



# Severe Methemoglobinemia Due to Nitrite Intoxication in a Child Who was Misdiagnosed with Sepsis

## Yanlışlıkla Sepsis Olarak Değerlendirilen Bir Çocukta Nitrit İntoksikasyonuna Bağlı Ciddi Methemoglobinemi

Aykut Çağlar<sup>1</sup>, Anıl Er<sup>1</sup>, Utku Karaarslan<sup>2</sup>, Emel Ulusoy<sup>1</sup>, Fatma Akgül<sup>1</sup>, Gözde İnci<sup>1</sup>, Tolga Fikri Köroğlu<sup>2</sup>, Murat Duman<sup>1</sup>, Durgül Yılmaz<sup>1</sup>

<sup>1</sup>Dokuz Eylül University Faculty of Medicine, Department of Pediatric Emergency Care, İzmir, Turkey

<sup>2</sup>Dokuz Eylül University Faculty of Medicine, Department of Pediatric Intensive Care Unite, İzmir, Turkey

### Abstract

We present here, a child with an extremely high methemoglobin level caused by inadvertently prepared sodium nitrite and potassium nitrite by a pharmacist. On physical examination, he had tachycardia and tachypnea. He had cyanosis, and mottled and blue-gray skin color. Oxygen saturation was 85% on room air. He was intubated due to seizure and arterial hypotension. Although he had no history of cyanotic heart disease, cyanosis was resistant to 100% oxygen therapy. Venous blood gas sampling revealed metabolic acidosis and methemoglobinemia (86.2%). Methylene blue dye at a dose of 2 mg/kg and ascorbic acid at a dose of 500 mg were administered intravenously and the clinical improvement was observed in 12 hours. Methemoglobinemia can cause severe systemic findings and death. The clinical findings can mimic septic shock. Emergency physicians should have awareness of methemoglobinemia in patients with cyanosis unresponsive to oxygen therapy.

**Keywords:** Emergency, intoxication, pediatrics, nitrite, methemoglobinemia

### Öz

Bu yazıda eczacı tarafından yanlış hazırlanmış ilaç alımı sonrası, sodyum nitrit ve potasyum nitrite bağlı ciddi bir methemoglobinemi olgusu sunulmaktadır. İlk fizik muayenesinde hasta taşikardik ve takipneikti. Hastanın siyanozu ve gri - mavi bir deri rengi vardı. Bilinen bir kardiyak hastalığı olmamasına rağmen, %100 oksijen ile satürasyonu %85 idi. Geldiğinde siyanoz, bilinç değişikliği, konvülsiyonu ve hipotansiyonu olan hasta entübe edildi. Alınan venöz kan gazında methemoglobinemi (%86,2) ve metabolik asidoz saptandı. Hastaya metilen mavisi 2 mg/kg intravenöz ve 500 mg intravenöz askorbik asit uygulandı. Takibinde methemoglobin seviyesi 12 saat içinde tedrici olarak geriledi ve klinik düzelleme görüldü. Methemoglobinemi, ciddi bulgulara ve ölüme neden olabilecek bir durumdur. Klinik bulgular septik şok ile karışabilmektedir. Acil hekimleri oksijene yanıt vermeyen siyanoz durumlarında methemoglobinemi olabileceğini mutlaka düşünmelidir.

**Anahtar Kelimeler:** Acil, zehirlenme, çocuk, nitrit, methemoglobinemi

### Introduction

Methemoglobinemia is a rare condition which refers to increased plasma methemoglobin (MetHb) levels due to oxidation of ferrous iron (Fe<sup>++</sup>) to ferric iron (Fe<sup>+++</sup>) within hemoglobin 1. Accidental nitrate or nitrite intoxication is one of the common causes of severe methemoglobinemia and it is usually related to an oxidizing agent which comprises nitrites, such as water, drugs and chemicals.<sup>1</sup> There are few reports about severe methemoglobinemia due to nitrite ingestion.<sup>2-6</sup> While levels above 50% may cause severe systemic findings, such as tachycardia, tachypnea, altered state of consciousness, and coma, levels above 70% may cause death 1 (Table 1). In reports of the cases of surviving

patients, the highest reported level of MetHb was 94%.<sup>7</sup> We present here, a child with an extremely high level of MetHb due to inadvertently prepared drug by a pharmacist. Additionally, he was previously misdiagnosed with sepsis and urinary tract infection and was barely diagnosed in the second episode. In this paper, since it can be life-threatening, we aim to emphasize the importance of diagnosis and proper management of methemoglobinemia.

### Case

A two-year-old boy with complaints of vomiting, rapid breathing and being pale was referred to our emergency

department with the pre-diagnosis of septic shock. On admission, he was conscious and had the signs of respiratory distress such as tachypnea, cyanosis and agitation. While we were performing general assessments, he had a generalized seizure. On physical examination, he had tachycardia (165 beats/min) and his blood pressure was 117/80 mmHg. His respiratory rate was 45/min and the chest was clear. He had cyanosis and, mottled and blue-gray skin color (Figure 1). Oxygen saturation (SpO<sub>2</sub>) was 85% on room air while receiving oxygen via non-rebreather mask. Midazolam

**Table 1. Clinical findings according to methemoglobinemia levels**

MetHb level (%)	Clinical findings
0-15	None
15-30	Mild (cyanosis, fatigue, dizziness, headache)
30-50	Moderate (weakness, tachypnea, mild dyspnea)
50-70	Severe (stupor, comai, convulsions, respiratory depression, cardiac dysrhythmias and acidosis)
>70	Potentially fatal

MetHb: Methemoglobinemia

**Table 2. Initial and serial blood gas measurements after the treatment of the patient**

	0. minute	30. minute	1. hour	2. hour	4. hour
pH	6.91	7.21	7.25	7.26	7.39
pCO <sub>2</sub>	45.1	35.1	41.7	46.1	39.5
HCO <sub>3</sub>	9.5	14.0	17.4	19.4	23.7
Lactate	8.8	11.1	9.4	5.0	1.4
MetHb	86.2	67.7	43.9	24.9	3.2

MetHb: Methemoglobin

**Table 3. Laboratory parameters of the patient**

Laboratory parameters	Values
Hemoglobin (g/dL)	7.6
Hematocrit (%)	23.6
MCV (fL)	64.2
RDW (%)	15.1
Platelet (10 <sup>3</sup> /μL)	338
AST (U/L)	28
ALT (U/L)	20
BUN (mg/dL)	12.7
Kreatinin (mg/dL)	0.39
Troponin - I (ng/mL)	0.8
CK-MB (ng/mL)	10.3

MCV: Mean corpuscular volume, RDW: Red cell distribution width, BUN: Blood urea nitrogen, CK-MB: Creatinine kinase MB fraction, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

was administered at a dose of 0.1 mg/kg intravenously to control seizure. He was intubated immediately for refractory cyanosis, but we did not observe increment in SpO<sub>2</sub> and improvement in cyanosis. Therefore, blood gas sampling and MetHb level were obtained and metabolic acidosis and methemoglobinemia were determined (Table 2). Methylene blue and ascorbic acid were administered at a dose of 2 mg/kg and 500 mg intravenously, respectively. 1 mEq/kg sodium bicarbonate was given intravenously for metabolic acidosis. 20 mL/kg saline bolus was administered. On follow-up, fluid refractory hypotension (77/42 mmHg) was observed. He had reduced peripheral perfusion and muffled heart sounds. Therefore, dobutamine (10 mcg/kg/min) and adrenalin (0.1 mcg/kg/min) infusions were administered and titrated to 0.3 mcg/kg/min.

Laboratory parameters of the patient are summarized in Table 3. His renal and liver function tests were normal, and cardiac enzymes were slightly elevated. He had anemia. Nitrite reaction was positive in urine screen test. In the medical history, the patient had been followed by a nephrologist with the diagnosis of medullary sponge kidney and he had been used Shohl's solution (sodium citrate and potassium citrate) for the treatment. Three days earlier, he had presented at a pediatric emergency department in a different center with the same signs and symptoms. He had been intubated and transferred to pediatric intensive care unit immediately and treated for urinary tract infection and sepsis. He was discharged with recovery after three days. Shohl's solution was not administered to the patient during that time. After being discharged, he took Shohl's solution just for one dosage. Thus, his family suspected about Shohl's solution and we realized that the pharmacist had prepared Shohl's solution with nitrite in lieu of citrate.

With the history and physical examination findings, the diagnosis of methemoglobinemia due to nitrite intoxication was made. After 12 hours, we obtained normal oxygen saturation and there was no requirement for inotrope agents;



**Figure 1.** Mottled and blue - gray color of skin

MetHb and lactate levels were decreased gradually. After 24 hours, he was entirely normal and had no symptoms.

## Discussion

Nitrite intoxication is one of the most common causes of acquired methemoglobinemia and usually secondary to accidental ingestion. In this case, the main reason of methemoglobinemia was a prescription error due to poor legibility of handwriting. Prescription errors are an important issue and may cause life-threatening events as in our case.<sup>8,9</sup> Computerized systems can be a preventive method for prescription errors.

Clinical features of methemoglobinemia vary depending on the MetHb level. Levels above 70% can cause life-threatening events and death.<sup>1</sup> To our knowledge, the MetHb level (86.2%) in this case was the highest among pediatric methemoglobinemia survivors. In the first episode, our patient was intubated and had been treated for sepsis and urinary tract infection due to positive reaction for nitrite in urine dipstick test. Although we had not any information to confirm this situation, we thought that our patient had had a slightly higher MetHb level in the first episode and the patient's MetHb level had decreased gradually because natural reduction of the oxidizing agent had not been given during hospital stay. On the contrary, MetHb levels may increase in patients with sepsis due to release of nitric oxide<sup>10</sup>; methemoglobinemia may be confused with sepsis if the patient has fever or hypothermia.<sup>11</sup> Additionally, this patient had been misdiagnosed with urinary tract infection due to positive reaction to nitrite in urine dipstick test. Urinary dipstick test can be useful in identifying nitrite ingestion.<sup>12</sup> Although in the second episode, his urine was positive for nitrite too; all these factors might show that he was misdiagnosed as sepsis.

Arterial saturation was 85% and there was no improvement with oxygen therapy. This phenomenon can be explained by absorbance ratio of MetHb. Pulse oximetry machines measure absorbance of hemoglobin at two wavelengths (660 and 940 nm). The ratio of these measurements (A<sub>660</sub>/A<sub>940</sub>) corresponds to saturation that previously calibrated from healthy volunteers' pulse oximetry data. The absorbance ratio of 0.43 corresponds to 100% saturation whereas a ratio of 3.4 corresponds to 0%. If the absorbance ratio is 1.0, it corresponds to 85% oxygen saturation. MetHb absorbs lights equally at two wavelengths. If the MetHb level exceeds above 35%, the ratio is 1 and therefore it corresponds to 85% oxygen saturation.<sup>12</sup> Therefore, if the patients have no

cyanotic cardiac disease and have 85% of SpO<sub>2</sub>, emergency physicians must consider a MetHb level above 35%.

The most widely known treatment is methylene blue dye which reduces MetHb levels gradually within less than one hour. If the patient has severe symptoms or a MetHb level above 30%, the patient should be treated immediately with methylene blue 1. We gave methylene blue and ascorbic acid and an improvement was rapidly observed. Although there are alternative treatments (N-acetylcysteine and cimetidine) to methylene blue dye<sup>13</sup>, we suggest that early administration of methylene blue was the most important point in this case for survival and must be available in all emergency room. Methemoglobinemia can cause functional anemia. If the patient has anemia, the clinical deterioration may be more obvious.<sup>14</sup> Our patient had also microcytic anemia, but there was no need for transfusion because of rapid response to methylene blue treatment.

In conclusion, nitrite intoxication can cause severe methemoglobinemia and may be confused with sepsis and urinary tract infection. Awareness of emergency physicians about methemoglobinemia in patients with cyanosis unresponsive to oxygen can be lifesaving.

## Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Durgül Yılmaz, Murat Duman, Tolga Fikri Köroğlu, Concept: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Durgül Yılmaz, Murat Duman, Tolga Fikri Köroğlu, Design: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Durgül Yılmaz, Murat Duman, Tolga Fikri Köroğlu, Data Collection or Processing: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Analysis or Interpretation: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Durgül Yılmaz, Murat Duman, Tolga Fikri Köroğlu, Gözde İnci, Literature Search: Aykut Çağlar, Utku Karaarslan, Emel Ulusoy, Fatma Akgül, Anıl Er, Writing: Aykut Çağlar.

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