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Case Report

Rhabdomyolysis: an unusual complication following diclofenac and amitraz consumption

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ABSTRACT

Amitraz is a pesticide with central alpha 2 agonistic action and diclofenac is a non- steroidal anti-inflammatory drug. Rhabdomyolysis is not commonly associated with either compound consumption. We report the case of a 28-year-old male who after presenting to us following 25ml of amitraz consumption, developed diffuse myalgia, muscle tenderness, cola coloured urine with oliguric acute renal failure which was followed by altered sensorium. Further probing revealed that he had also consumed 10 tablets of unknown dose of tablet diclofenac along with the amitraz. Rhabdomyolysis was suspected which was confirmed by an elevated creatinine phosphokinase. He was hydrated with IV fluids, given bicarbonate and N-acetylcysteine and in view of deteriorating renal function underwent 6 sessions of hemodialysis. Following the same, sensorium improved, urine output normalised, renal function improved and creatinine phosphokinase levels showed a decreasing trend indicating a reduction of the rhabdomyolysis. In poisoning cases it is often difficult to reliably confirm the drug consumed at the time of presentation. Therefore, like in our case, in addition to initial supportive measures, a periodic review of history, examination, regular monitoring of vitals and timely appropriate blood investigations can help confirm the nature of the poison and detect early the possible complications, and thus enable the early initiation of life saving treatment with improved patient outcomes.

Keywords: Amitraz, Diclofenac, Rhabdomyolysis, Poisoning

INTRODUCTION

Amitraz, a triazapentadiene compound, is a pesticide with central alpha 2 adrenergic agonistic action. Off late, many cases of poisoning with this compound have been reported. Its toxicity has been reported to cause central nervous system, cardiovascular and respiratory depression, hyperglycemia and reduced gastrointestinal motility.[1,2]

Diclofenac (2-[2,6-dichloranilino] phenylacetic acid) is a commonly prescribed non- steroidal anti-inflammatory drug with analgesic and anti-inflammatory action, inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) with relative equipotency, used in the management of many painful and inflammatory conditions like osteoarthritis. It has been described to cause dose related gastrointestinal, cardiovascular and renal adverse effects.[3]

Considering the easy accessibility to diclofenac and amitraz, its misuse and toxicity has started gaining importance.

Rhabdomyolysis, involving the disintegration of skeletal muscle releasing the muscle constituents into the bloodstream, is a potentially life-threatening condition due to multiple traumatic and non-traumatic causes.[4,5] However, it has rarely been associated with the consumption of either of the above two compounds.

We report an unusual occurrence of rhabdomyolysis in a patient following amitraz and diclofenac consumption.

CASE REPORT

A 28-year-old male with no prior co-morbidities or complaints, presented to the casualty with an alleged history of consumption of about 25 ml of amitraz, about 24 hours after the consumption. He had already been given a gastric lavage at a local hospital about four hours after the intake. The patient denied consumption of alcohol or other illicit drugs. At the time of presentation, patient was asymptomatic, afebrile, conscious and oriented with stable vitals of pulse rate 92/min, BP 100/60 mmHg, saturation 97% room air and respiratory rate 20/min. Pupils were 3mm bilaterally and reactive to light.

All systems examination was normal. Baseline ECG revealed normal sinus rhythm. COVID Rapid and RTPCR tests done were negative. For continuous vitals monitoring and further management, he was admitted to the emergency ward and was started on supportive measures.

About six hours after admission, he developed diffuse myalgia and muscle tenderness. An hour later, cola colour urine was noticed in the catheter bag and the patient became disoriented. Urine output was also noticed to be reduced. He however remained afebrile. Blood investigations revealed mixed metabolic acidosis with respiratory alkalosis, deranged renal function tests, isolated elevation of serum Aspartate transaminase (AST) and alanine transaminase (ALT). thrombocytopenia and hypoalbuminemia with normal other liver function tests, normal plasma pseudocholinesterase levels and peripheral smear.

Table 1: Blood investigations.

Lab test	Day 1-5	Day 5-9	Day 10-15
Arterial blood GAS – Day 1	pH-7.3, pCO2- 26.2, pO2=197.5, Lactate-3, bicarbonate- 15.7		
CBC			
Hemoglobin (g/dl)	15.6	14	7.2
Total count (per mm^3)	9300	9400	16000
Platelet count (per mm^3)	140,000	94,000	184,000
Peripheral smear	Normocytic normochromic picture		Normocytic normochromic anemia
Renal function tests (mg/dl)			
Blood urea/ serum creatinine	119.9 / 2.97	222/7.18-280/8.4	73 / 2.7
Liver function tests:			
Total bilirubin (mg/dl)	0.59	0.53	
Direct bilirubin	0.16	0.16	
Total protein (g/dl)	4.1	3.6	
Albumin (g/dl)	2.3	2	
AST (U/L)	1005	805	
ALT (U/L)	231	211	
ALP (U/L)	79	67	
Serum electrolytes (Sodium/Potassium/ chloride) mmol/L	138/4.8/114	144/4.6/122	145/5.5/123
Serum Creatinine Phosphokinase (CPK) U/L	1400	515	229
Plasma pseudocholinesterase U/L	7086		
Fever workup-			
Dengue panel	All negative		
Peripheral smear for Malarial parasite			
Blood and urine cultures			
PT/INR/APTT	11.8 / 1.23 / 36.5		

Dengue panel and peripheral smear for malarial parasite were negative (Table 1). USG abdomen revealed normal sized kidneys. Thus, rhabdomyolysis was suspected, which was confirmed by an elevated serum Creatinine phosphokinase (Table 1). Patient was shifted to the intensive care unit due to the deterioration. Further probing with the patient attenders revealed that the patient had also consumed about 10 tablets of unknown dose of diclofenac a few hours prior to the amitraz consumption.

Following a nephology consultation, the patient was started on IV fluids normal saline/half normal saline at 150ml/hour and N-acetylcysteine at a dose of 100 mg/kg/day in DNS which was to be given for five days. 25mEq of sodium bicarbonate was added to each IV fluid. Despite the above measures, the patient became oliguric and renal function tests worsened. Patient also started to develop recurrent hypoglycemic episodes. Hence patient was initiated on Hemodialysis. Patient was given 6 sessions of hemodialysis following which sensorium improved, urine output normalised, urine became straw coloured, renal function improved, urine routine was normal and thrombocytopenia resolved (Table 1). Creatinine phosphokinase levels revealed a decreasing trend suggesting a reduction in the rhabdomyolysis (Table 1). Since there was a normocytic decrease in the hemoglobin levels from 14 to 7.2 (Table 1), patient was transfused packed red blood cells. Peripheral smear had revealed normocytic normochromic anemia. After regaining sensorium, the patient revealed weakness of bilateral upper and lower limbs with 3/5 power in both upper limbs proximally and distally, and 1/5 in both lower limbs proximally and distally. Bilateral deep tendon reflexes were 1+ with a normal sensory examination. A differential diagnosis of critical illness neuropathy or myopathy induced weakness was considered. Due to the critical condition of the patient, nerve conduction studies and other neurophysiological tests could not be done for the same. However, patient spontaneously regained power of both upper and lower limbs within a week.

The plan was to continue to monitor the patient's complete blood counts and renal function. However, the patient went discharge against medical advice and could not be followed up.

DISCUSSION

In this case, on initial presentation, the patient had reported consumption of amitraz, a pesticide with central alpha 2 agonistic action. However, the patient developed none of the features frequently reported with amitraz like central nervous system depression, hypotension, bradycardia, respiratory depression or hyperglycemia.[1,2] In addition, he developed features suggestive of rhabdomyolysis and resultant acute renal injury, a complication never reported with amitraz previously. Due to this, the history was reviewed again, which revealed that he had consumed about 10 tablets of an unknown dose of diclofenac a few hours prior to the amitraz intake.

Although diclofenac can be associated with gastrointestinal, cardiac and renal side effects, rhabdomyolysis is not frequently associated with its use.[3]

Rhabdomyolysis involves the disintegration of striated muscles, resulting in the release of intracellular muscle constituents, in particular, myoglobin, into the circulation. The myoglobin, normally is bound to plasma globulins in circulation, thereby preventing its glomerular filtration. In situations like rhabdomyolysis, the amount of myoglobin exceeds the binding capacity of the plasma proteins, thus resulting in excess free myoglobin in the circulation. The free myoglobin reaches the renal tubules after filtration by the glomeruli. Myoglobin results in acute tubular necrosis through renal vasoconstriction, formation of intratubular casts and the direct toxicity of myoglobin on renal tubular cells.[4,5,8-10] The complications include hyperkalemia, hypocalcemia, acute renal failure, disseminated intravascular coagulation and cardiac arrest. It can occur due to a variety of causes including crush injury, viral infections, inflammatory myopathies, extremes of body temperature, drugs of abuse like cocaine and medications like statins, antipsychotics, antidepressants, antihistamines, antiepileptic agents, sedative and hypnotic agents.[4,5] Considering the life-threatening implications of this condition, an early detection and initiation of treatment is necessary.

There have been a few case reports about the occurrence of rhabdomyolysis following diclofenac consumption.[4-7] While in the cases reported by Manigandan et al, Delrio et al and Knobloch et al, rhabdomyolysis occurred after cumulative accumulation of diclofenac consumed for the purpose of pain, in the case reported by Ertekin it was consumed along with pantoprazole.[4-7] Diclofenac is postulated to cause rhabdomyolysis by its effect on the cation exchange proteins, thus affecting the transport of diclofenac and its pharmacokinetics causing the induction of the side effects.[4,11] The relatively rare occurrence of rhabdomyolysis with diclofenac could indicate that certain factors exist that can increase individual susceptibility to develop this complication with diclofenac.[5] Drugs like pantoprazole are reported in animal studies to inhibit the cytochrome p450 system, more so in weak metabolizers. They also inhibit P-glycoprotein involved in xenobiotic elimination. Thus, the elimination of diclofenac, which is metabolized by CYP2C9, may be reduced causing potential toxicity.[5,11] It is unsure whether such an interaction exists between amitraz and diclofenac.

In patients presenting to the emergency room following poisoning, it is often difficult confirm the nature of the compound consumed. Sometimes, patients who may present with no symptoms, may go on to develop life threatening complications, similar to what was seen in the case we reported.[12] It is also a challenge when the patient develops rare complications like in our case. Keeping this in mind, it is necessary to initiate supportive measures early, periodically review the history with the patient and attenders, regularly monitor vitals and look for the occurrence of new symptoms and signs. An ECG and initial basic metabolic panel are generally recommended for all patients.[13] In addition appropriate investigations need to be done as per the periodic history and examination. In the event of a rare complication occurrence like in the case reported, following this orderly approach will help eliminate other possible causes of the complication. It may also facilitate the early detection of life-threatening complications and enable timely

lifesaving treatment, thereby potentially improving patient outcomes.

CONCLUSION

Rhabdomyolysis can occur as a rare complication of diclofenac and possibly amitraz consumption. In patients where the nature of drug consumed is uncertain, who are asymptomatic at presentation or develop rare complications, an orderly stepwise approach is needed to detect early life-threatening complications and initiate appropriate treatment.

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