Clinical Toxicology

Nitrite-induced methaemoglobinaemia

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Summary: Three patients developed methaemoglobinaemia after eating meat contaminated with excessive nitrites. Diagnosis was delayed in the first two mild cases but was promptly made in the third most severely affected case.

Introduction

Acquired methaemoglobinaemia is rare but may occur after ingestion of nitrates or nitrites in food¹ or water, or after using drugs such as sulphonamides, phenacetin² or nitroglycerin.³ Sodium nitrite and nitrate solution is widely used to retard bacterial growth and to preserve the colour of lean meat.⁴ The upper legal limit of nitrite concentration in meat is 200 ppm. We report an outbreak of methaemoglobinaemia, due to ingesting meat contaminated with high concentrations of nitrite.

Case reports

Cases 1 and 2

A 41 year old woman and her 18 year old son presented 2 hours after eating pickled pork, complaining that they were nauseous and weak, and had turned blue. They were centrally cyanosed but not dyspnoeic. There was no evidence of cardiopulmonary or other disease, and no history of drug ingestion. Chest X-ray electrocardiogram, full blood count and serum biochemistry were normal. Blood gas analysis showed hypoxia (Table I). The blood samples were noted to be dark brown but the significance of this was not immediately appreciated. The patients were treated with 35% oxygen and improved symptomatically. The cyanosis cleared and blood gas analysis became normal within 12 hours. Methaemoglobin concentrations, measured later on the admission blood samples,

were 23% in the woman and 7.7% in her son (normal <1%). (A third family member who had also eaten the meat was admitted at the same time to another hospital with similar symptoms, signs and clinical course.)

Case 3

Four days later, an unrelated 36 year old man was admitted unconscious. No history was available. He was deeply centrally cyanosed, and had a tachycardia of 120 beats/min and a respiratory rate of 28/min. Physical examination was otherwise normal and chest X-ray, electrocardiogram and serum biochemistry were also normal. Blood gas analysis showed profound hypoxia (Table I). The sample was noticed to be dark brown. In view of this, the clinical presentation and knowledge of the previous cases, methaemoglobin concentration was measured immediately and found to be 66%. The patient was treated with high concentration oxygen and 10 ml of 1% methylene blue were injected intravenously. He recovered consciousness and the cyanosis cleared within minutes. He subsequently told of eating pickled pork one hour before the episode.

The meat in both instances had been bought in the

Table I Blood gas analysis on room air in 3 cases of methaemoglobinaemia

	pH	PO ₂ (kPa)	PCO ₂ (kPa)
Case 1 (Female aged 41)	7.47	5.8	4.1
Case 2 (Male aged 18)	7.42	10.6	4.8
Case 3 (Male aged 36)	7.36	0.4	5.0

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same shop on the same day. The butcher had treated the fresh meat with nitrite solution himself. In the first two cases the meat contained nitrite at a concentration of 15,000 ppm, and in the third case 10,000 ppm. The butcher was successfully prosecuted by the Health Authority and sued for compensation by the patients.

Discussion

Methaemoglobin is spontaneously produced in the erythrocytes by the oxidation of haem iron from the ferrous (Fe^{++}) to the ferric (Fe^{+++}) form. Methaemoglobin concentration is normally kept below 1% by an NADH-dependent methaemoglobin reductase. Hereditary deficiency of this enzyme causes congenital methaemoglobinaemia in the homozygote and increases susceptibility to drug-induced methaemoglobinaemia in the heterozygote.² Enzyme activity was not measured in our patients, as there was clear evidence of the source of intoxication.

Affected haemoglobin cannot interact reversibly with oxygen, and the affinity of unaffected haemoglobin for oxygen is increased, so that the oxygen dissociation curve is shifted to the left. The delivery of oxygen to the tissues is reduced and symptoms are due to anoxia. Cyanosis occurs with methaemoglobin concentrations above 10% and symptoms at concentrations above 20%. Concentrations of 60–70% are often fatal. Treatment of methaemoglobinaemia is with oxygen, methylene blue or ascorbic acid and in severe cases, exchange transfusion.² Methylene blue speeds methaemoglobin

breakdown by acting as a coenzyme in an alternative NADPH-dependent reductase pathway.²

Nitrite is one of the most common methaemoglobin-forming agents, but the mechanism by which it increases the formation of methaemoglobin is unknown. Nitrate may be converted to nitrite in the gut and cause similar effects. Infants are particularly susceptible, either because their higher gastric pH facilitates bacterial conversion of nitrate to nitrite, or because of high physiological concentrations of fetal haemoglobin, or because of immaturity of the reductase enzymes.⁵ There has been concern recently about high inorganic nitrate concentrations (derived from agricultural fertilizers) in the drinking water in parts of Britain, although no cases of methaemoglobinaemia have been reported from this source.⁶

Oxidised iron causes the characteristic brown colour which does not turn red on shaking the blood with air. The detection of the brown colour of methaemoglobin in the blood as a screening test has been stressed in neonates⁷ but not in adults. In our first two cases, the clinical suspicion was low and the diagnosis was delayed. In the third case, delay in diagnosis could have been fatal. Methaemoglobinaemia should be considered in cyanosed patients in the absence of cardiopulmonary disease.

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