Acquired methemoglobinemia in infants

Süt çocuklarında edinsel methemoglobinemi

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Abstract

Objective: This study aimed to determine the etiologic factors of acquired methemoglobinemia in infants younger than three months in our region.

Material and Methods: This study was carried out retrospectively in infants with methemoglobinemia admitted to Karadeniz Technical University, Pediatric Clinic, during the period 2000-2009. Infants with methemoglobinemia were identified according to the medical records or ICD-10 code.

Results: Nine infants with acquired methemoglobinemia (8 male, 1 female) were included in the study. Seven cases were associated with the use of prilocaine for circumcision, one case with the use of prilocaine-lidocaine for local pain therapy, and one case with neonatal sepsis caused by *Staphylococcus aureus*.

Conclusion: Prilocaine should not be used in infants less than three months of age because of the risk of methemoglobinemia. Ascorbic acid is an effective therapy if methylene blue is not obtained. It should not be forgotten that sepsis caused by *S. aureus* may cause methemoglobinemia in infants. *(Turk J Hematol 2011; 28: 131-4)*

Key words: Methemoglobinemia, infant, local anesthetics, sepsis

Özet

Amaç: Bölgemizde üç aydan küçük bebeklerde meydana gelen akkiz methemoglobinemilerin etiyolojisini araştırmak.

Yöntem ve Gereçler: Bu çalışma, 2000-2009 yılları arasında pediatri kliniğine başvuran ve ICD-10 koduna veya hasta kayıt defterine göre akkiz methemoglobinemi tanısı alan hastaların kayıtlarının retrospektif incelenmesi ile gerçekleştirildi.

Bulgular: Sekizi erkek olmak üzere, dokuz akkiz methemoglobinemili infant çalışmaya alındı. Yedi vaka; sünnet için prilokain kullanımı ile ilişkili iken, bir vaka; lokal anestezi için kullanılan prilokain–lidokain ile ve diğer vaka ise; *Staphylococcus aureus* sepsisi ile ilişkili idi.

Sonuç: Üç aydan küçük infantlarda prilokain methemoglobinemi riski nedeniyle kullanılmamalıdır ve metilen mavisi elde edilemediği durumlarda vitamin C effektif bir tedavi şeklidir. *Staphylococcus aureus*'a bağlı sepsisin infantlarda methemoglobinemiye neden olabileceği unutulmamalıdır. *(Turk J Hematol 2011; 28: 131-4)*

Anahtar kelimeler: Methemoglobinemi, infant, lokal anestezikler, sepsis

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Introduction

Methemoglobinemia is an uncommon cause of cyanosis. It should be suspected in an infant with cyanosis who has no respiratory distress or cyanotic congenital heart disease. Cyanosis is recognized in patients with methemoglobin (MetHb) concentrations higher than 1.5 g/dl [1,2]. It develops due to both acquired and congenital factors. Congenital causes of methemoglobinemia are NADH-cytochrome b5 reductase and NADPH-MetHb reductase deficiencies or presence of abnormal Hb such as Hb M [2]. Acquired methemoglobinemia is caused by some drugs such as local anesthetics, some foods or water containing high levels of nitrate, gastrointestinal infection, and sepsis [2-4]. Most of the acquired methemoglobinemia cases in clinical practice are due to local anesthetics. In this report, nine infants with methemoglobinemia are presented and the etiologic factors are discussed.

Materials and Methods

This study was carried out retrospectively in infants with methemoglobinemia admitted to Karadeniz Technical University, Pediatric Clinic, during the period 2000-2009. Infants with methemoglobinemia were identified according to the medical records or ICD-10 code. Medical charts of all infants with methemoglobinemia were reviewed for birth weight (g), gender, postnatal age, Hb levels, presenting symptoms, etiologic causes, type of feeding, MetHb levels, treatment, recovery time of methemoglobinemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Blood MetHb levels were measured by using a Rapidlab® 1200 Blood Gas Analyzer (Siemens Healthcare Diagnostics) with spectrophotometric method. Blood MetHb levels were measured at four-hour intervals. Sepsis was considered in infants having two or more of the following criteria associated with positive blood culture: (a) fever or hypothermia, (b) tachycardia, (c) tachypnea or apnea, and (d) abnormal white blood cells or increase in band/total neutrophils. Written informed consent was obtained from the patients' family.

Results

Nine infants with methemoglobinemia (8 male, 1 female) were included in the study. Mean birth weight and postnatal age were 3655±270 (3300-4100) g and 33.7±16.6 d (5-60) days, respectively. Cyanosis was present in all infants, fever in three (33%), and hypotonia and refusal to breast-feed in two (22%). Mean percentage of MetHb levels of the infants was 28.8±9.8 (14.7-44%). Seven cases were associated with the use of a local anesthetic agent (prilocaine; Citanest® 0.5%) for circumcision. The applied prilocaine doses were not determined. One case was associated with the use of prilocaine–lidocaine (EMLA®, 5%, Astra Zeneca) for local pain therapy after scalding to 3% of the body surface, and three cases were associated with neonatal sepsis. No phenol disinfectant was used for floor cleaning in the hospital during this period.

Staphylococcus hominis was grown in blood cultures of two infants (Case 3 and Case 5) associated with the use of prilocaine. *Staphylococcus aureus* was grown in the blood culture of Case 6. Acute phase reactants (procalcitonin and C-reactive protein [CRP]) were positive in these neonates, and they met sepsis criteria. They were treated with vancomycin. All of the neonates were receiving only breast milk. Their mothers denied the use of any medications and consumption of any foods containing a high nitrate level.

Two neonates were treated with methylene blue (1-2 mg/kg) intravenously, and the others were treated with vitamin C (300 mg) intravenously because methylene blue was not obtained. Repeated doses were not necessary. Mean recovery time was 10.2±3.5 [4-16] hours. The plasma G6PD levels were normal in all neonates. Cytochrome b5 reductase activity could not be measured in the neonates because of the lack of technical facilities. Demographic, clinic and laboratory characteristics of the neonates associated with methemoglobinemia are shown in Table 1.

Discussion

Methemoglobinemia is characterized by oxidation of the iron in Hb from a ferrous (Fe++) to a ferric (Fe+++) form. Methemoglobinemia occurs in healthy persons but the intraerythrocytic MetHb-reducing system maintains its concentration at less than 1% of the total Hb [5]. There are two MetHb-reducing systems (NADH-cytochrome b5 reductase and NADPH-MetHb reductase) in erythrocytes. Under physiological conditions, NADH-cytochrome

Table 1. Demographic, clinic and laboratory characteristics of the patients with methemoglobinemia

	Birth Weight (g)	Postnatal age (day)	Gender	Complaints	Hb (gr/dL)	MetHb (%)	Etiologic causes	Treatment	Recovery time (h) (MetHb <5%)	G6PD level
Case 1	4000	45	Male	Cyanosis	10.9	24.1	Prilocaine	300 mg C vit	8	Normal
Case 2	3700	60	Male	Cyanosis	11.2	39.9	Prilocaine	300 mg C vit	12	Normal
Case 3	4100	5	Male	Cyanosis, hypotonia, fever, refusal to breast-feed	14.7	14.7	Prilocaine Sepsis caused by *S. hominis??*	300 mg C vit +Antibiotics	4 1	Normal
Case 4	3300	22	Male	Cyanosis	8.8	33.7	Prilocaine	300 mg C vit	12	Normal
Case 5	3600	35	Male	Cyanosis, fever, refusal to breast-feed	13.5	19.0	Prilocaine-lidocaine Sepsis caused by *S. hominis??*	300 mg C vit +Antibiotics	8	Normal
Case 6	3300	17	Female	Fever, hypotonia, cyanosis	13.5	20.9	Sepsis caused by *S. aureus*	300 mg C vit +Antibiotics	8	Normal
Case 7	3600	45	Male	Cyanosis	10.5	44	Prilocaine	Methylene blue (1 mg/kg)	16	Normal
Case 8	3700	37	Male	Cyanosis	11.5	30.4	Prilocaine	300 mg C vit	12	Normal
Case 9	3600	48	Male	Cyanosis	11.8	26.8	Prilocaine	Methylene blue (1 mg/kg)	12	Normal

G6PD: Glucose-6-phosphate dehydrogenase, Hb: Hemoglobin, MetHb: Methemoglobin

b5 reductase is responsible for the removal of 95-99% of the MetHb [5]. NADPH-MetHb reductase usually plays only a minor role in the removal of MetHb. This enzyme system utilizes NADPH, which is produced by G6PD. NADPH-MetHb reductase has a more important role in MetHb regulation in infants with cytochrome b5 reductase deficiency. MetHb has an increased affinity for oxygen, and causes a leftward shift in the oxygen dissociation curve, and hypoxemia and lactic acidosis develop [1,2,6]. If MetHb level is higher than 10%, cyanosis occurs, and a MetHb level of 70% is lethal. Cyanosis was observed in all of our infants and all of them improved after the appropriate treatments.

Prilocaine is widely used in children and adults as a local anesthetic agent, and its metabolite o-toluidine can cause methemoglobinemia. The dose of prilocaine and the age of the infant are the most important predictive factors for higher MetHb formation [7]. Infants are more vulnerable to met-hemoglobinemia because they have higher gastric pH than that in older children, and this causes greater bacterial proliferation of the intestinal flora that can convert the ingested nitrate to nitrite [6]. Fetal Hb is the predominant form of Hb in infants, and is oxidized more readily to MetHb by nitrite [6]. The cytochrome b5 MetHb reductase activity is reduced 50% in infants compared with older children and adults [6,8]. Guay [9] suggested that prilocaine should not be used in children younger than six months and the doses should not exceed 2.5 mg/kg in children older than six months. In this study, MetHb in seven neonates was associated with the use of prilocaine for circumcision, and all of them were younger than two months.

Symptomatic methemoglobinemia may develop due to the application of EMLA® on the injured skin [10]. Methemoglobinemia was observed in Case 5 due to the application of EMLA® for local pain therapy.

Blood MetHb levels may be increased in patients with sepsis [3,4]. Large amounts of nitric oxide (NO) are released in sepsis and septic shock [11,12]. NO interacts with Hb, and leads to methe-moglobinemia [13]. *S. aureus* has a respiratory type of nitrate reductase enzyme system. This enzyme system may convert nitrate to nitrite, and methemo-globinemia may develop [14]. Vancomycin-related methemoglobinemia has not been reported in the literature. We believe that methemoglobinemia was related with sepsis rather than vancomycin [15];

nevertheless, methemoglobinemia related with vancomycin could not be completely ruled out. As far as we know, *S. hominis* does not have this enzyme system. Therefore, we believe that prilocaine was responsible for the methemoglobinemia in the neonates (Case 3-Case 5).

Methylene blue accelerates the NADPH-dependent MetHb reduction pathway [16]. Methylene blue was given (1-2 mg/kg) in only two infants because it was not obtained for the others. Ascorbic acid directly reduces MetHb and it is effective when used alone [17]. Intravenous 300 mg ascorbic acid was used in seven cases, and all cases recovered between 8-16 hours.

Prilocaine should not be used in infants less than three months of age because of the risk of methemoglobinemia. Ascorbic acid is an effective therapy if methylene blue is not obtained. It should not be forgotten that *S. aureus* may cause methemoglobinemia in infants.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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