MINIREVIEW

FOOD-BORNE NITRATES AND NITRITES AS A CAUSE OF METHEMOGLOBINEMIA

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Abstract. Methemoglobinemia is a potentially fatal condition. Previous reports of toxic methemoglobinemia due to food-borne nitrates and nitrites are reviewed. Contamination of food during manufacture or degradation of nitrates in vegetables appear to be the most important factors. Some food items, such as refrigerated "dim-sum", stuffed pork and Chinese sausages, are very popular among some Asian populations; a stringent control against the excessive use of nitrates and nitrites is required in order to prevent outbreaks of toxic methemoglobinemia. Patients with glucose-6-phosphate dehydrogenase deficiency, a common condition in some Asian populations, may present with methemoglobinemia and intravascular hemolysis following exposure to oxidant drugs or chemicals. Methylene blue is inefficient and may exacerbate hemolysis in these patients; partial exchange transfusion may be required.

INTRODUCTION

Acquired methemoglobinemia may occur after ingestion of nitrates or nitrites in food (Orgeron *et al*, 1957) or water (Miller, 1971), or after using oxidant drugs such as sulphonamides, nitroglycerin and benzocaine (Mansouri and Lurie, 1993). Methemoglobin, in which the heme iron has been oxidized from the ferrous to ferric form, is incapable of carrying oxygen. Furthermore, it interferes with the ability of the remaining normal hemoglobin molecules to bind oxygen (Dinneen *et al*, 1994). Consequently, tissue hypoxia and even deaths may occur.

Sodium nitrite and nitrate solution are widely used to retard bacterial growth and to preserve the color of lean meat (MacDougall *et al*, 1975). Nitrates must first be converted to nitrites either prior to or after ingestion before they can cause methemoglobinemia (Committee on Nutrition, 1970). The newborn and young infant are at a greater risk for acquired methemoglobinemia following nitrate/nitrite ingestion than older children or adults (Committee on Nutrition, 1970; Kross *et al*, 1992). The relatively higher gut pH in infants results in an increased conversion of nitrate to nitrite. Fetal hemoglobin is more readily oxidized by nitrites to methemoglobin. Infants have half the $NADH^+$-dependent methemoglobin reductase activity of older children and adults and are less capable of metabolizing excess methemoglobin (Kross *et al*, 1992).

The article briefly summarizes previous reports of food-borne nitrates or nitrites as a cause of methemoglobinemia in the past 30 years. The particular relevance of this problem to some Asian populations is highlighted.

OUTBREAKS REPORTED FROM HONG KONG

In Hong Kong, food poisoning has been a notificable disease since 1974. Details on these outbreaks were published since 1992 by the Department of Health in the Public Health and Epidemiology Bulletin.

The first documented outbreak of toxic methemoglobinemia occurred in September 1981 (Wong, 1993). Seven children (5 males, 2 females) aged 1.5 to 6 years who had attended the Chinese banquets over five days in three restaurants became unwell 20 minutes to 2.5 hours (median 0.5 hour) after eating stuffed pork slices in an assorted meat dish. Clinical and laboratory features in these children included central cyanosis (n = 7), tachycardia (n = 2), tachypnea (n = 2), hypotension (n = 1), nausea/vomiting (n = 1), abdominal pain (n = 1),

irritability (n = 1), ST depression in ECG (n = 1), and reduced P_aO_2 in arterial blood (n = 3). At the time of admission to hospital, none had methemoglobin detectable in the blood. Intravenous methylene blue was given to four children with immediate relief of cyanosis. Intravenous ascorbic acid was given to another patient with similar relief. For the two remaining two milder cases, ascorbic acid was given orally. The source of the stuffed pork slices used by the three restaurants was traced to an unlicensed food factory. Analysis of five samples taken from the three restaurants and from the supplier showed the presence of excessive nitrate (mean 6,361, range 720-8,820 ppm) and nitrite (mean 977, range 200-1,760 ppm), although the permitted levels in Hong Kong were 200 and 500 ppm, respectively. More than the usual amount of nitrite had been added to the pork to prolong its shelf-life because of low current demand.

In 1991, our drug and poisons information service received one report of methomoglobinemia occurring in a child who had eaten some kind of refrigerated "dim-sum" (meat ball) bought from a supermarket (Chan *et al*, 1993). According to the enquirer, several similar cases had been treated in the same hospital before.

Between 1992 and 1993, one outbreak of food poisoning attributed to the nitrites in bacon was notified to the Department of Health (Tam and Tam, 1995). Further details were not available.

OUTBREAKS REPORTED FROM OTHER COUNTRIES

Due to contamination of food during manufacture

A 48-year old man in the United States had an acute episode of acquired methemoglobinemia mimicking cardiopulmonary catastrophe 30 minutes after he had eaten one pound of kiszka (blood sausage) (Bakshi *et al*, 1967). A residual portion of the same sausage ring from which he had eaten showed an acceptable nitrite concentration. The nitrite was being used as a curing and preservative. It was suspected that the ingested portions contained poorly distributed clusters sufficient to induce methemoglobinemia.

A 2-year old girl in Australia presented with intense cyanosis, vomiting and abdominal pain two hours after eating raspberry-flavored custard (Mackenzie, 1984). She completely recovered within 30 minutes of receiving intravenous methylene blue. Analysis of the custard powder revealed dangerously high levels of nitrites.

Three adult patients in Ireland developed methemoglobinemia after eating contaminated meat (Walley and Flanagan, 1987). A 41-year old woman and her 18-year old son presented with nausea, weakness and cyanosis two hours after eating pickled pork. 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. Four days later, an unrelated 36-year old man was admitted in coma and intense cyanosis one hour after eating pickled meat. He responded within minutes of intravenous methylene blue. The meat in both instances had been bought from the same shop on the same day. The butcher had treated the fresh meat with nitrite 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.

More than 40 children from one elementary school in the United States developed acute onset of blue lips and hands, vomiting, and headache during and after the school lunch periods (Askew *et al*, 1994). This outbreak of methemoglobinemia was due to soup contaminated by nitrites in a boiler additive.

Contamination of food during transportation

Methemoglobinemia has been reported from Holland after eating food that had been contaminated during transportation by a leaking cooling fluid (Ten Brink *et al*, 1982); the sodium nitrite was used as an anticorrosive agent.

Mistaken for sodium chloride

A group of 10 adults in South Africa suffered from moderate to severe methemoglobinemia after accidental poisoning with a sodium nitrite salt (Kaplan *et al*, 1990); pickling salt, mistaken for table salt, had been sprinkled over a meat and cabbage meal.

Degradation of nitrates in vegetables

Cases of sodium nitrite poisoning have been reported from vegetables grown with the excessive

use of nitrogen fertilizer with subsequent bacterial degradation of nitrate to nitrite during preparation or storage (L'Hirondel *et al*, 1971; Sernia *et al*, 1984; Simon, 1966). As suggested by an infant case of methemoglobinemia due to carrot juice (Keating *et al*, 1973), chemical reduction may occur in plants with high nitrate content after harvest without definite bacterial contamination.

AREAS PARTICULARLY RELEVANT TO ASIA

Two areas of particular relevance to some Asian populations should be addressed further. Some food items, such as refrigerated "dim-sum", stuffed pork and Chinese sausages, are popular in Hong Kong; a stringent control against the excessive use of nitrates and nitrites is required in order to prevent outbreaks of toxic methemoglobinemia (Wong, 1993). Glucose-6-phosphate dehydrogenase (G6PD) deficiency is common among some Asian populations (Yeung, 1973). Following exposure to oxidant drugs or chemicals, patients with G6PD deficiency may present with both methemoglobinemia and intravascular hemolysis (Finielz *et al*, 1992). There is also the problem associated with the effective treatment of patients with G6PD deficiency and methemoglobinemia. In such patients, methylene blue is inefficient and may on the contrary exacerbate hemolysis (Rosen *et al*, 1971). If the methemoglobin level is very high and the patient is deficient in G6PD, patients could be treated by partial exchange transfusion (Hibbard *et al*, 1973).

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