Clinical experience in diagnosis and management of acquired methaemoglobinaemia: a case report and retrospective review

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Case reports

Case 1

In June 2008, a 9-month-old boy with unremarkable medical and developmental history presented to the emergency department with acute cyanosis. The child had been fed about 200 g of congee containing rice, vegetables, fish, and egg. He was then noted to have pallor of face and perioral cyanosis. He was conscious and irritable and reported to have vomiting. His respiratory rate was 40 breaths per minute and heart rate was 190 beats per minute. Pulse oximetry showed 90% oxygen saturation on 100% oxygen via a face mask. Physical examination was otherwise unremarkable. He was admitted to the paediatric intensive care unit. During blood sampling, his blood was noted to be chocolate brown. While on 100% oxygen, his arterial blood gas showed a pH value of 7.33, PaO_2 51.8 kPa, $PaCO_2$ 4.2 kPa, and bicarbonate 17 mmol/L. Blood methaemoglobin (MetHb) level was 51%. He was treated with intravenous methylene blue 15 mg (about 1.5 mg/kg) and urine was observed to be light blue (Fig). His cyanosis resolved within 1 hour after treatment and blood oxygen saturation returned to normal without oxygen supplementation. The MetHb level dropped to 1% within 30 minutes after treatment. Mutation screen of cytochrome B5 reductase gene (CYB5R3) was negative for the patient and both parents.

A high urinary nitrate level of 315 mg/L (reference range, 41.0-55.6 mg/L) was detected. Toxicology showed high nitrate and nitrite content in the congee consumed by the infant, 150 mg/L and 47.7 mg/L, respectively. The uncooked vegetable Amaranthus remnant contained nitrate but at a safe level. Water used for cooking had come from a regular tap, not from a well that could otherwise have been a source of contamination.

The advised daily intake of nitrates and nitrites is 0 to 3.7 mg/kg and 0 to 0.07 mg/kg body weight, respectively. Our patient weighted 9.2 kg and his single-day consumption of nitrates and nitrites was 34 mg and 0.644 mg, respectively. When he consumed 200 g of congee, he consumed 31.8 mg of nitrates and 9.74 mg of nitrites in one meal. The prescribed advised daily intake is for adults; a lower limit should apply for children. The patient has been followed up for 5 years with no recurrence of methaemoglobinaemia.

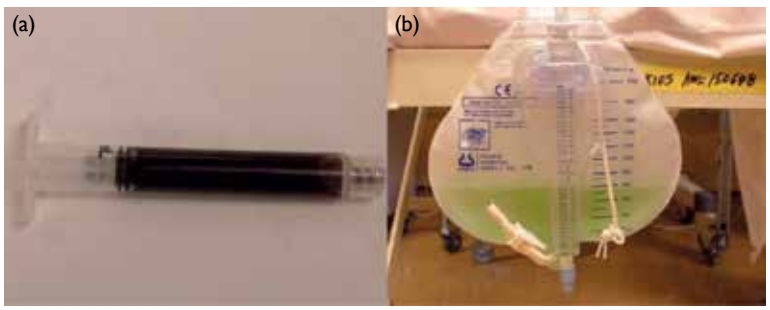

FIG. Case 1: a 9-month-old boy with methaemoglobinaemia. (a) Chocolate brown blood taken after admission and (b) light blue urine after intravenous methylene blue treatment

Case 2

In November 2018, a 50-year-old man with a history of schizophrenia was admitted following massive zopiclone overdose. He had taken more than 100 tabs of the hypnotic of 7.5 mg each. There was no evidence of carbon monoxide inhalation. His presenting symptoms were dizziness, nausea, and reduced urine output. He was noted to be cyanotic and with oxygen saturation of 85% on 100% oxygen. During blood sampling, his blood was noted to be chocolate brown. Serum MetHb level was 40.3% initially. Methylene blue 70 mg (around 1 mg/kg) as a slow intravenous bolus was administered in the

emergency department and 1 hour later serum MetHb level had fallen to 19.3%. Carboxyhaemoglobin was 3.8%. He was admitted to the adult intensive care unit and received a further dose of intravenous methylene blue 70 mg. His saturation improved to 96% on pulse oximetry on oxygen supplementation at 1 litre per minute. Repeat measurement of MetHb showed it to be <0.1%. Carboxyhaemoglobin level peaked at 10% and gradually decreased. Urine was deep green in colour after methylene blue treatment. He also developed acute kidney injury (creatinine level peaked at 1239 μmol/L) that required haemodialysis and a normochromic normocytic anaemia (trough haemoglobin level 6.2 g/dL). Haptoglobin level was low, indicative of haemolytic anaemia. Although evidence of oxidative haemolysis, such as Heinz bodies, was not documented on blood film examination, zopiclone-induced oxidative stress was probably the cause of haemolysis. Renal ultrasonography showed only mild renal parenchymal disease. His condition stabilised after an 11-day stay in the intensive care unit.

Retrospective analysis

To supplement the above cases, we searched through the computerised medical record system of our institution and identified all in-patients with International Classification of Diseases-9 code of 289.7, 'Methemoglobinemia', from January 2000 to December 2018. We identified 21 patients with acquired methaemoglobinaemia, aged 14 days to 67 years (Table). The most common cause was deliberate self-harm by overdosing with zopiclone. The most common clinical presentation was unexplained desaturation on pulse oximetry despite oxygen supplementation. Nine patients received methylene blue. One patient with coexisting glucose-6-phosphate dehydrogenase (G6PD) deficiency was given ascorbic acid. Response to methylene blue was prompt in all cases, with MetHb falling to a non-toxic level soon after treatment.

Discussion

Infants or young children may be more susceptible to methaemoglobinaemia as the haemoglobin enzymes, such as cytochrome-b5 MetHB reductase, are immature. As in Case 1, nitrates in vegetables can cause methaemoglobinaemia, and this underlying cause is preventable. Nitrates are commonly found in agricultural products and well water, and can be formed by bacteria from nitrates. Home-prepared vegetables should be avoided in infants younger than 3 months of age.[1] Farmers should avoid excessive use of nitrate-containing products during vegetable production, as suggested by agricultural guidelines.[2] Well water should be monitored for nitrate contamination. Nitrate content can be converted to nitrite due to improper storage in a flask. Nitrate can also be reduced to nitrite by nitrate reductase intrinsic to plants or bacteria. Thus, proper washing, cooking and storage of food rich in nitrates is essential.

Medication is a main cause of acquired methaemoglobinaemia. Zopiclone overdose accounted for a significant portion in our series. As a non-benzodiazepine hypnotic, zopiclone is widely prescribed. Massive zopiclone overdose is relatively more common in Hong Kong because it can be obtained without a prescription. Intentional overdose has been reported in those attempting suicide.[3] Zopiclone is known to be associated with methaemoglobinaemia especially following massive overdose, and with haemolytic anaemia and kidney injury. The elevated carboxyhaemoglobin in Case 2 was possibly endogenous due to haemolysis, as metabolism of haem via haem oxidase produces one molecule of CO per molecule of haem degraded.[4]

Other substances that can lead to methaemoglobinaemia include dapsone, nitrogen, and alanine. They induce oxidative stress in erythrocytes. In susceptible subjects who lack antioxidative enzymatic activity, the ferrous ion in the haem group is oxidised to a ferric state, forming MetHb that is incapable of binding oxygen. The oxygen dissociation curve is shifted to the left; oxygen desaturation, around 85%, is common in methaemoglobinaemia. The underlying mechanism is related to the absorption of light wavelengths employed by emitter and detector of the pulse oximeter.

Clinical presentations of methaemoglobinaemia include both central and peripheral cyanosis, dizziness, headache, dyspnoea, and malaise. In extreme cases, coma or death may occur if MetHb exceeds 30% to 40%. G6PD deficiency can exacerbate the methaemoglobinaemia and concomitant haemolysis. Vigilance is needed for clinical diagnosis. Unexplained cyanosis or poor oxygen saturation should prompt clinicians to consider methaemoglobinaemia. Medication and dietary histories, chemical contacts, recent medical or dental procedures and occupational exposure are conducive to diagnosis. Treatment mainly depends on the level of MetHb. For low levels, no specific treatment is needed. Methylene blue is usually indicated if MetHb exceeds 20%. It acts as a cofactor to increase erythrocyte reduction of MetHb to haemoglobin in the presence of NADPH. Therapeutic response is usually prompt. In our series, MetHb level dropped in all cases to below 20% after a single dose of methylene blue. Methylene blue should be used with caution in patients with G6PD deficiency as haemolysis can result from repeated use. An excessive cumulative dose of methylene blue can also potentially induce haemolysis. Ascorbic

TABLE. Clinical features of patients with acquired methaemoglobinaemia

Sex	Age	Presenting features	MetHb on presentation (%)	Maximum recorded MetHb (%)	G6PD deficiency	Aetiology	Treatment	MetHb immediately after treatment (%)	Remarks
M	9 mo	Oxygen desaturation upon pulse oximeter monitoring; cyanosis	51%	51%	N	Nitrates/nitrites from amaranth	MB, 15 mg IV	1%	Case 1
M	50 y	Cyanosis and oxygen desaturation upon pulse oximeter monitoring	40.3%	40.3%	N	Zopiclone OD	MB, 70 mg IV each, 2 doses	19.3%	Case 2 Concomitant acute kidney injury and anaemia
M	61 y	Not documented	3%	3%	Not documented	Unknown	MB, 50 mg oral every other day	NA	
F	60 y	Oxygen desaturation upon pulse oximeter monitoring	4%	13%	N	Zopiclone OD	MB, 50 mg IV	4%	
M	38 y	Oxygen desaturation upon pulse oximeter monitoring; cyanosis	41%	41%	N	Unknown	MB, 70 mg IV	0	
M	10 mo	Oxygen desaturation upon pulse oximeter monitoring	6%	6%	Y	Unknown	Vitamin C, 500 mg oral	4%	Concomitant haemolytic anaemia
F	34 y	Oxygen desaturation upon pulse oximeter monitoring	8%	8%	N	Dapsone	Nil	NA	
M	14 d	Oxygen desaturation upon pulse oximeter monitoring	5%	5%	Not documented	Anaesthesia with nitrous oxide	MB, dose not documented		
M	51 y	Oxygen desaturation upon pulse oximeter monitoring; cyanosis	34%	34%	N	Zopiclone OD	MB, dose not documented	81%	
M	45 y	Dyspnoea	66%	66%	N	Aniline	MB, 70 mg IV	2%	Accidental occupational aniline exposure
F	29 y	Malaise	21%	21%	Not documented	Zopiclone OD	MB, 100 mg IV	0	
F	52 y	Oxygen desaturation upon pulse oximeter monitoring	11%	12%	N	Dapsone	Nil	NA	
M	54 y	Oxygen desaturation upon pulse oximeter monitoring	6%	15%	Y	Herbal medicine (suspected)	Nil	NA	
M	43 y	Oxygen desaturation upon pulse oximeter monitoring	2.1%	2.1%	N	Zopiclone OD	Nil	NA	
F	55 y	Asymptomatic	1.2%	1.2%	N	Zopiclone OD	Nil	NA	
M	65 y	Oxygen desaturation upon pulse oximeter monitoring	2.4%	2.4%	N	Zopiclone OD	Nil	NA	
F	53 y	Oxygen desaturation upon pulse oximeter monitoring	0.9%	1.8%	N	Zopiclone OD	Nil	NA	
F	29 y	Oxygen desaturation upon pulse oximeter monitoring	2.3%	2.3%	N	Zopiclone OD	Nil	NA	
M	16 y	Oxygen desaturation upon pulse oximeter monitoring	1.9%	1.9%	N	Zopiclone OD	Nil	NA	
F	35 y	Asymptomatic	1%	1%	N	Zopiclone OD	Nil	NA	
F	67 y	Oxygen desaturation upon pulse oximeter monitoring	2%	2%	N	Zopiclone OD	Nil	NA	

Abbreviations: F = female; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; M = male; MB = methylene blue; MetHb = methaemoglobin; N = no; NA = not available; OD = overdose; Y = yes

acid, an antioxidant, may be used as an alternative, either orally or intravenously.[5] It works by scavenging free radicals and protects cells against oxidative stress, acting as a co-factor for NADP reductase and directly reducing MetHb.

In conclusion, methaemoglobinaemia can affect a wide age range of patients and be due to a variety of agents. Effective treatment exists and the response is usually satisfactory.

Author contributions

Concept or design: All authors.
Acquisition of data: TT Chan, RSK Chang.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: TT Chan, RSK Chang.
Critical revision for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Ethics approval

The patients were treated in accordance with the Declaration of Helsinki, and provided informed consent for all treatments and procedures. The retrospective analysis of patient data was approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster institutional review board (Ref UW 19-205) and the requirement for patient consent for publication was waived.

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Answers to CME Programme
Hong Kong Medical Journal August 2021 issue

Hong Kong Med J 2021;27:266–75

I. Utility of cardiac magnetic resonance imaging in troponin-positive chest pain with non-obstructive coronary arteries: literature review

A	1. False	2. True	3. True	4. False	5. False
B	1. False	2. True	3. False	4. True	5. True

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II. Initial intravenous fluid prescription in general paediatric in-patients aged >28 days and <18 years: consensus statements

A	1. True	2. True	3. False	4. True	5. False
B	1. True	2. False	3. False	4. True	5. True