CASE REPORT

Benzocaine-induced methaemoglobinaemia: a life-threatening complication after a transoesophageal echocardiogram (TEE)

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SUMMARY

Acquired methaemoglobinaemia is a potentially fatal impairment in oxygen delivery if not recognised early and treated appropriately. Benzocaine used as an anaesthetic for endoscopic procedures is an uncommon but clinically important precipitant of acquired methaemoglobinaemia. We present a case of an elderly woman who developed perioral cyanosis and desaturation 20 min after a transoesophageal echocardiogram. Further evaluation led to the diagnosis of benzocaine-induced methaemoglobinaemia and timely treatment with intravenous methylene blue was initiated.

BACKGROUND

Benzocaine is a commonly used topical anaesthetic for mucous membranes prior to transoesophageal echocardiography (TEE). Although generally considered safe, it can on rare occasion lead to life-threatening complications such as methaemoglobinaemia.¹

The incidence of benzocaine-induced methaemoglobinaemia in TEE is low. A review of 4336 TEE examinations by Novaro *et al*² suggested an incidence of 0.115%. Nevertheless, recognition of this complication by clinicians is crucial as untreated methaemoglobinaemia can lead to cardiopulmonary compromise, neurological sequelae and even death.³

This article depicts a case of benzocaine induced methaemoglobinaemia in a patient following TEE. Timely diagnosis and treatment in our case led to a good outcome.

CASE PRESENTATION

A 71-year-old woman presented to the hospital with numbness and tingling in her right thumb and index finger. Her medical history was significant for hypertension, hypercholesterolaemia, gastro-oesophageal reflux disease (GERD) and a nephrectomy was carried out for renal cell carcinoma. She denied any tobacco or alcohol use. Physical examination revealed elevated blood pressure of 224/102 mm Hg, pulse was regular at 77 bpm with an oxygen saturation of 96% breathing on room air. Cardiopulmonary examination was unremarkable. Further evaluation with a CT scan and an MRI of the brain confirmed the diagnosis of ischaemic stroke. The patient did not meet the criteria for tissue plasminogen activator administration. The patient was subsequently scheduled for an ultrasound-guided TEE to rule out a cardioembolic aetiology for her stroke. Her oxygen saturation was 96% on room air and haemoglobin level was

14.1 g/dL on arrival to the TEE suite. After informed consent was obtained, she was given 2 mg intravenous midazolam, 75 µg intravenous fentanyl and a hurricane lollipop (20% benzocaine gel impregnated on a stick that the patient was asked to take into her mouth). TEE revealed mild left ventricular hypertrophy, normal wall motion, ejection fraction of 65% and absence of any intracardiac thrombus or shunt including patent foramen ovale. The patient's haemodynamics and oxygen saturation were normal during the entire procedure. However, 20 min after the procedure, her oxygen saturation dropped to 72% and she was noted to have cyanosis in her lips and fingers. Otherwise, she was asymptomatic without any respiratory depression.

INVESTIGATIONS

A stat arterial blood gas revealed a chocolate-brown colour to her blood with pH of 7.4, PaO₂ 252 mm Hg, oxygen saturation 76%, PCO₂ 35.9 mm Hg, bicarbonate 24.8 mEq/L and base excess 1.4 mEq/L. Owing to clinical suspicion for methaemoglobinaemia, a methaemoglobin level was measured and noted to be 44.2% (normal 0.4–1.5%).

DIFFERENTIAL DIAGNOSIS

Other aetiologies of hypoxaemia that can occur post-TEE include hypoventilation, aspiration pneumonia, right-to-left shunting, low cardiac output shock, asthma, pulmonary oedema and pulmonary embolus. These were ruled out on the basis of a normal echocardiogram, chest X-ray, clinical examination and haemodynamic parameters.

TREATMENT

Following the episode of hypoxaemia, the patient was taken to the intensive care unit (ICU). She was first administered 100% oxygen on a non-rebreather mask which partially raised her oxygen saturation to 83%. She was also given 1 mg/kg of intravenous methylene blue and started on incentive spirometry.

OUTCOME AND FOLLOW-UP

Within a few hours of administration of methylene blue, her oxygen saturation normalised to the high 90s. A methaemoglobin level measured 4 h later was 0.8%. Methaemoglobin levels were repeated every 6 h to monitor for late recurrence of methaemoglobinaemia. Her remaining ICU stay was uneventful and she was transferred to the stroke

To cite: Aryal MR, Gupta S, Giri S, *et al.* *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009398

unit the following day. At the time of transfer, she had stable vital signs and was maintaining an oxygen saturation of 95% on room air.

DISCUSSION

Methaemoglobin is the oxidised form of haemoglobin formed in response to exposure of blood to oxidative stress.⁴ The oxidation of the iron of the haeme group from the ferrous to the ferric state interferes with its ability to bind to oxygen. On the other hand, methaemoglobinaemia prevents oxygen release to the tissue as it shifts the oxygen haemoglobin dissociation curve to the left, further aggravating the tissue hypoxia.⁵

The presence of oxidising agents in blood can induce significant methaemoglobinaemia.⁶ Some of the common oxidising agents are nitrites, aniline dyes, antimalarial agents and nitrate containing drugs like nitroglycerine and sodium nitroprusside.⁶ Although nearly all topical anaesthetic preparations have been associated with methaemoglobinaemia, benzocaine spray is the most commonly reported.⁷ Topical benzocaine is used for a variety of procedures including dental procedures, upper gastrointestinal endoscopy, endotracheal intubation and TEE.

TEE is a commonly performed cardiac procedure in the USA with a low incidence of complications.³ Local anaesthetic agents are used prior to TEE to anaesthetise the upper airway for the purpose of oesophageal intubation. In our case, a hurricane lollipop was used as the anaesthetic agent, which is a 20% benzocaine gel impregnated on a stick. The patient is then instructed to hold the stick in the mouth much like a lollipop and let the drug melt and run down the tongue. As in our case, the use of benzocaine can rarely lead to a potentially fatal complication such as methaemoglobinaemia. Benzocaine induced methaemoglobinaemia during TEE, although rare, has been reported before.^{2 3 5 6 8–10}

None of the other medications that the patient was taking have been associated with methaemoglobinaemia. In addition, there was no recurrence of methaemoglobinaemia after the resumption of the rest of her medications except benzocaine. Hence, we conclusively identified benzocaine as the culprit of her methaemoglobinaemia.

The clinical manifestations of methaemoglobinaemia range from mild symptoms such as headaches to serious complications such as coma and even death. The clinical presentation is largely dependent on the methaemoglobin blood level. Cyanosis is a typical presentation when methaemoglobin levels are 10–20%.¹¹ Levels of 35–40% can lead to headache, fatigue, dizziness and dyspnoea. Higher levels of 60–70% may lead to seizures, arrhythmia, vascular collapse and even death.³

The diagnosis should be suspected in someone with hypoxaemia with a compatible history of exposure to an oxidising agent, chocolate-coloured blood, discrepancy between PaO₂ and SaO₂ and failure to increase oxygen saturation despite adequate oxygen administration.¹² Several risk factors may predispose a patient to develop methaemoglobinaemia on exposure to benzocaine. These include excessive dose, elderly age, enzyme deficiencies, hypoxia, malnutrition, mucosal erosion/damage and sepsis.² Our patient may have been at risk because of her elderly age as well mucosal damage secondary to chronic GERD.

Methaemoglobinaemia, when diagnosed, needs to be aggressively treated. The offending agent should be promptly discontinued and high-flow oxygen should be administered. Methylene blue in a dose of 1–2 mg/kg, is the treatment of choice and results in reduction of methaemoglobin.³ Repeated doses may be necessary if levels of methaemoglobin persistently

increase. Methylene blue, particularly in low concentration, acts as a cofactor converting methaemoglobin to haemoglobin in erythrocytes. It combines with nicotinamide adenine dinucleotide phosphate reduced, in the presence of NADPH methaemoglobin reductase, to produce leukomethylene blue which then reduces methaemoglobin to haemoglobin. In higher concentration, methylene blue acts as an oxidising agent further increasing methaemoglobin level. Intravenous route is the standard as it has poor oral bioavailability. Exchange transfusions or haemodialysis are sometimes necessary, particularly in patients with glucose-6-phosphate dehydrogenase deficiency.²

Learning points

- ▶ Transoesophageal echocardiogram (TEE), although a relatively safe procedure, can rarely lead to life-threatening complications such as methaemoglobinaemia. This is particularly true if benzocaine is used as a topical anaesthetic prior to the procedure.
- ▶ The diagnosis of methaemoglobinaemia is clinical, corroborated by diagnostic tests: patients with cyanosis and low oxygen saturation unresponsive to oxygen therapy are likely to have this condition. Arterial blood gases will reveal a discrepancy between PaO₂ and SaO₂ and the diagnosis is confirmed by measuring methaemoglobin levels.
- ▶ The treatment of choice is prompt administration of intravenous methylene blue. This drug should be available in all facilities that perform TEE.

Contributors MRA and SG were involved in drafting the initial manuscript. SG and JDF edited the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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