Mepiquat Poisoning – Report of a Patient with Mepiquat Poisoning Presenting with Bradycardia and Hypoglycemia

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Abstract

Mepiquat chloride is a quaternary ammonium salt which is used as a plant growth regulator. We report the case of 18 year old tribal girl who had consumed Mepiquat chloride (5%) in an attempt of deliberate self-harm. The patient had symptomatic bradycardia and hypoglycaemia at presentation both resolved with supportive treatment. Unlike Chlormequat which can be fatal in humans when ingested mepiquat which lacks the choline subunit and has only a weak effect on the muscarinic and nicotinic receptors in the human body causing only mild bradycardia and hypoglycemia. Patient has been followed up for 1 year and she doing well with no sequelae.

***Key words** : Mepiquat, Bradycardia, hypoglycemia, nicotinic effects , muscarininc effects, Giberrelic acid inhibitors, organophosphorus mimics*

Background

Mepiquat chloride (MChl) (syn: piperindinium chloride , 1,1dimethyl 1,1 dimethylpipierindinium chloride) is a quaternary ammonium ion that has 2 methyl groups and 1 pentamethylene - 1.5 diyl group attached to nitrogen (Figure 1). It is an agrochemical, plant growth retardant and a Maillard reaction product. It is used as a plant growth regulator in agriculture to reduce sprout suppression in garlic, onions and in cereals to reduce unwanted longitudinal shoot growth [(1)]. It acts by inhibiting gibberellic acid synthesis. The study by Edwards et al shows that gibberellic acid is a plant hormone which helps in plant development by stimulating rapid stem and root growth, inducing mitotic division in the leaves of some plants, and increase seed germination rate[2]

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Studies that have investigated the short term toxicity of MChl have shown that dogs (mammals) are more susceptible to its toxicity compared to rodents. These studies have shown that dogs had excessive salivation and mortalities among the dogs after mepiquat ingestion. Post mortem studies in these animals revealed vaculolisation in the kidneys and siderin deposition in the liver , but the mechanism for these changes in these organs has not been elucidated [3,4]. However as per the Finnish safety and chemical agency study , currently there is no data in published literature on Mepiquat poisoning in humans[5]. We present a patient with mepiquat induced hypoglycemia and bradycardia which resolved with medical management.

Case Presentation

An 18 year old girl from Javadhi hills a tribal area presented to our Emergency department within 6 hours of an attempted deliberate self harm. She had consumed 25 ml of a liquid following a domestic conflict with her mother. On enquiring; the relatives produced the container which was labeled as a liquid formulation of 5% Mepiquat chloride called Chamatkar. (Figure 2) Within an hour of consumption of the toxin, she had 3 episodes of non bilious, non projectile vomiting.

She also reported dizziness and light headedness which lasted for a period of 1 hour. She was initially taken to a community health centre by her relatives, where she was symptomatically treated with intravenous fluid and antiemetics and referred to a higher for further management. Gastric lavage or forced emesis was not done.

On arrival in our accident and emergency department, she was conscious with normal sensorium. Her GCS was 15/15 and her vital signs were stable with a pulse rate of 63/min, blood pressure 110/60 mmHg and respiratory rate 20/min. On examination of the central nervous system: her pupils were dilated 4 mm but were equal and reacting to light. She was moving all 4 limbs with normal power and her plantars were flexor. The neck holding time and single breath count was normal. There was no focal neurological deficit. Her abdomen, cardiovascular and respiratory examination was normal. However within 1 hour of her presentation to casualty she complained of light headedness and dizziness, on examination she had bradycardia (pulse rate -56/ min). Due to the presence of bradycardia patient was investigated for other toxins such as Organophosphorus , but her serum pseudocholinesterase levels were normal 7287 Units/L (normal range - 3000-8000 Units/L) . Her blood sugars tested at admission were low (60 mg/ dl). Other investigations done at admission to look for other causes of hypoglycemia including renal, hepatic dysfunction, but all her metabolic parameters were normal (Table 1). Her arterial blood gas and bleeding parameters were also normal. There was leucocytosis (14,100 cells/ml) which resolved by day 2.

Patient was treated with atropine injection for the management of symptomatic bradycardia in the accident and emergency department with which the bradycardia resolved.

Course in the Hospital

She was transferred to the medical ward for monitoring and management of symptomatic bradycardia and also for close observation of the possible evolving toxidrome of Mepiqaut. Apart from the initial episode of bradycardia treated with atropine, she subsequently didn't have any further episodes of bradycardia. She continued to have hypoglycaemia in the range of (60-70 mg/dl) for the initial 24 hours. She was managed with a continuous infusion of dextrose with continuous blood sugar monitoring. Her blood sugar levels became normal by day 3 of admission. Patient was observed till the fifth day post incident, she did not have any further symptoms and signs of any residual toxicity clinically. Patient was counseled by the psychiatrist and discharged. Patient is on telephonic follow up and 1 year later has no residual symptoms.

Toxicological Analysis:

In order to confirm the presence of Mepiquat, toxicology analysis was done on patient's urine. HPLC was done in urine and also from the compound obtained from the container. Briefly, the processed urine sample was injected into a C-18 column (Discovery HS) with 10% acetonitrile as the mobile phase with 1ml/min as 46min which confirmed the presence of Mepiquat chloride. There were no other metabolities identified in the patients urine. The chromatograms were analysed using Labsolutions software.the flow rate; the detection wavelength was set at 200nm and the retention time of the compound was 2.

Table 1 baseline characteristics

Haemoglobin (gm/ dL)	10.3
WBC Counts (per cu. mm)	14,100 (N-73)
Platelets (per cu. mm)	4,16,000
Sodium / Potassium (mmol/L)	143/4.2
Calcium/Phosphate (mg/dL)	8.80/4.8
Urea/ Creatinine (mg/dL)	16/0.55

Cont... **Table 1: baseline characteristics**

Liver function test	0.62/0.20/7.6/4.4/18/9/96
PT/INR/APTT	11.7/1.08/35.3
Pseudocholinesterase (Unit/L)	7287

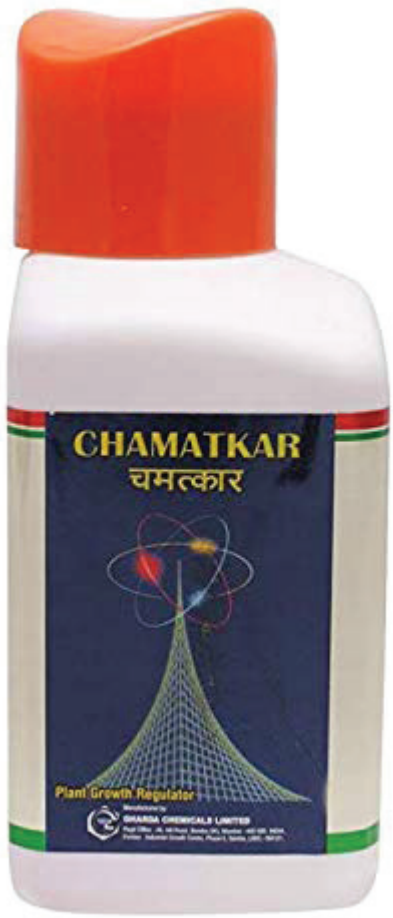

Figure 1 Chamatkar Mepiquat Chloride

Discussion

Mepiquat chloride is a plant growth retardant and has not been reported to cause poisoning in humans. As per animal studies in rats it has been shown that when ingested orally mepiquat chloride is well absorbed and extensively distributed in the tissues. The bioavailability after oral ingestion is around 85%. Mepiquat is excreted unchanged mainly in the urine. Our patient's urine analysis by HPLC also showed mepiquat and there were no other metabolites detected. The fecal excretion of mepiquat chloride is around 15% only [(1)].

Acute oral toxicity studies done on Wistar rats showed that the LD50 of Mepiquat was 464mg/kg/bw (equivalent to 270mg/kg).[4,5] The United States environmental protective agency (US EPA) study has placed Mepiquat in the class II or the moderately toxic category[4] and recently in 2020, the European Chemical Agency has placed Mepiquat in hazard class of Acute Tox. 3 as per the CLP classification [5].

The only two toxic manifestations which were noted in our patient following Mepiquat poisoning were transient symptomatic bradycardia and hypoglycaemia both of which resolved by 48 hours with supportive management.

In animals mepiquat acts on the nicotinic receptors though its affinity is 10 times lower than that of acetylcholine at these receptors. It can bind to the muscarinic receptors where its affinity is 5 times lower than atropine. Due to its affinity for the nicotinic receptor in cases of Mcl overdose patients can present with tremors, ataxia, abnormal posturing and motor incoordination, but our patient had none of these symptoms.

The Finnish safety agency also said that studies in rats and mice showed evidence of neurotoxicity due to its effect on the nicotinic receptors (tremors, convulsions, gasping, impairment of coordination and eye lid closure) after a single dose of mepiquat chloride (doses ≥ 270 mg/kg by oral route and ≥ 1.50 mg/L by inhalation) [5]. However, none of these signs of neurotoxicity were seen in our patient during her course of hospitalisation and subsequent follow-up.

The EFSA scientific report on the pesticide risk assessment of mepiquat showed that due to its activity on the muscarinic receptors it can cause bradypnoea, excess salivation and bradycardia; our patient presented with bradycardia which improved with intravenous

atropine [3].

Statement from the registration department of agricultural chemicals quotes studies with New Zealand rats using mepiquat chloride dissolved in 0.9% normal saline at the dose of 1mg/kg; showed that this compound induced short lived reduction in heart rate and blood pressure and this effect was blocked by premedicating with atropine and to some extent by diphenhydramine hydrochloride [6].

Studies in mice have shown that muscarinic receptors especially subtype M3 play an important role in the release of insulin from the pancreatic cells after cholinergic stimulation [7]. This release of insulin could have caused hypoglycemia in our patient. Hence based on animal studies, both bradycardia and the hypoglycaemia in our patient can be explained by effect of mepiquat on the muscarinic receptors

There are reports by Brdale , Vijitharan and Yang on chlormequat poisoning a similar plant growth regulator which also has similar quaternary ammonium structure but has choline as a chlorinated derivative [8-10],. Case reports of chlormequat poisoning in humans have documented respiratory failure secondary to its action on neuromuscular junction of the diaphragm muscles. This action was due to its choline subunit acting as a partial agonist on the acetylcholine nicotinic receptor in the neuromuscular junction of the diaphragmatic muscles. Our patient didn't have any of the severe cholinergic symptoms neither did she have any muscle weakness or respiratory distress. This could have been due to lack of choline subunit in Mepiquat; hence mepiquat has only weak activity on the muscarinic and the nictotinic receptors in comparison to chlormequat. Both Chlormequat and Mepiquat can cause bradycardia similar to organophosphorus poisoning but there are no SLUDGE symptoms and cholinesterase levels are normal.

Mepiquat is a plant growth inhibitor, when ingested by humans with intent of deliberate self-harm can present with bradycardia and hypoglycaemia due to its effect on the nicotinic and the muscarinic receptors

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