Short Report

Exchange transfusion as a therapeutic modality for aniline dye-induced methaemoglobinaemia

NIDHI GUPTA, SONALI DHAGIA, ARJUN KELAIYA, RUKSAR SAMA, KIRAN PADHY

ABSTRACT

Methaemoglobinaemia and a Heinz-body haemolytic anaemia are uncommon but potentially treatable complications of aniline poisoning. Management of aniline poisoning is mainly removing the source of aniline exposure and management of methaemoglobinaemia. Management of methaemoglobinaemia is guided by blood methaemoglobin levels and patient symptoms. Blood methaemoglobin level < 30% requires only supplemental oxygen while for methaemoglobin level >30%, intravenous methylene blue is the mainstay of treatment. All patients treated with methylene blue should be observed for delayed haemolysis, acute renal failure and cardiac complications. In patients with contraindication to methylene blue, exchange transfusion can be used while haemodialysis is reserved for complicated cases. We successfully managed 6 patients of methaemoglobinaemia due to aniline poisoning by methylene blue. Two of these patients who developed Heinz-body haemolytic anaemia with acute renal failure as a complication also required exchange transfusion.

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INTRODUCTION

The use of aniline in chemical industries is almost two centuries old and so is human toxicity associated with aniline. Aniline is a simple aromatic amino compound, pale yellow in colour with a rotten fish odour. It is an oxidizing agent used as a solvent in dyes, antioxidants, rubber accelerators, drugs, photographic chemicals, isocyanates, herbicides and fungicides. Common routes of occupational exposure are inhalation, ingestion and absorption through the skin and it is rapidly absorbed through all routes.[1,2] Aniline poisoning results in a conglomeration of symptoms called methaemoglobinaemia and Heinz-body haemolytic anaemia. Since the late 19th century, a large number of case reports and series have been published on aniline poisoning and its management. Despite decades of experience, the guidelines for the treatment of aniline poisoning are still not well defined and somewhat controversial.[3]

We report our experience of successful management of 6 cases of methaemoglobinaemia following aniline poisoning in a chemical plant through inhalation and dermal absorption. Two of these patients developed Heinz-body haemolytic anaemia with acute renal failure following treatment with methylene blue. Both the patients were successfully treated with exchange transfusion.

THE CASES

Six people working in a chemical factory were brought to the emergency department of our hospital 8 hours after dermal and inhalational exposure to aniline following spillage while packaging and loading of the bags. They all complained of headache, nausea, vomiting, cyanodermosis and perioral cyanosis.

At admission, all the patients were conscious, oriented and mildly dyspnoeic, and complained of severe headache. Their vitals were stable. A yellowish brown powder was laced on the arms and legs of all 6 workers. There was cyanosis of the fingers and toes and perioral cyanosis. There were no jaundice or pallor. Cardiac, respiratory and abdominal examinations were normal.

All the patients were admitted. Clothes were removed and the whole body was washed with generous amounts of warm soap water and rinsed with plain water. Oxygen inhalation at a flow of 10 L by mask was started. Routine blood investigations, electrocardiogram and chest X-ray were normal on presentation. Methaemoglobin level (quantitative MetHb determined by visible spectrophotometer) ranged from 52.5% to 73.4%. In arterial blood gas (ABG) analysis, partial pressure of oxygen (pO_2) was >150 mmHg and partial pressure of carbon dioxide (pCO_2) was between 35 and 45 mmHg. Oxygen saturation (SpO_2) varied from 61.1% to 83.4% (Table I).

All the patients were admitted in the ICU and injection methylene blue 2 mg/kg and 500 mg ascorbic acid in 5% dextrose was administered intravenously slowly over 10 minutes. Over the next 1 hour, their skin colour improved, and dyspnoea and headache decreased in all the patients. Repeat ABG after 1 hour showed pO_2 >200 mmHg and SpO_2 >75%. The MetHb levels decreased to <30% in patient #1, #2 and #5 while MetHb levels were >35% in patient #3, #4 and #6. In patients #3, #4 and #6, another dose of methylene blue (2 mg/kg) and ascorbic acid (500 mg) was administered after 2 hours. After 4 hours, all the patients improved symptomatically and MetHb levels decreased below 10%. They were kept under observation for rebound methaemoglobinaemia and intravascular haemolysis. Repeat ABG after 24 hours of admission showed normal pH and pCO_2 levels, pO_2 >200 mmHg and SpO_2 >95%. Repeat MetHb levels were less than 3% in all the patients. Patient #1, #2, #4 and #5 continued to improve and were discharged from the hospital after 48 hours.

At 36 hours following admission, mild dyspnoea and jaundice was noticed in patient #3 and #6. In both patients, haemoglobin was <9 g/dl, unconjugated bilirubin was present and serum creatinine increased despite good urine output. Heinz-body preparation of peripheral smear showed the presence of Heinz bodies and spherocytes. Suspecting haemolytic anaemia,

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TABLE I. Change in laboratory and arterial blood gas values of the patients at different time-points

Patient	1	2	3	4	5	6
At admission						
Hb (g/dl)	10.5	11.3	11.4	11.0	12.2	10.8
Peripheral smear	Normal	Normal	Normal	Normal	Normal	Normal
Creatinine (mg/dl)	0.77	0.71	0.80	0.84	0.77	0.85
Total bilirubin (mg/dl)	0.5	0.7	0.7	0.8	1.0	0.85
MetHb (%)	58.4	55	57.5	63	55	73.4
pH	7.37	7.39	7.37	7.41	7.46	7.39
pO_2 (mmHg)	188	210	213	175	189	197
pCO_2 (mmHg)	37	39	41	41	43	38
SpO_2 (%)	63.2	61.1	81.0	83.4	67.5	74.8
After the first dose of methylene blue and ascorbic acid						
MetHb (%)	27.7	25	38.5	45.3	19	53.5
pH	7.35	7.39	7.41	7.35	7.40	7.47
pO_2 (mmHg)	264	285	213	225	278	202
pCO_2 (mmHg)	37	38	41	44	37	38
SpO_2 (%)	77.5	78.4	87.8	93.5	79.8	87.9
Methylene blue: Dose 2	No	No	Yes	Yes	No	Yes
After the second dose of methylene blue and ascorbic acid						
After 4 hours	7.4	5.7	7.8	8.7	4.3	9.8
After 24 hours	1.4	1.8	2.8	2.8	1.1	1
pH	7.37	7.38	7.41	7.37	7.41	7.43
pO_2 (mmHg)	267	275	248	257	199	284
pCO_2 (mmHg)	37	39	39	39	42	40
SpO_2 (%)	95.5	97	98.5	98.8	99	99
At 36 hours of admission						
Hb (g/dl)	10.5	11.3	8.5	11.0	12.2	7.4
Peripheral smear	Normal	Normal	Heinz bodies, Spherocytes	Normal	Normal	Heinz bodies, Spherocytes
Creatinine (mg/dl)	0.75	0.77	1.83	0.80	0.75	1.92
Bilirubin (mg/dl)	0.6	0,85	3.5	0.8	1.1	5.3
MetHb (%)	<1	<1	25.5	<1	<1	30
Free Hb (mg/dl)	–	–	843	–	–	915
Haptoglobin (mg/dl)	–	–	5.5	–	–	9.3
Lactate dehydrogenase (i.u./L)	–	–	3650	–	–	4280
Urine microscopy	–	–	Normal	–	–	Normal
At 60 hours after admission						
Hb (g/dl)	–	–	7.3	–	–	6.7
Creatinine (mg/dl)	–	–	2.1	–	–	2.22
Exchange transfusion	–	–	Yes	–	–	Yes
Haemodialysis	–	–	No	–	–	No
Outcome	Survive	Survive	Survive	Survive	Survive	Survive

Hb haemoglobin MetHb methaemoglobin

investigations were sent for serum-free haemoglobin, serum haptoglobin and serum lactic dehydrogenase (LDH) levels. Serum-free haemoglobin and LDH were raised while serum haptoglobin levels were decreased (Table I). Urine analysis revealed no abnormality. Glucose-6-phosphate dehydrogenase (G6PD) levels were not sent as they may be falsely normal in the presence of haemolysis. Repeat MetHb levels in patient #3 and #6 increased to 25.5% and 30%, respectively, possibly suggesting refractory methaemoglobinaemia, which prompted consideration of exchange transfusion. Both the patients were managed with oxygen by mask and intravenous hydration for the next 24 hours. However, their renal function continued to deteriorate and the haemoglobin level dropped to <7.5 g/dl. After conservative management for 24 hours, the decision to do an exchange transfusion was taken, although MetHb levels were not done again after 24 hours as haemolytic anaemia and deteriorating renal function were the major concerns. In both the patients, exchange transfusion was done with 4 units of blood over 12 hours. Both the patients responded to exchange transfusion with stabilization of haemoglobin and decrease in MetHb, free haemoglobin and serum creatinine. Both patients were discharged on day 6. During follow-up at 2 weeks and 4 months after discharge, all patients were well with complete clinical and biochemical recovery including G6PD levels.

DISCUSSION

An acutely cyanotic patient is of immediate concern to the emergency physician. Methaemoglobinaemia is an uncommon, albeit potentially fatal and easily treatable cause of acute cyanosis. It occurs due to oxidation of iron present in haemoglobin from ferrous (Fe^{2+}) to ferric (Fe^{3+}) form. The resultant MetHb cannot act as a source of oxygen supply in the blood due to its inability to reversibly bind with the oxygen molecule. Further, MetHb also causes an unfavourable shift in the oxygen dissociation curve of the residual haemoglobin. This results in an acute functional anaemia with severe impairment in tissue

oxygenation without affecting the pO_2 or pCO_2. Normally, less than 1%–2% of haemoglobin circulates in the blood as MetHb. When the MetHb concentration in the blood is >2%, methaemoglobinaemia is said to exist.[4] The presentation of methaemoglobinaemia ranges from mild asymptomatic cyanosis to fatal coma depending on the concentration of MetHb in the blood. MetHb concentration of 0%–20% produces cyanoderma only; 20%–40% produces headache, anxiety, vertigo and tachycardia; 40%–60% produces clouding of consciousness and respiratory failure; and >60% results in arrhythmia, convulsion, coma and death.[5–8] Though there is no absolute correlation between MetHb levels and clinical features, in our patients, despite high MetHb levels (52.5% to 73.4%) in all 6 patients on presentation, none of them had major cardiovascular or CNS involvement possibly due to general awareness of the chemical factory authorities, leading to early recognition of symptoms and referral for early treatment.

Methaemoglobinaemia can be congenital or acquired. Acquired methaemoglobinaemia mostly occurs through non-occupational exposure. However, in the last century, several reports of methaemoglobinaemia due to occupational exposure of aniline have been reported. Aniline results in methaemoglobinaemia not by itself but, due to oxidative effect of its intermediary metabolite 'phenyl-hydroxylamine'. The most common symptoms of aniline poisoning are due to methaemoglobinaemia; however, aniline itself can result in Heinz-body positive haemolytic anaemia and cardiac and central nervous system (CNS) toxicity.[9]

Diagnosis of methaemoglobinaemia

A high index of suspicion, good clinical history and examination, and laboratory analysis are the mainstays of diagnosis. Two important clinical observations, i.e. patient less unwell than one would expect from the severity of 'cyanosis' and 'cyanosis' unresponsive to oxygen therapy give a clue to the diagnosis. Bedside pulse oximetry in this condition is unreliable, with falsely low and falsely high oxygen saturation measurements with low and high MetHb levels, respectively. This is because the pulse oximeter measures the relative absorbance of two wavelengths of light (660 nm and 940 nm) to differentiate oxyHb from deoxyHb and converts the ratio of absorption into calibrated oxygen saturation values. However, MetHb increases absorption at both wavelengths more at 940 nm, as a result oxygen saturation in methaemoglobinaemia plateaus at 80%–85% at any given value of MetHb levels. Therefore, direct measurement of MetHb and ABG analysis is mandatory. ABG reveals normal pO_2 and pCO_2, a normal 'calculated' haemoglobin O_2 saturation, an increased MetHb concentration and possibly metabolic acidosis. Accurate O_2 saturation determination requires co-oximeter measurements.[10,11]

In healthcare facilities with limited access to sophisticated laboratory equipment as in rural India, certain bedside investigations to diagnose methaemoglobinaemia may be useful in guiding therapy or timely referral in a cyanosed patient. First, the blood sample that is chocolate-brown in colour and remains dark despite bubbling with 100% oxygen is likely to contain >20% MetHb concentration and the patient needs treatment with methylene blue. The same test can be performed by placing 1–2 drops of the patient's blood on a white filter paper and exposing it to oxygen. If the blood contains MetHb, it will remain dark. Second, chocolate-brown appearance of the blood does not change with time if it contains MetHb, whereas deoxy-haemoglobin becomes bright after exposure to atmospheric oxygen. Third, the cooking test: Place the clotted sample of the patient's blood in a boiling water bath. After cooking and cooling, the blood sample will turn pink if it contains MetHb, whereas normal blood remains dark brown.[12] The emphasis should be on the need for early diagnosis and referral of any patient who develops severe methaemoglobinaemia or Heinz-body haemolytic anaemia as a complication of aniline dye toxicity. This can be successfully managed by exchange transfusion at a higher centre, leading to reduction in mortality associated with a common occupational hazard.

Management

Management of methaemoglobinaemia can be grouped into five categories: (i) reducing toxin's systemic absorption; (ii) reduction of MetHb to haemoglobin via reducing agents; (iii) treatment of the 'functional anaemia' with oxygen; (iv) extracorporeal removal of the chemical; and (v) replacement of maethemoglobin with a functional oxygen-carrying pigment.[12]

Initial management of suspected or confirmed aniline poisoning

The most important step is to limit the exposure by removing the patient from the site. Evaluate and support airway, breathing and circulation for patients with hypotension, seizures or arrhythmias. Active decontamination of the patient includes removing the contaminated clothing, washing the patient twice with copious warm soapy water and rinsing thoroughly with plain water, and irrigation of eyes with tepid water for at least 15 minutes if exposed. An asymptomatic patient should be observed for at least 6 hours for the delayed development of methaemoglobin-aemia. Symptomatic patients and those with elevated MetHb levels need to be admitted to hospital.

Laboratory investigations

Apart from MetHb level and ABG, other investigations include complete blood count (CBC) with peripheral blood smear, glucose, electrolyte, renal function tests, unconjugated bilirubin and G6PD levels. Chest X-ray and ECG should be done if cyanosis or dyspnoea are present. MetHb level should be repeated at frequent intervals for 24 hours to ensure that it is decreasing.[3,10] In patients with suspected Heinz-body haemolysis, serum-free haemoglobin, LDH and haptoglobin level should also be tested.

Management of methaemoglobinaemia

High-flow oxygen through mask should be given to maximize oxygen carriage by the remaining haemoglobin. Patients who have blood MetHb concentration <30% usually require only supplemental oxygen and decontamination as the cyanotic or slate-grey colour discolouration is imparted by the MetHb pigment rather than by the deoxygenated haemoglobin. Methaemoglobin present in the blood is reduced to haemoglobin over several hours by the intrinsic activity of MetHb reductase.[3]

Role of methylene blue

Methylene blue (methylthioninium chloride), a water-soluble dye, is used as an antidote for methaemoglobinaemia. Studies have found two possible reactions between methylene blue, haemoglobin and MetHb: (i) reduction of MetHb to haemoglobin (a nicotinamide-adenine dinucleotide phosphate [NADPH]-dependent reaction in intact red blood cells); and (ii) direct

haemoglobin oxidation (a reaction favoured by the presence of haemolysis and/or high methylene blue concentrations). Within intact red blood cells, an NADPH reductase catalyses the conversion of methylene blue to leucomethylene blue, which then non-enzymatically transfers the electrons to MetHb, so restoring functional haemoglobin and methylene blue. This reaction is sustained by the regeneration of NADPH via the G6PD-dependent pentose phosphate pathway (hexose monophosphate [HMP] shunt). In the absence of methylene blue, NADPH-methaemoglobin reductase contributes only 6% to the methaemoglobin-reducing activity of the red blood cells. Methylene blue can increase the reducing capacity of NADPH-methaemoglobin reductase enzyme by 400-fold *in vitro* and at least 6 times *in vivo*.[6]

Patients with G6PD deficiency are deficient in NADPH. In NADPH-depleted individuals, there is a competition for NADPH between glutathione striving to protect against haemolysis and methylene blue serving to protect against methaemoglobinaemia, making methylene blue ineffective. It may also exacerbate haemolytic anaemia, which may be delayed for several days.[13] Therefore, all the patients treated for methaemoglobinaemia should be observed for Heinz-body haemolytic crisis. Heart, liver and kidney may be affected secondary to haemolysis resulting in acute renal failure and arrhythmias. In our series, 2 patients developed Heinz-body haemolysis with acute renal failure.[3,14]

Contraindications and adverse effects of methylene blue. Methylene blue is contraindicated in G6PD deficiency, NADPH methaemoglobin reductase deficiency and sulph-haemoglobinaemia. It is also not effective in haemoglobin M (Hb M). It is listed as a category X teratogen. The US Food and Drug Administration (FDA) warns against using methylene blue concurrently with serotonergic drugs as it may increase serotonin levels in the CNS by MAO-A inhibition increasing the risk of serotonin syndrome.[15]

Administration of methylene blue is not without complications. Rapid intravenous injection of methylene blue may be painful and extravasation may lead to tissue necrosis. Administration of intravenous methylene blue 7 mg/kg to individuals without methaemoglobinaemia results in self-limiting symptoms such as nausea, vomiting, tachypnoea, tachycardia, tremor, mydriasis, blue staining of the skin and mucous membranes, mild methaemoglobinaemia (up to 7%) and ECG changes (T wave flattening or inversion). Intravenous methylene blue administration at 100 mg/kg can itself cause transient reduction in SpO_2 to 82% without change in skin colour.[1,3]

Guidelines for methylene blue treatment

In symptomatic patients with MetHb concentrations between 30% and 50%, intravenous methylene blue should be administered at a dose of 1–2 mg/kg body weight. When the methaemoglobin concentration is >50%, methylene blue is administered at a dose of 2 mg/kg body weight. Aqueous diluted methylene blue is injected slowly over 5–10 minutes. Methaemoglobin levels should be repeated 1 hour after administration of methylene blue as maximal response to methylene blue occurs within 30–60 minutes. Repeat doses of methylene blue must be spaced at least 1 hour apart and should be given only after evaluating the response to the last dose both clinically and by measuring the MetHb levels. The maximum advised safe dose of methylene blue is 7 mg/kg over 24 hours. If a patient has a negligible initial response to methylene blue administration, then G6PD levels should be measured. It is advisable to continue to monitor MetHb levels even after an initial response to methylene blue because there are chances of continued production of MetHb by aniline. Most patients can tolerate 30% MetHb level without symptoms; however, an anaemic patient, with a MetHb level <30%, may manifest hypoxic symptoms and consequently would benefit from the administration of methylene blue. Methylene blue should be discontinued if there is either a negligible response or an increase in MetHb levels after two consecutive doses or if the total dose exceeds 7 mg/kg. Dextrose should be co-administered to increase the formation of NADPH. In our series, all 6 patients were symptomatic and had MetHb level >50% at the time of presentation; therefore, methylene blue 2 mg/kg was administered apart from oxygen and other supportive treatment. The second dose of methylene blue was administered only in patient #3, #4 and #6 as their MetHb levels were still >30% after the first dose of methylene blue.

Other therapies

Supplemental antioxidants such as ascorbic acid, *N*-acetylcysteine and vitamin E are used along with methylene blue therapy as adjuvants without proven benefit. Ascorbic acid is an effective alternative if methylene blue is not available or contraindicated.[16] Ascorbic acid, a potential urinary acidifier, may actually increase the risk for renal toxicity in the presence of haemolysis because of an increased potential for precipitation of haemoglobin in acidic urine. Hyperbaric oxygen may allow oxygenation of tissues in the absence of normal oxygen-carrying haemoglobin. This can provide time for reduction of MetHb to haemoglobin and removal of the offending chemical to occur. However, with aniline, because of its potential for prolonged production of MetHb and persistence in the body, hyperbaric oxygen may not be feasible.[17]

Exchange transfusion

The use of exchange transfusion is limited to patients with life-threatening and refractory methaemoglobinaemia with severe haemolysis and when methylene blue is relatively contra-indicated, e.g. G6PD deficiency. A repeat dose of methylene blue may be required after the exchange transfusion to bring down the MetHb levels. Advocates of exchange transfusion assert the dual benefit of exchange transfusion—it removes a quantity of the toxin from the blood and it increases the functional oxygen-carrying haemoglobin pigment. Yet, inherent risks of exchange transfusion such as a large volume of blood necessary for the procedure and the time involved must be kept in mind.

In our series, 2 patients required exchange transfusion due to acute Heinz-body haemolytic anaemia. We are not sure of the cause of haemolytic anaemia in our patients as we had not checked G6PD levels at the time of admission; it may be related to aniline poisoning or the antidote methylene blue. Both, aniline and methylene blue can cause oxidative stress resulting in damage to the red blood cells. Patients with G6PD deficiency are more prone to haemolytic anaemia; however, it may occur in patients with normal G6PD levels as in patient #3 and #6 in our series. Both the patients responded well to exchange transfusion and did not require the third dose of methylene blue.[3,14,18–22]

Haemodialysis

The first successful use of haemodialysis in the management of severe methaemoglobinaemia was reported in 1964. Since then, few case reports have been published with variable outcome. Presently, there are no clear guidelines for use of haemodialysis in methaemoglobinaemia; however, limited past experience suggests that haemodialysis may have a role in the management of aniline poisoning. Haemodialysis may be indicated for aniline poisoning if a patient's clinical state is deteriorating or not improving despite the use of methylene blue and good supportive and symptomatic management.[17,23,24] In our series, no patient required haemodialysis.

Conclusion

Acquired methaemoglobinaemia, either aniline or other chemical-induced, needs early recognition, diagnosis and appropriate intervention and/or referral. The emergency physician should be aware of the clinical and diagnostic aspects of methaemoglobinaemia. Apart from other investigations, blood G6PD levels should be checked at the time of admission both to guide therapy and in anticipation of complications. Methylene blue and ascorbic acid are the treatment of choice. Blood exchange transfusion and hyperbaric oxygen therapy are usually reserved for patients who are resistant to standard treatment.

Conflicts of interest. None declared

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