Korean Journal of Pediatrics Vol. 52, No. 3, 2009
DOI : 10.3345/kjp.2009.52.3.385
Case report

Methemoglobinemia development after ingestion of a chinese herbal medicine: A case report

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= Abstract =

An 8-year-old girl visited the emergency room with perioral cyanosis and dyspnea, which had developed 20 hrs prior to the hospital visit. She had taken a Chinese herbal medication for 3 days prior to the onset of the symptoms. A co-oximeter examination revealed a methemoglobin level of 23.7%. An intravenous infusion of methylene blue was administered. Chemical analysis of the herbal medication revealed an ammonia (NH_3) level of 239.41 mg/L. More studies are needed on the correlation between methemoglobinemia and the components of Chinese herbal medicines. (Korean J Pediatr 2009;52:385-388)

Key Words : Methemoglobinemia, Nitrate, Ammonia, Chinese herbal medicines, Children

Introduction

Methemoglobinemia is a condition characterized by the increased oxidation of heme iron to the ferric (Fe3+) form. Methemoglobin normally composes less than 1 percent of hemoglobin in circulating red blood cells[1] and it is useless as an oxygen carrier. Thus increased methemoglobin levels cause a varying degree of cyanosis[2]. In patients who have cyanosis and dyspnea that are unrelated to a cardiopulmonary condition, one possible but rare diagnosis is methemoglobinemia[3].

We present the case of a girl who developed cyanosis after ingestion of a Chinese herbal medication, whose condition was finally diagnosed as methemoglobinemia.

Case report

An 8 year-old girl visited the emergency room with perioral cyanosis and dyspnea which had developed 20 hours before the hospital visit. These symptoms had never appeared in the past. She was born via vaginal delivery at 40 weeks of gestation weighing 2,800 g. She had mild atopic dermatitis, but was not receiving any specific medication for it. Her family history was negative for any disease. She had taken the Chinese herbal medication for 3 days before the onset of symptoms for the purpose of health promotion (Fig. 1).

On arrival, blood pressure, pulse rate, respiratory rate and body temperature were 120/80 mmHg, 102 bpm, 24 bpm, and 36.6℃, respectively. Oxygen (O_2) saturation, measured by plulse oximetry, was 85-90%. The patient was slightly cyanotic, but with a good respiratory effort, a clear airway, and alert mental status. Breathing sounds were clear in the bilateral lung fields, and there were no audible cardiac murmurs.

On the laboratory examination, a complete blood count showed a hemoglobin concentration of 14.6 g/dL, hematocrit of 41.8%, and a white blood cell count of 9,370/mm^3 with a normal differential count and a platelet count of 414,000/mm^3. The electrolytes and blood chemistry including aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine were within the normal range. Arterial blood was drawn for gas analysis, and the results were as followings; pH 7.465, pCO_2 25.3 mmHg, pO_2 115 mmHg, HCO_3 17.8 mmol/L, base excess -4.2 mmol/L, and O_2 saturation 98.5% under inhalation of oxygen 5 L/min via nasal prolong. In spite of normal blood gas levels, she complained persistent dyspnea, and the pulse oximetry value

Received : 18 August 2008, Revised : 25 September 2008,
Accepted : 26 October 2008
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Fig. 1. The Chinese herbal medicine preserved in a vacuum state. (A) anterior portion (B) posterior portion.

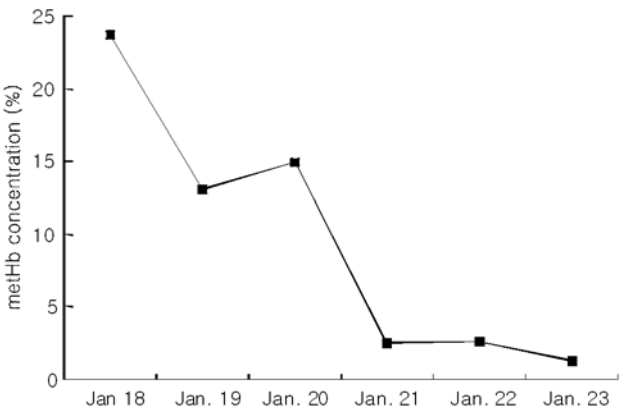

Fig. 2. Decrease in methemoglobin concentration over time. Vertical axis represents methemoglobin concentration. Horizontal axis represents hospital days. Abbreviations : MetHb, methemoglobin; Jan., January.

was around 85%. Finally, the co-oximeter exam revealed the methemoglobin level of 23.7% (normal range 0-1.5).

A chest X-ray showed no active lung lesion, and an electrocardiogram showed no abnormal finding except for sinus tachycardia. Her echocardiogram was also normal.

Table 1. Analysis Results for the Chinese Herbal Medicine Ingested by the Patient

Chemical component (normal range)	Cl^- (0-250)	NO_3^- (0-10)	SO_4^{2-} (0-200)	NH_3 (0-0.5)
Concentration (mg/L)	26.00	6.55	105.00	239.41

Intravenous infusion of methylen blue (1% solution, 2 mg/kg) was administered, and her cyanosis and dyspnea were improved. The methemoglobin level had decreased to 13.1% on the following day, and we repeated the treatment. The methemoglobin level decreased to 2.5% and 1.3% on the 3rd and 4th hospital days, respectively (Fig. 2). There were no further symptoms of cyanosis or dyspnea, and she was discharged on the 6th hospital day.

We requested a chemical analysis of the herbal medicine from the National Instrumentation Center for Environmental Management at Seoul National University. The ion chromatography and the Kjeldahl method revealed ammonia (NH_3) level of 239.41 mg/L (normal range 0-0.5) (Table 1).

Discussion

The most common cause of acquired methemoglobinemia is ingestion of, or exposure of skin or mucous membranes to, oxidizing agents. Some of this oxidized hemoglobin directly forms methemoglobin; in other cases, it forms indirectly by reducing oxygen to the free radical O_2, which in turn oxidizes hemoglobin to methemoglobin[2]. There are some reports of methemoglobinemia being induced through the ingestion of dapsone, one such oxidizing agents[4, 5]. A study done in Russia revealed the hazards of drinking water with high concentration of nitrate (NO_3). The Russian researchers noted an association between increased methemoglobin levels of up to 7% in school children, and NO_3 concentrations in drinking water[6]. An outbreak of methemoglobinemia occurred due to nitrite (NO_2), an oxidizing agent, in contaminated water[7]. In addition, There are reports concerning about the hazards of NO_3-contaminated water for young infants[8]. An infant fed powdered formula mixed with NO_3-contaminated ground water developed methemoglobinemia in Korea[9], and an epidemiologic study identified the cause of infantile methemoglobinemia as NO_3[10]. In addition, diarrhea, acidosis, infection and dehydration may predispose neonates and young infants to methemoglobinemia[11-14]. No definite consensus has been established yet concerning how these conditions lead to

methemoglobinemia. It has been suggested that young infants are particularly susceptible to this condition because of their low gastric acid production, large number of nitrite-reducing bacteria, and the susceptibility of fetal hemoglobin to oxidative stress[2], and the lower level of cytochrome b reductase in infants erythrocyte[15].

A case report from Hong-Kong noted that patients developed methemoglobinemia after drinking a Chinese herbal medicine, which was revealed to contain a large amount of sodium nitrite[16]. Chan et al[17] reported a case of a 9-day-old newborn who ingested home-made herbal medication and developed cyanosis with methemoglobinemia. The causative agent identified in the herbal medicine was sulfamethazine. Our patient appears to be the third known case worldwide of methemoglobinemia developed after the ingestion of Chinese herbal medications.

Few surveys have been performed about these medications so far, and we have little information about which component of herbal medicine causes methemoglobinemia. There are few studies about the correlation between methemoglobinemia and NH_3 concentration. In our case, only the NH_3 level was highly increased. The concentrations of other components including nitrate were in the normal range. It is well-known that nitrate is reduced to ammonia via nitrite in anoxic condition[18-20]. In contrast, ammonia is oxidized to nitrate when nitrite acts as an electron donor in an oxidative environment. The herbal medication we referred to had been closed in an absolute vacuum for 2 months prior to analysis (Fig. 1). Therefore we can suggest the possibility that the conversion of NO_3 to NH_3 had occurred in this anaerobic environment, including methemoglobin formation.

For drug-induced methemoglobinemia, the traditional first-line therapy is an infusion of methylene blue[21]. Treatment should be considered when the methemoglobin level is 30% or more in an asymptomatic patient, and 20% or more in a symptomatic patient[2]. In our patient, by pulse oximetry, O_2 saturation increased from 85% to 98% at 60 min after methylen blue infusion. Administration of a second dose may be required in severe cases, when there is evidence of continuous chemical absorption or prolonged methemoglobin formation[21].

In conclusion, nitrate-induced methemoglobinemia is a rare condition, but potentially fatal if unrecognized. Chinese herbal medications, which may contain significant amount of nitrate, may be harmful. As many people in Korea traditionally tend to take these medications, physicians should consider these medicines as a possible cause of methemoglobinemia. More studies are needed on the correlation between methemoglobinemia and elevated NH_3 levels.

한 글 요 약

한약 복용 후 발생한 메트헤모글로빈혈증 1예

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8세 여아가 증상 발현 3일전부터 한약을 복용 후, 내원 20시간 전에 발생한 청색증과 호흡곤란을 주소로 응급실에 내원하였다. 내원 당시 메트헤모글로빈 수치가 23.7%로, 메트헤모글로빈혈증 진단 하에 methylene blue로 치료하였다. 한약 성분은 암모니아가 239.41 mg/L로 높게 측정되었다. 이에 한약 복용 후 발생한 메트헤모글로빈혈증 1예를 보고하고자 한다.

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