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Case Report

Clinical features and management of poisoning due to nitrobenzene containing pesticide and plant growth stimulator: a case report

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ABSTRACT

Nitrobenzene poisoning is a rare life threatening event with lethal outcomes if not intervened promptly. Nitrobenzene is an oxidizing compound and is an active ingredient of pesticides, plant growth stimulators, lubricating oils, etc. It leads to accumulation of methemoglobin (MetHb) in blood which hampers oxygen carrying capacity of RBC. Depending on its level in blood it can present with range of symptoms most prominent being cyanosis. We present a case of 19-year-old male patient with accidental nitrobenzene poisoning. He presented with cyanosis, headache, vomiting and his oxygen saturation (SpO_2) was 89% on room air which didn't improve with oxygen therapy. Patient informed use of pesticides on his farm one day back. On asking further the chemical was identified which contained nitrobenzene as its key ingredient. Venous blood samples were taken which were chocolate dark in color. On basis of clinical features and history given methemoglobinemia due to nitrobenzene poisoning was suspected. He was treated with intravenous (IV) methylene blue, vitamin C, multivitamins and fluid and oxygen therapy. Patient recovered completely after ten days with all blood reports within normal range and later was discharged. Patient was good at health at his follow up after three weeks of discharge. Therefore, it is advisable to be expeditious in diagnosing nitrobenzene poisoning and treating subsequent methemoglobinemia with its antidote methylene blue to prevent fatal results.

Keywords: Nitrobenzene poisoning, Methemoglobinemia, Methylene blue, Cyanosis, Oxygen saturation

INTRODUCTION

Poisoning is one of the frequent cause of premature death in India which falls into a category of medical emergency. While accidental poisoning is common in children because of consumed household products, intentional poisoning is prevalent in adult males owing to financial debts, family issues, psychiatric illness, etc. Poisoning attributed to pesticides is eminent and of them organophosphorus poisoning(OP) being the most common.[1]

Nitrobenzene is another such compound with potential to cause harm. It is frequently used in pesticides and plant growth stimulators. Acute nitrobenzene poisoning primarily presents as cyanosis, dyspnea, headache, dizziness, confusion, tachycardia etc. These symptoms are ascribed to methemoglobinemia owing to oxidation of hemoglobin from ferrous to ferric state. Cyanosis not improving with supplemental oxygen and chocolate color dark venous blood are indicators of methemoglobinemia.[2] Given the rarity of nitrobenzene poisoning, we here present this case report highlighting its clinical features, diagnosis

and treatment. Our aim is to communicate to the treating physician to be alert and keep nitrobenzene poisoning in mind as differential diagnosis of cyanosis. This report will also give motive to law makers to implement better workplace safety guidelines, safe handling procedures and ensuring availability of protective equipment to vulnerable populations. This case has been reported according to CARE criteria.[3]

CASE REPORT

A 19-year-old male with alleged history of spraying Bazooka (pesticide and plant growth stimulator; 90% nitrobenzene and 5% amino acids) on his farm one day ago, presented to casualty department with complaints of four to five episodes of vomiting, chest pain, diffuse headache, giddiness, breathlessness and bluish discoloration of his lips and fingers. The patient had no known comorbidities. On examination patient was afebrile, conscious and oriented to time, place and person. Patient was vitally stable except pulse rate which was 110/min. SpO_2 was 89% on room air and both pupils were normal and reactive to light. Cyanosis was present over his lips, tip of tongue, fingers and nails. On auscultation no abnormal breath sounds and murmurs were heard. Blood samples were taken which were chocolate dark in color and Arterial Blood Gas Analysis (ABGA) was performed.

Table 1: ABGA test.

	Day 1 on admission	Day 1 after two hours of initiating treatment	Day 2	Reference values
pH	7.40	7.40	7.40	7.35-7.45
pCO_2 (mmHg)	26	30	30.8	35-45
pO_2 (mmHg)	140	265	112	80-100
HCO_3^-(mmol/l)	15.7	18.5	21.6	22-26
SO_2 (%)	90	99.7	98.3	95-100
Na^+(mmol/l)	113	133	128	135-145
K^+(mmol/l)	3.8	3.04	2.59	3.5-5
Cl^-(mmol/l)	82	98	95	98-107
Ca^{2+}(mmol/l)	0.24	0.59	0.48	1.1-1.3

Table 2: Hemogram, LFT and RFT.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Ref. value
Hb (gm/dl)	12.2	12.05	11.43	11.55	10.6	9.46	9.58	9.02	9.08	9.19	13-17
RBC (_*10^6)	5.44	5.56	5.32	5.38	4.98	4.8	4.55	4.23	4.16	4.19	4.5-5.5
WBC (k) (_/cmm)	12.2	10.2	7.0	5.3	5.1	6.2	8.2	9.2	7.7	7.5	4-11
PC (l) (_/cmm)	2.68	2.2	1.91	2.14	2.48	3.02	2.78	1.70	2.24	2.25	1.5-4
MCV (fl)	74.1	72.8	73.1	72.8	72.2	70.6	70.7	71.4	71.4	71.6	80-100
MCH (pg)	22.4	21.6	21.4	21.4	21.2	21	21	21	21.9	21.9	27-32
MCHC (gm/dl)	30.2	29.7	29.3	29.4	29.4	29.8	29.7	29.5	30.4	30.6	32-36
S.TBIL (mg/dl)	-	2.51	2.91	3.7	4.1	2.88	3.02	3.58	2.33	2.07	0.2-1.5
S.IBIL (mg/dl)	-	1.87	2.43	3.31	3.65	2.24	2.52	3.12	1.69	1.45	0.2-0.8
S.DBIL (mg/dl)	-	0.64	0.48	0.39	0.45	0.64	0.50	0.46	0.64	0.62	0-0.5
S.LDH (U/l)	-	-	-	630	638	566	540	-	270	-	125-220
ALT (IU/l)	-	16	16	18	20	19	20	23	31	30	0-45
S.Na^+ (mEq/l)	143	142	136	138	140	141	138	137	140	140	136-145
S.K^+ (mEq/l)	3.23	4	3.5	3.6	5.3	3.7	4	4.5	3.8	3.6	3.5-5.1
S.Creatinine (mg/dl)	0.84	0.75	0.66	0.63	0.74	0.64	0.67	0.74	0.74	0.73	0.72-1.25
S.Urea (mg/dl)	18	18	19	20	23	24	19	19	21	20	12-40

Hb (hemoglobin), RBC (red blood cell), WBC (white blood cell), k (in thousands), l (in lakhs), PC (platelets), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), S. (serum), TBIL (total bilirubin), IBIL (indirect bilirubin), DBIL (direct bilirubin), LDH (lactate dehydrogenase), ALT (alanine aminotransferase).

After examination, patient was put on non-rebreather mask (NRBM) oxygen at rate of 10 l/min, ryles tube was inserted, electrocardiogram revealed generalized ST depression, chest X-ray showed no abnormality and eventually he was shifted to critical care unit (CCU). Complete hemogram revealed mild leukocytosis, liver function test (LFT) and renal function test (RFT) were within normal limits. Plasma cholinesterase level was normal ruling out OP poisoning. Due to lack of facilities for detecting MetHb levels along with described history,

cyanosis not responding to oxygen and probable symptoms, patient was diagnosed as suspected methemoglobinemia. In CCU, patient was treated with IV methylene blue at dose of 10 ml in 450 ml saline (1ml=10 mg methylene blue) over 30 minutes. A multivitamin infusion was given. Patient was injected with 50 mg/kg N acetyl-cysteine after one hour. Supportive management included oxygen supplementation and IV fluids. Following treatment patient's symptoms improved, oxygen saturation was maintained at 96% with NRBM mask and there was no new complain except patient passing green color urine.

From day 3 to day 8 of admission patient's hemoglobin gradually decreased and LDH and indirect bilirubin gradually increased due to oxidative stress induced hemolysis and peripheral smear showed normocytic normochromic RBCs with few microcytes which returned to normal within ten days of admission with active treatment. After ten days of admission patient was discharged with normal blood reports, adequate SpO_2 and no other complaints. Patient was advised to have good diet, to take safety precautions while using nitrobenzene containing compound and with complete hemogram and liver function test as follow up after three weeks. At his follow up patient was doing well and his blood reports were within normal range.

DISCUSSION

Nitrobenzene is an oxidizing aromatic compound and is an active ingredient of azo dyes, paints, rubber, pharmaceuticals, explosive, lubricating oils, pesticides and plant growth stimulators. Its poisoning can occur via ingestion, inhalation or through percutaneous route and it gets distributed in various organs quickly due to its lipophilic nature. Once inside the body, nitrobenzene gets metabolized by oxidative and reductive reactions which have direct toxicological effects on body. It is excreted in urine in form of phenols. Nitrobenzene in excessive amount leads to formation of MetHb where instead of ferrous form (Fe2+) iron is unrestrainedly oxidized to ferric form (Fe3+) which impairs oxygen carrying capacity of hemoglobin. The resultant MetHb imparts chocolate brown dark color to blood. Normally, our body keeps an eye on accumulation of MetHb in blood. Firstly, glutathione produced from nicotinamide adenine dinucleotide phosphate (NADPH) from hexose monophosphate (HMP) shunt pathway in RBC provides protective mechanism against MetHb. Reduced glutathione maintains the integrity of RBC membrane. When glutathione gets scarce due to nitrobenzene and its metabolite induced depletion, RBC's get hemolysed easily. The metabolites also cause denaturation of globin molecules which condenses and precipitates as hearn corpuscles in RBC's. These corpuscles are another reason behind hemolysis and consequent decrease in hemoglobin and RBC level and rise in indirect bilirubin levels in blood. Secondly our body rely on diaphorase I and II which utilizes nicotinamide adenine dinucleotide hydrogen (NADH) and NADPH enzyme system respectively for MetHb reduction. An acute episode of nitrobenzene poisoning overwhelms these check system causing its toxicity.[4,5]

The clinical symptoms of poisoning are attributable to levels of MetHb in blood. With increasing concentration in blood it presents from cyanosis (1.5-3 g/dl) to anxiety, tachycardia, tachypnea, disorientation, (3-7.5 g/dl) and seizures, arrhythmias, acidosis (7.5-10.5 g/dl) and even death (>10.5 g/dl).[6] Methemoglobin levels between 40% and 50% of total hemoglobin profoundly depresses the central nervous system and cardiovascular system. At this level conversion of aerobic to anaerobic respiration is at peak which manifests as stupor, arrhythmias, hypotension, respiratory depression and encephalopathy.[6] Lethal doses of MetHb can present with hepatosplenomegaly, elevated liver enzymes, leukocytosis and hemolytic anemia. Anemic or G6PD deficient people can present with severe form of disease depending on levels of MetHb in blood.[4]

Nitrobenzene can be suspected from history given by patient, evidence of using chemicals containing nitrobenzene, peripheral and central cyanosis not improving with supplemental oxygen therapy, chocolate color dark blood, discrepancy between oxygen saturation determined by pulse oximetry and the oxygen saturation computed from PaO_2 (partial pressure of oxygen in blood) (normal here in this case), detecting MetHb levels in blood and excretion of phenols in urine. Confirmatory test like CO-oximetry which uses spectrophotometer holds highest significance.[2,4] It is also advised to rule out congenital or acquired methemoglobinemia. Drugs like benzocaine, dapsone and nitrates are also responsible for methemoglobinemia.[6] Sulfhemoglobinemia is another differential diagnosis.[4] In our case patient had chocolate brown color venous blood, cyanosis not responding to oxygen therapy, lowered SpO_2 gave indication of methemoglobinemia. Additionally, when patient showed bottle containing insecticide which unveiled nitrobenzene in 90% amount in it, gave robust evidence of its poisoning.

Treatment goals of nitrobenzene poisoning includes using specific antidote and antioxidants to neutralize its effect, improving oxygen saturation and ensuring adequate vitals and circulation. Methylene blue is medicament of choice. It exploits NADPH produced from glucose-6-phosphate dehydrogenase dependent HMP pathway and gets converted to leucomethylene blue, which reduces MetHb into hemoglobin. Therefore, dextrose if given proves beneficial as it yields NADPH from HMP pathway. The recommended dose of methylene blue is 1-2 mg/kg IV over 5 minutes which can be repeated after 30 minutes if symptoms does not improve or can be given if symptoms recur after few days due to release of tissue stores. Passage of blue-green urine along the course of therapy is considered normal as the unchanged blue pigment combines with urochrome in urine. Methylene blue is contradicted in G6PD deficient individuals due to risk of fatal hemolysis. In such cases of contradiction, vitamin C is given in high dose (10 g IV). It is an antioxidant and acts

as free radical scavenger which reduces NAD+ to NADH. Vitamin C is also given as adjuvant therapy or as maintenance purpose. It is recommended at doses 1 g IV thrice a day in 5% dextrose solution.[2,4,6] N-acetyl cysteine has been proved salutary in attaining reduction of MetHb levels in blood. It exerts its effect by restoring intracellular glutathione, antioxidant nature and direct reducing action through sulfhydryl group on NAC.[7] Patient was maintained on good nutrition and oxygen therapy throughout treatment.

Lastly, it is crucial to know the cause of poisoning, whether intentional or accidental. Here in this case it was accidental poisoning and patient was counselled regarding hazards of nitrobenzene toxicity and its symptoms and precautionary steps to take while handling it. To mitigate the risk of accidental poisoning it is essential to promote public awareness about handling of hazardous chemical and ensuring availability of safety equipments. In case of poisoning with suicidal intent patient should be sent for psychiatric reference prior to discharge.

CONCLUSION

Nitrobenzene poisoning though rare is potentially a fatal event. Early identification of its signs and symptoms (central and peripheral cyanosis not improving with oxygen, chocolate color dark blood), detailed history and prompt treatment can reverse its deadly outcomes. Methylene blue, vitamin C, fluid and oxygen therapy and correction of acidosis is mainstay of management in initial phase. Compounds containing nitrobenzene should be properly labelled with danger signs and people who are at high risk of coming in contact with such compounds must be trained regarding its safe handling, initial symptoms and advice of quick reach to nearby hospital.

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