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Methemoglobinaemia Following Insecticide Poisoning-A Case Series

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ABSTRACT

Methemoglobinaemia is an impaired state of oxygen delivery to tissues, seen when Ferrous iron of haem is oxidized to Ferric iron. Ingestion of nitrobenzene (rarely indoxacarb) containing pesticides either accidentally or with a suicidal intent leads to Methemoglobinaemia. Nitrobenzene is a pale yellow oily liquid with a characteristic bitter almond smell. It is used as an intermediate in the synthesis of aniline dyes, manufacture of benzidine, quinoline, azobenzene, rubber chemicals, screening paints, etc. Methemoglobinaemia results due to the intermediates (nitrobenzene and phenylhydroxylamine) formed during the metabolism of nitrobenzene by the reduction of aniline. Indoxacarb is an oxadiazine pesticide used for the control of cotton ball worm and native budworm in cotton and soya beans. Indoxacarb metabolizes to produce aniline metabolites and aromatic compounds that produce methemoglobin on further metabolism. Here we are reporting a case series of 5 cases of methemoglobinemia following insecticide poisoning which presented to our ICU between 2013-2015. Methemoglobinaemia has remarkably normal pulse oximetry finding with significant cyanosis which presents a diagnostic dilemma. Due to the non-availability of co-oximetry in our institute, which is the most accurate tool to diagnose dyshemoglobinemia, we tried to prognosticate the outcome based on the duration from exposure, clinical history and presentation followed by pulse oximetry findings and lab investigations like ABG and Liver function tests throughout the stay.

Keywords: Nitrobenzene, Indoxacarb, Methemoglobinaemia, Methylene blue, Co-oximetry, MODS

INTRODUCTION

Methemoglobinemia is an impaired state of oxygen delivery to tissues, seen when ferrous iron of haem is oxidized to ferric iron. Ingestion of nitrobenzene (rarely Indoxacarb) containing pesticides either accidentally or with a suicidal intent leads to methemoglobinemia.

Exposure to nitrobenzene-containing compounds can occur via ingestion, inhalation, and absorption through the skin which can result in methemoglobinemia [1-5]. Methemoglobinemia is a condition where red blood cells contain methemoglobin at levels higher than 1%. It has a clinical spectrum ranging from mild, underdiagnosed cases to fatal cases [6].

Methemoglobinemia has remarkably normal arterial oxygen saturation with significant cyanosis which presents a diagnostic dilemma. The non-availability of co-oximetry, which is the most accurate tool to detect and measure dyshemoglobinemia, is a problem faced by most peripheral hospitals in India. In our study, we have tried to prognosticate the outcome of these patients based on the time from exposure, history and clinical presentation, pulse oximetry findings, laboratory investigations like Arterial blood gas analysis, and liver function tests, throughout their hospital stay.

Here we present a series of five cases of Methemoglobinemia who presented to us over 2 years (2013-2015). Written informed consent has been taken from the patient's relatives by institutional protocol.

CASE PRESENTATION

Case 1

A 30 years old female patient with a history of nitrobenzene compound consumption 5.5 hours prior, came in an unconscious state with signs of central cyanosis. Vitals were unstable with a saturation of 83% on room air. She was intubated and a stomach wash was given. Arterial Blood Gas (ABG) (Table 1) was consistent with methemoglobinemia. Her laboratory reports (Table 2) showed neutrophil leucocytosis. Methylene blue 2 mg/kg and ascorbic acid (500 mg) TID were started and continued on day 2 since the saturation remaining 80% (70% FiO_2). Ionotropes started on day 3. GCS dropped to 3/15 and she succumbed on day 4.

Table 1 ABG findings of all patients through their course of stay

Time since Admission	Case 1				Case 2				Case 3				Case 4				Case 5			
	pH	PCO_2	PO_2	SO_2	pH	PCO_2	PO_2	SO_2	pH	PCO_2	PO_2	SO_2	pH	PCO_2	PO_2	SO_2	pH	PCO_2	PO_2	SO_2
0 hr	7.291	20.5	223	90	7.408	5.3	118.9	98.9	7.156	23.6	245	94.5	7.076	18.7	226	91.2	7.348	33	188.6	91.2
12 hr	7.512	21.3	261	93.9	7.108	20.9	96	94.6	7.405	31.9	280	92	7.345	24.1	225	90.8	7.416	32.4	232.4	90.8
24 hr	7.506	18.9	350	90.6	7.516	17.3	134.6	99.4	7.375	29.9	182	90.7	7.44	30.3	112	97	7.38	28	330	92
36 hr	7.324	42	288	91.2	7.597	12.6	305.1	99.8	7.377	22.1	300	96.7	7.405	33.3	131	93.2	7.41	26	310	93
48 hr	7.291	20.5	223	90	7.108	20.9	96	94.6	7.156	23.6	245	94.5	7.076	18.7	226	91.2	7.39	145	27	95

Table 2 Clinical parameters and lab investigations of all patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	30	22	30	28	27
Sex	Female	Male	Male	Male	Male
GCS (Arrival)	3	15	Sedated and Paralysed	3	13
Presented After	5.5	4	4	4.5	15
BP (Arrival)	90/60	100/70	130/80	100/70	140/80
SPO_2(Arrival)	85%	70%	89% ON (FIO2 100%)	80%	84%
Inotropes	Norad started on day 4	Dopamine and norad started on day 4	Norad on day 2 and Dopamine on day 4	None	None
Examination	Pallor, Central cyanosis	Pallor, Central cyanosis, Icterus	Pallor, Cyanosis	Cyanosis	Pallor and Cyanosis
Intubated	Yes	Yes	Yes	Yes	No
HB	13	14.4	11.3	13.6	15.8
TLC	20600	19400	15800	17000	11100
DLC	Neutrophila to Lymphocytosis	Neutrophilia	Neutrophilia to Lymphocytosis	Neutrophilia	Neutrophilia
Na	134	143.9	144.5	144.7	137
K	2.5	3.7	3.1	3.6	4.8
Cl	104	114	111	107	100
RFT	Urea 18	Urea 34	Urea 18	Urea 24	Urea 26.2
	CREAT 0.7	CREAT 1.8	CREAT 1.1	CREAT 1.5	CREAT 1.33
Total Bilirubin	N	3.3	0.5 →10.7 on day 4	N	3.5
AST	N	143	28→429 on day 4	N	10032

ALT	N	137	42→ 150 on day 4	N	34.7
ALP	N	140	38 → 51 on day 4	N	37.8
Outcome	N	Death on day 4	Death on day 5	Survived	Survived

Case 2

A 22 years old male presented in an unconscious state and central cyanosis with a history of unknown agricultural compound consumption 4 hours prior. Vitals were unstable with a saturation of 85% (face mask 5 lt/min). He was intubated. ABG analysis (Table 1) was consistent with methemoglobinemia. Laboratory report (Table 2) showed neutrophilic leucocytosis and deranged LFT and RFT. Blood drawn for analysis was chocolate brown. Intravenous methylene blue 2 mg/kg and ascorbic acid 500 mg started TID. Though GCS and SO_2 improved on day 2, he needed ionotropic support and GCS dropped by day 4, and he succumbed on the same day.

Case 3

A 30 yrs old male patient with a history of nitrobenzene compound consumption 4 hours prior brought with mechanical ventilation through a 6ET tube had peripheral and central cyanosis. Vitals were unstable, saturation was 89% (100 FiO_2). ABG analysis (Table 1) was consistent with methemoglobinemia. Laboratory reports (Table 2) showed neutrophil leucocytosis and deranged LFT (day 4). Inj. Methylene blue 2 mg/kg and ascorbic acid 500 mg intravenous thrice daily started. Though saturation picked up to 89% (50% FiO_2), he deteriorated further with a drop-in GCS and saturation of 82% (FiO_2-90%) by day 4. He succumbed on day 5.

Case 4

A 28 years old male patient with a history of Bloom flower insecticide consumption 4.5 hours prior, came unconscious, with deranged vitals central and peripheral cyanosis, and a saturation of 80% (room air). He was intubated. ABG analysis (Table 1) was consistent with methemoglobinemia. Laboratory reports (Table 2) showed neutrophil leucocytosis. Methylene blue 2 mg/kg and ascorbic acid 500 mg thrice daily started. He was weaned off the ventilator with improvement in GCS and saturation (92% on 40% FiO_2). He was discharged on day 6.

Case 5

A 27 years old male patient was brought with altered sensorium, central cyanosis, icterus, unstable vitals and a saturation of 84% (room air) with a history of Indoxacarb pesticide agent consumption 5 hrs prior. The blood drawn was chocolate-coloured. ABG (Table 1) and clinical signs were consistent with methemoglobinemia. Methylene blue 2 mg/kg and ascorbic acid 500 mg intravenous with high flow oxygen (face mask) started. He was discharged on day 6 since cyanosis resolved and the saturation improved (95% room air).

DISCUSSION

Methemoglobinaemia is caused by exposure to an oxidizing chemical or drug, leading to the removal of an electron from ferrous haemoglobin (Fe^{2+}) to create ferric haemoglobin (Fe^{3+}) at a rate that surpasses the endogenous reducing mechanisms. This methemoglobin is unable to transport oxygen to the tissues [1]. This results in a left shift of the oxygen-haemoglobin dissociation curve and subsequent tissue hypoxia [5]. The mechanisms that maintain the methemoglobin levels less than 1% are the endogenous HMP shunt, and the diaphorase I and II enzyme pathways [1]. Excessive oxidative stresses produce MeHb at a very high rate, leading to a rise above 1% [1,2]. The estimated lethal dose ranges from 2 g to 6 g in adults [3,6].

Nitrobenzene, an oxidizing nitrite compound leads to the rapid development of methemoglobinemia after acute ingestion [2,7-11]. Methemoglobinemia occurs due to the intermediates (nitroso benzene and phenylhydroxylamine) formed during the metabolism of nitrobenzene to aniline [7]. All cases presented to us were of ingestion of nitrobenzene products except case 5 of Indoxacarb poisoning. Our patients had features of pallor, cyanosis, and decreased consciousness. Four patients required intubation and ventilator support. The time of presentation ranged from 4 hours-5.5 hours after consumption and had no bearing on the outcome. In case 4, the nature of the compound was unknown, symptoms at presentation, graded desaturation with normal SO_2 led us to the diagnosis of methemoglobinemia and treatment

accordingly. Indoxacarb, an oxadiazine pesticide is used for the control of cotton ball worm and native budworm in cotton and soya beans. The indoxacarb metabolizes to aniline and aromatic compounds producing methemoglobin [12].

The symptomatology depends on the percentage of methemoglobin in the blood (Table 3) [5]. Diagnosis is made by eliciting a history of chemical ingestion, the characteristic smell of bitter almonds, persisting cyanosis on oxygen therapy, low arterial oxygen saturation, with normal ABG (calculated) oxygen saturation. This is because the arterial blood gas analysis measures any haemoglobin as normal and results in overestimation compared to calculated saturation. This is a "saturation gap" [11]. A gap of more than 5% indicates the presence of carboxyhemoglobin, sulfhemoglobin, or methemoglobin [11]. Dark brown blood that fails to turn bright red on shaking, suggests methemoglobinemia [1-5]. Once suspected, measurement of methemoglobin levels must be done using co-oximetry or spectrophotometry [1,5]. However, in our setup, laboratory measurement of methemoglobin levels was not possible, hence, clinical judgment was relied upon.

Table 3 Clinical manifestations of methemoglobinemia

fMetHb (%)	Signs and Symptoms
<3 (normal)	None
3-15	Frequently none
	Grayish skin
15-30	Cyanosis
	Chocolate-brown blood
30-50	Dyspnea
	Headache
	Fatigue, weakness
	Dizziness, syncope
	SpO_2~85%
50-70	Tachypnea
	Metabolic acidosis
	Cardiac aarhythmias
	Seizures
	CNS depression
	Coma
>70	Death
CNS: Cental Nervous System	

Neutrophilic leukocytosis was a finding in all our patients as has been noted from previously reported cases. [10]. Liver dysfunction was noted in three cases. Severe derangement with high bilirubin levels and deranged enzyme levels culminated in the death of two of the patients suggesting patients probably setting into MODS.

Treatment includes supportive measures like gastric lavage, high flow oxygen, correction of electrolyte and acid-base abnormalities [1,5,8]. Inject methylene blue, a thiazine dye that accelerates the NADPH-dependent methemoglobin reductase system diaphorase II by five times reducing its half-life from 15 hours-20 hours to 40 minutes-90 minutes [11]. It is given at a dose of (1-2) mg/kg as a 1% solution over 5 minutes [1,5]. It is indicated if MeHb levels are >30%, or the patient has comorbidities that worsen hypoxia [5,9]. All our patients had symptoms of severe methemoglobinemia and were started on methylene blue and ascorbic acid. Ascorbic acid acts as an antioxidant and increases levels of NADH and NADPH [10]. All patients received blood transfusions based on clinical diagnosis. Exchange transfusion can be used as the second line of treatment [1,3,9].

Three of the five cases succumbed around the fourth or fifth day of admission. They showed initial improvement in pulse oximetry saturation with methylene blue, confirming methemoglobinemia. Sudden deterioration thereafter with hypotension refractory to inotropes and brain death followed. Similar clinical waxing and waning have been reported previously [1,8,9]. We attribute this to the delayed release of nitrobenzene from adipose tissue and the gastrointestinal tract [1,8,9]. Studies conducted on rats showed that nitrobenzene accumulates ten times more in adipose than in the blood [7]. This stresses the need for constant vigilance while treating a patient who has seemingly improved. Facilities to measure methemoglobin levels are also required to track the progress of treatment, which was lacking in our institute. In their absence, titration of methylene blue dose and identification of the second redistribution is not optimally possible. Methylene blue doses should be limited up to 7 mg/kg as overdose itself can cause methemoglobinemia [3,5,9].

CONCLUSION

A series of rare but fatal cases of methemoglobinemia following self-poisoning with nitrobenzene or indoxacarb (Case 5) containing pesticides is reported. Due to the non-availability of co-oximetry in our institution, we focused on the prognostication of the patient's outcome based on the time from consumption, history and clinical presentation, pulse oximetry, series of ABG analysis, and lab investigations. Though time from consumption did not have any bearing on the outcome, deranged LFT and clinical findings could be used to guide management and prognostication. Since the number of cases studied is small, further research needs to be done to prove the findings of our case series.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Saxena, Hema, and Anand Prakash Saxena. "Acute methaemoglobinaemia due to ingestion of nitrobenzene (paint solvent)." *Indian Journal of Anaesthesia,* Vol. 54, No. 2, 2010, pp. 160-62.

[2] Agrawal, Avinash, et al. "Acute cardiogenic pulmonary oedema with multiorgan dysfunction-Still to learn more about nitrobenzene poisoning." *Case Reports,* Vol. 2011, 2011.

[3] George, Tarun, et al. "Severe methemoglobinemia due to insecticide poisoning." *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine,* Vol. 18, No. 2, 2014, pp. 113-14.

[4] Lee, Chang Hwan, et al. "Two cases of methemoglobinemia induced by the exposure to nitrobenzene and aniline." *Annals of Occupational and Environmental Medicine,* Vol. 25, No. 1, 2013, pp. 1-7.

[5] do Nascimento, Tatiana Souza et al. "Methemoglobinemia: From diagnosis to treatment." *Brazilian Journal of Anesthesiology*, Vol. 58, No. 6, 2008, pp. 651-64.

[6] Harris, John C., et al. "Methemoglobinemia resulting from absorption of nitrates." *JAMA,* Vol. 242, No. 26, 1979, pp. 2869-71.

[7] National Research Council, and Safe Drinking Water Committee. "Toxicity of selected organic contaminants in drinking water." *Drinking Water and Health: Volume 4*, National Academies Press (US), 1982.

[8] Perera, Mark, et al. "Acute methaemoglobinaemia after massive nitrobenzene ingestion." *Case Reports,* Vol. 2009, 2009, p. bcr0720080515.

[9] Palange, PB, et al. "A fatal case of nitrobenzene poisoning with severe methemoglobinemia and ARDS due to drowning." *International Journal of Biomedical Research*, Vol. 5, No. 12, 2014, pp. 783-84.

[10] Singh, Ranju, Stalin Vinayagam, and Homay Vajifdar. "Methemoglobinemia as a result of accidental lacquer thinner poisoning." *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine,* Vol. 16, No. 1, 2012, pp. 44-47.

[11] Messmer, Anna Sarah, Christian Hans Nickel, and Dirk Bareiss. "P-chloroaniline poisoning causing methemoglobinemia: A case report and review of the literature." *Case Reports in Emergency Medicine,* Vol. 2015, 2015.

[12] Solecki, Roland. "Toxicology of miscellaneous insecticides." *Pesticide Toxicology and International Regulation,* 2004, p. 159.