as persistence of such risk factors will continue to predispose the patient to suicide thoughts. In the management of such patients, clinical psychologists employ psycho-education, behaviour modification and cognitive restructuring. Persons who have attempted suicide in the past and persons who are suffering from neuropsychiatric disorder which predisposes them to suicide ideation require long term follow-up at the out-patient clinics. In the course of their management, they should be screened from time to time for evidence of suicide ideation, suicide plans and suicide attempts. This will help the managing team to determine how successful the treatment of the patient has been. It will also help the managing team to determine the likelihood of the patient succumbing to suicide attempt.

The Prognosis of a patient presenting with pharmacological poisoning by amitraz depends on several factors which include the amount of poison the person was exposed to as well as the time and quality of intervention. The nature of the underlying neuropsychiatric disorder, if any, is a very important prognostic factor. The psychiatric disorder (depression) and the suicidal attempt seen in the index patient are both associated with stigma (Chime et al, 2020). The problem with stigma is that the patient may feel too shy to avail himself of the expert treatment available in the hospital even when he knows that such treatment is available. This is among the problems the clinical psychologist should address.

4. Conclusion

Amitraz poisoning may not be commonly encountered but it can be fatal if severe and unrecognised. The majority of cases are seen in children, and are due to accidental ingestion. In adults and older children presenting with amitraz poisoning, it is important to determine whether the poisoning is intentional or accidental because of the treatment and prognostic implications. Expeditious intensive care management and supportive care may suffice for the medical treatment of accidental amitraz poisoning. However, in intentional amitraz poisoning as a suicide attempt, intervention by the psychiatrist and by the clinical psychologist is necessary for the treatment to be comprehensive. Manufacturers, regulatory authorities and national poison control centres have a significant role to play in primary prevention of amitraz poisoning, via public education and appropriate warnings on amitraz containing insecticides.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no grant/financial or personal relationship(s) that may have inappropriately

affected their report of the findings of this research.

Statement of Informed Consent

The participation was on voluntary basis and informed consent was obtained from the individual who participated in this case report.

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