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Two cases of methemoglobinaemia caused by suspected sodium nitrite poisoning

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Summary

Among the causes of acute methemoglobinaemia are the ingestion and inhalation of over 40 oxidising substances, including nitrite, nitrate, carbon monoxide, some medicines, chlorine. The authors describe a case of acute methemoglobinaemia in two people that most probably suffered from food poisoning resulting from the consumption of a preparation of a dish called turkey *alla canzanese* that contained significant amounts of sodium nitrite. Both subjects who were treated promptly with methylene blue and hyperbaric oxygen therapy room recovered fully. Epidemiological investigations performed to clarify the dynamics of the episode suggested that among the causes of contamination were the swapping of products at the time of sale and the non-compliance to rules for the preparation of foods for human consumption.

Keywords

Acute methemoglobinaemia, Contamination, Food, Methylene blue, Poisoning, Sodium nitrite, Turkey *alla canzanese*.

Introduction

Acute methemoglobinaemia is a metabolic disorder that occurs when haemoglobin is oxidised to methemoglobin (metHb) which is unable to bind and transport oxygen (28). The condition can be extremely serious if not treated suitably (5, 27). Ingestion and inhalation of oxidising agents, such as nitrites and nitrates, are among the most frequent causes (3, 4, 6, 7, 9, 14, 17, 18, 20, 21, 22, 23, 24, 25). The condition generally occurs in individuals whose age (children) or enzyme deficiencies make them susceptible (18, 27) but cases are also observed in healthy adults through accident or intent. The World Health Organization (WHO) has indicated a toxic dose of 0.4-200 mg/kg body weight and a lethal dose of 33-250 mg/kg body weight for nitrites taken orally (27). Symptoms of poisoning include cyanosis which becomes pronounced when the methemoglobinaemia affects approximately 10% of red blood cells. When over 20% of the erythrocytes are affected, other symptoms appear, including headaches, dizziness, panting, tachycardia and general weakness. When 60% of cells are affected, serious disorders, such as loss of consciousness, can arise, while at over 70%, untreated poisoning rapidly becomes fatal (5, 8, 21, 27). Acute nitrite poisoning is treated with a therapeutic protocol using intravenously administered methylene blue 1% (1-2 mg/kg body weight) as the antidote (5).

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With respect to human consumption, nitrites are authorised solely for the preservation of meats (2) as no other chemical additives currently available are able to provide the same properties: antibacterial action, pinking of meat and aroma and flavour enhancement (12, 15, 16, 17, 19).

In 2002, the European Food Safety Authority (EFSA) indicated that 50-100 mg/kg of added nitrites (such as sodium nitrite) was sufficient to 'control' microbiological hazards. To reduce the risk of overdose, the EFSA recommended the exclusive use of nitrite-based additives containing 50% sodium chloride (12, 18). A much lower quantity (1-14 mg/kg) is required for pinking of meat (15, 16).

Contamination of food with toxic doses of nitrites may occur accidentally or intentionally. Intentional contamination involves a wilful action aimed at harming oneself or others (26). Accidental contamination may occur through negligence, inexperience or lack of caution, such as the use of nitrites in the preparation of salt substitutes or other ingredients that have a similar appearance (3, 6, 7, 14, 20). It may also occur through contamination of foods containing nitrites (detergents, cleaners, rust removers, cosmetics, etc.) (24). However, in such cases, the consumer would normally be alerted by the presence of an unusual smell or flavour and would not eat the food.

The authors describe a case of acute methemoglobinaemia in two subjects that were probably caused by food poisoning following the consumption of a meat-based dish called turkey *alla canzanese* that contained high levels of sodium nitrite.

This is a traditional dish prepared in the Canzano area, Teramo. A turkey is baked in the oven for about 5 h with water, salt to taste and flavourings (garlic, bay leaf and peppercorns). Fats are skimmed off and cooled cooking juices produce gelatine which is an essential part of the commercial preparation.

Case description

At about 1.00 pm on 22 September 2006, in the province of Teramo, a woman aged 40 (body weight about 70 kg) and her nine-year-old son (body weight about 50 kg) were taken seriously ill 10-15 min after lunch. The mother reported a cold sensation and presented cyanotic lips, chest constriction and tachycardia. The son presented cyanosis of the lips and hands, chest constriction and loss of consciousness. A third male (husband and father of the two victims), who had eaten only a small quantity of the dish, did not present any symptoms. The emergency service sent the two victims for immediate admission to the *Maria SS dello Splendore* hospital in Giulianova (Teramo Province). After phoning the Niguarda Poisons Centre in Milan and upon a reading of the results of the laboratory tests (Tables I and II), suspected poisoning with substances inducing methemoglobinaemia was diagnosed. The patients were therefore

Table I
Methemoglobin values and other significant parameters of blood samples taken from two patients with acute methemoglobinaemia

Test performed	Date and time					
	22 Sept 2006 (14:50)[a]		22 Sept 2006 (19:38)[b]		23 Sept 2006 (08:49)[b]	
	Mother	Son	Mother	Son	Mother	Son
methaemoglobin (0.0-1.5%)	32.70	63.00[c]	1.60	20.03	2.20	2.30
pH (7.35-7.45)	7.50	7.48	7.39	7.37	7.42	–
pCO_2 (35-45 mm Hg)	28.00	30.40	33.00	36.00	36.00	–
pO_2 (75-100 mm Hg)	77.40	568.80	88.00	357.00	89.00	–
O_2 saturation (92.0-98.5%)	98.10	99.50	98.00	100.00	97.00	–

(a) test performed at Maria SS dello Splendore Hospital in Giulianova
(b) test performed at Umberto I General Hospital in Rome
(c) MetHb =72.3 at 15:16

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Table II
Complete blood counts and other significant parameters of blood samples from two patients with acute methemoglobinaemia

Test performed	Date and time					
	22 Sept 2006 (14:50)[a]		22 Sept 2006 (19:38)[b]		23 Sept 2006 (08:49)[b]	
	Mother	Son	Mother	Son	Mother	Son
White blood cells (×10³ ml)	11.26	14.86	9.38	10.90	12.00	12.20
Red blood cells (×10⁶ ml)	4.87	4.96	4.30	4.27	3.96	4.98
Haematocrit (%)	43.90	38.10	36.50	31.60	33.30	38.40
Haemoglobin (g/100 ml)	14.50	12.30	12.80	11.20	11.50	13.50
Platelets (×10³/ml)	342.00	423.00	188.00	190.00	159.00	277.00
Prothrombin time (70-120%)	107.00	93.10	118.00	117.00	112.00	0.00
Glucose (76-110 mg/100 ml)	128.00	168.00	122.00	119.00	135.00	277.00
Urea (10-15 mg/100 ml)	29.00	3.00	14.00	13.00	11.00	16.00
Creatinine (0.50-1.30 mg/100 ml)	1.00	0.93	1.00	0.80	0.90	0.90
Total bilirubin (0.20-1.00 mg/100 ml)	0.72	0.55	0.00	0.00	0.00	0.93
AST (0-50 IU/l)	50.00	29.00	43.00	32.00	32.00	59.00
ALT (0-50 IU/l)	58.00	20.00	74.00	40.00	53.00	52.00

AST aspartate aminotransferase
IU international unit
ALT alanine aminotransferase

(a) test performed at Maria SS dello Splendore Hospital in Giulianova
(b) test performed at Umberto I General Hospital in Rome

administered methylene blue 1 mg/kg of body weight in a saline solution. The mother also received a gastric lavage and the son a blood transfusion, sedation and intubation. Both patients were transferred to Umberto I General Hospital in Rome on the same day; there they underwent hyperbaric oxygen therapy. The treatment contributed to the mother's rapid improvement, but was less effective in the son, whose metHb levels were still elevated (20.03%) after the treatment (Table I). The mother was considered to be out of danger the next day (2.2% metHb) and was discharged. Although the son's metHb value (2.3%) was no longer a cause for concern, he remained in hospital until 26 September 2006 for an unrelated condition.

Investigations

Following this episode of acute methemoglobinaemia , the authorities took a series of samples from the victims' home to reveal possible sources of the toxin. Foods, drinks, utensils in contact with the food, herbal products and waste bin contents were sampled.

Given the hypothesis of food poisoning, the authorities also sampled food products from the delicatessen which had made and sold much of the food consumed by the two victims (turkey *alla canzanese*).

All samples were sent to the *Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise 'G. Caporale'* (IZS A&M) for tests to detect any methemoglobinaemia-inducing agents. Considering the symptoms of the patients and the time of onset (18), is was decided to commence testing on the foods consumed by the victims during the meal that preceded the onset of symptoms.

Given the foods and drinks consumed, priority was given to chlorates, nitrites and nitrates among the various substances which induce methemoglobinaemia (28).

The tests revealed the presence of a significant quantity of nitrites only in the turkey *alla canzanese* from the victims' home (6 000-10 000 mg/kg in the meat and approximately 10 000 mg/kg in the gelatine).

After identifying the food and compound that was probably responsible for the poisoning, some other consumers who had bought the same product from the same retailer were traced; none of them had shown any symptoms of acute methemoglobinaemia.

Leftovers of the turkey product were also taken from the home of one of the other purchasers and were found to contain about 3 000 mg/kg of nitrites, supporting the theory that this product was the most likely source of the poison.

To trace the source of the nitrites, the investigation involved the following:

- the delicatessen (where the dish was prepared)
- the slaughterhouse where the turkey had been slaughtered and stored
- the manufacturer of the flavourings, gelatine preparation and additives.

While the delicatessen kitchens were found to be in clear breach of hygiene regulations (10) (e.g. sanitary fitting drainpipes on the kitchen ceiling with obvious water leakage, presence of motor vehicles in working areas, etc.), there were no signs of the presence or purchase (invoices) of products containing methemoglobinaemia-inducing substances.

Samples from animals butchered at the same time as the nitrite-positive turkey, taken as required by law (11) from the slaughterhouse, tested negative for nitrites. Here too, there were no signs of the presence or purchase (invoices) of products containing methemoglobinaemia-inducing substances.

At the supplier of the other ingredients (gelatine preparation, flavourings etc.), two products (gelatine preparation and the additive Salnit N, containing 50% sodium chloride and 50% sodium nitrite) were found to have identical packaging. There was also non-conformity with Salnit N's labelling (1, 2). Furthermore, it was revealed that the manufacturer sold a 'semi-processed sodium chloride/potassium nitrate powder' under the same name, 'Salnit N', not 'sodium chloride and sodium nitrite' as found at the inspected retailer shop.

During the investigation, turkey *alla canzanese* was prepared experimentally using the delicatessen's traditional recipe but substituting the salt (sodium chloride) with Salnit N. This substitution was necessary to check the distribution of the nitrite between the meat and gelatine and if the ingredients had indeed been swapped. This event has been described in the literature (4, 6, 14, 20).

Tests on the experimental samples revealed different nitrite concentrations in the various parts of the turkey (from 510 mg/kg to 3 329 mg/kg), and higher values in the gelatine (8 926 mg/kg) (Table III).

Table III
Concentration of nitrite used to replace sodium chloride in experimentally prepared turkey and gelatine dishes

Material examined	Nitrite concentration (mg/kg as $NaNO_2$)		
	Turkey 1	Turkey 2	Turkey 3
Tail	1 079	2 151	3 102
Thigh	893	1 383	1 852
Breast	1 033	510	1 006
Wings	1 435	690	568
Neck	2 039	3 329	2 695
Gelatine*		8 926	

* obtained from the cooking juices of the three dishes

Discussion

This serious episode of methemoglobinaemia in two subjects was probably traceable to food poisoning by nitrites. Diagnosis cannot be certain due to the absence of analytical findings of the toxin in the two patients. However, the pathogenetic hypothesis of nitrite poisoning is supported by the correlation of: consumption of turkey *alla*

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canzanese contaminated with toxic quantities of nitrites; immediate onset of methemoglobinaemia in the two victims; rapid resolution of the condition with the administration of methylene blue.

The quantity of contaminated food ingested (about 100 g a head, containing 600-1 000 mg of nitrites) may have caused the toxic dose threshold (≥280 mg a head) to have been exceeded in the two subjects, causing moderately severe effects in the adult and very severe effects in the child (18, 27).

The lack of reports of other episodes following consumption of the same turkey would appear to be due to the extremely variable concentration of nitrites found (approximately 3 000-10 000 mg/kg), as also demonstrated in the experimental dish (approximately 500-9 000 mg/kg). Therefore, it cannot be excluded that the same food preparation may have resulted in the ingestion of doses causing only mild general symptoms that passed unnoticed in the other consumers, or doses that were below the toxicity threshold (18).

With respect to the dynamics resulting in the contamination of the turkey *alla canzanese*, it can be asserted that the compound was not present in the live animal in doses that were toxic for humans.

The addition of the product after cooking is also highly unlikely, as the nitrite would be unable to spread through the muscle mass due to protein coagulation in the cooked turkey (13, 15, 17, 18).

Voluntary or involuntary contamination may therefore have occurred in three different places: at the slaughterhouse, during transport of the meat or at the delicatessen.

The investigation reasonably excluded contamination at the slaughterhouse and during transport for at least two reasons, namely: lack of evidence of the presence of nitrite-based products and the presence of high nitrite concentrations in the gelatine. This latter aspect revealed that contamination could only have taken place at the delicatessen during preparation of the dish, as previously contaminated turkey would not have been able to produce gelatine with such a high nitrite concentration.

However, no substances containing nitrites were found at the delicatessen either.

The investigation thus suggested the exchange of ingredients during purchase (identical packaging of two different products and the name 'Salnit N' used for two products with different ingredients), or the fraudulent or inexperienced use of nitrite-based additives.

Conclusion

The episode of acute methemoglobinaemia appears to be strongly related to nitrite intoxication through consumption of contaminated turkey *alla canzanese*. While the possibility of wilful contamination aimed at harming others or fraudulent use cannot be excluded, the investigation also suggested the possibility of products being exchanged during purchase and the non-observance of the rules of diligence, prudence and experience in preparing food products for human consumption.

The episode highlights the rigorous procedures that must be observed in every phase of food preparation and management of raw materials and ingredients, as substances such as nitrites which are permitted by law can still constitute a severe health hazard to consumers when used improperly.

References

1. Anon. 1962. Law No. 283 of 30 April 1962: Disciplina igienica della produzione e della vendita delle sostanze alimentari e delle bevande. *Gazz Uff*, **139**, 4 June.
2. Anon. 1996. Ministry Law No. 209 of 27 February 1996: Regolamento concernente la disciplina degli additivi alimentari permessi nella preparazione per la conservazione delle sostanze alimentari in attuazione delle direttive n. 94/34/CE, n. 94/35/CE, n. 94/36/CE, n. 95/2/CE e n. 95/31/CE. Suppl. Ord. n. 69. *Gazz Uff*, **96**, 24 April.

3. Askew G.L. Finelli L., Genese C.A., Sorhage F.E., Sosin D.M. & Spitalny K.C. 1994. Boilerbaisse: an outbreak of methemoglobinemia in New Jersey in 1992. *Pediatrics*, **94** (3), 381-384.
4. Bacon R. 1997. Nitrate preserved sausage meat causes an unusual food poisoning incident. *Commun Dis Rep Rev*, **7** (3), R45-47.
5. Beers M.H. & Berkow R. 2005. Merck manual. Poisoning: general principles. Table 3 (www.merck.com/mmpe/sec21/ch326/ch326b.html# accessed on 8 January 2008).
6. Centers for Disease Control and Prevention (CDC) 2002. Methemoglobinemia following unintentional ingestion of sodium nitrite – New York, 2002. *MMWR*, **51** (29), 639-642.
7. Chan T.Y. 1996. Food-borne nitrates and nitrites as a cause of methemoglobinemia. *Southeast Asian J Trop Med Public Health*, **27** (1), 189-192.
8. Deeb B.S. & Sloan K.W. 1975. Nitrates, nitrites and health. Agricultural Experiment Station, Urbana-Champaign, Illinois, 1-52.
9. Ellis M., Hiss Y. & Shenkman L. 1992. Fatal methemoglobinemia caused by inadvertent contamination of a laxative solution with sodium nitrite. *Isr J Med Sci*, **28** (5), 289-291.
10. European Commission (EC) 2004. Regulation (EC) No. 853/2004 of the European Parliament and the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin. *Off J*, **L 139**, 29.04.2004, 55-205.
11. European Commission (EC) 2004. Regulation No. 854/2004 of the European Parliament and the Council of 29 April 2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption . *Off J*, **L 139**, 29.04.2004, 206-320.
12. European Food Safety Authority (EFSA) 2003. Opinion of the Scientific Panel on biological hazards (BIOHAZ) to the effects of nitrites/nitrates on the microbiological safety of meat products. *EFSA J*, **14**, 1-34 (www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620777851.htm accessed on 29 April 2008).
13. Fantazzini P., Bortolotti V., Garavaglia C., Gombia M., Riccardi S., Schembri P., Virgili R. & Soresi Bordini C. 2005. Magnetic resonance imaging and relaxation analysis to predict noninvasively and nondestructively salt-to-moisture ratios in dry-cured meat. *Magn Reson Imaging*, **23**, 359-361.
14. Gautami S., Rao R.N., Raghuram T.C., Rajagopalan S. & Bhat R.V. 1995. Accidental acute fatal sodium nitrite poisoning. *J Toxicol Clin Toxicol*, **33**, 131-133.
15. Heaton K.M., Cornforth D.P., Moiseev I.V., Egbert W.R. & Carpenter C.E. 2000. Minimum sodium nitrite levels for pinking of various cooked meats as related to use of direct or indirect-dried soy isolates in poultry rolls. *Meat Sci*, **55** (3), 321-329.
16. Holownia K., Chinnan, M.S. & Reynolds A.E. 2004. Cooked chicken breast meat conditions related to simulated pink defect. *J Food Sci*, **69**, 3.
17. Iammarino M., Muscarella M., Di Taranto A. & Palermo C. 2005. Indagine sulla presenza di nitrati e nitriti nelle carni fresche. Società Italiana delle Scienze Veterinarie, LIX Convegno Nazionale Sezione 4: Ispezione degli alimenti di origine animale, 21-24 September, Viareggio. SISVET, Brescia, 393-394.
18. International Programme on Chemical Safety (INCHEM) 1996. Nitrates and nitrites, International Programme on Chemical Safety Poisons Information Monograph (Group Monograph) G016 Chemical (www.inchem.org/documents/pims/chemical/pimg016.htm ultimo accesso 29 Ottobre 2007).
19. Jay B. & Fox J.R. 1980. Diffusion of chloride, nitrite, and nitrate in beef and pork. *J Food Sci*, **45** (6), 1740-1744.
20. Kaplan A., Smith C., Promnitz D.A., Joffe B.I. & Seftel H.C. 1990. Methemoglobinaemia due to accidental sodium nitrite poisoning. Report of 10 cases. *South Af Med J*, **77**(6), 300-301.
21. Kortboyer J.M., Boink A.B.T.J., Zeilmaker M.J., Slob W. & Meulenbelt J. 1997. Methemoglobin formation due to nitrite: dose-effect relationship *in vitro*. Report No. 23580-2006, National Institute of Public Health and Environment (RIVM), Bilthoven, 41 pp.
22. Liebenow H. 1972. Nitrates and nitrites in relation to man and animals. 8. Losses of animals from nitrate and nitrite and the detection of nitrate and nitrite in animal material. *Archiv Tierernahrung*, **22** (4), 281-293.
23. Perez O.A. & Mancebo V.V. 1994. Methaemoglobin in sheep due to poisoning by nitrites and nitrates. *Vet Arg*, **11** (101), 13-16.
24. Saito T., Takeichi S., Yukawa N. & Osawa M. 1996. Fatal methemoglobinemia caused by liniment solutions containing sodium nitrite. *J Forensic Sci*, **41** (1), 169-171.

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25. Sandberg A.S., 1976. Nitrate and nitrite; supply and metabolism in man. *Naringsforskning*, **20** (4), 233-249.
26. Shadnia S., Rahimi M., Moeinsadat M., Vesal G., Donyavi M. & Abdollahi M. 2006. Acute methemoglobinemia following attempted suicide by Dapson. *Arch Med Res*, **37**, 410-414.
27. World Health Organization (WHO) 2006. WHO Food Additives Series: 50. Nitrite (and potential endogenous formation of *N*-nitroso compounds). WHO, Geneva (first draft prepared by G.J.A. Speijers) (www.inchem.org/documents/jecfa/jecmono/v50je05.htm accessed on 8 January 2008).
28. Wright R.O., Lewander W.J. & Woolf A.D. 1999. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med*, **34**, 646-656.