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Prilocaine induced methemoglobinemia after tube thoracostomy: case report

Tüp torakostomisi sonrası prilokainin yol açtığı methemoglobinemi: Olgu sunumu

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ABSTRACT

Treatment of empyema thoracis in children is generally performed via tube thoracostomy under local anesthesia. Prilocaine, the most preferred local anesthetic agent, is also the most common cause of acquired toxic methemoglobinemia even in therapeutic doses. In this article, we present a 10-year-old boy who developed cyanosis after chest tube insertion under local anesthesia due to empyema and diagnosed as toxic methemoglobinemia. Methemoglobin level was measured as 18.7% and patient was successfully treated with ascorbic acid.

Keywords: Ascorbic acid; chest tube; methemoglobinemia; prilocaine.

ÖZ

Çocuklarda toraks ampiyemi tedavisi genellikle lokal anestezi altında tüp torakostomisi ile gerçekleştirilir. En sık tercih edilen lokal anestetik ajan olan prilokain, terapötik dozlarda dahi akkiz toksik methemoglobineminin en yaygın nedenidir. Bu yazıda, ampiyem nedeniyle lokal anestezi altında göğüs tüpü takılması sonrası siyanoz gelişen ve toksik methemoglobinemi tanısı konulan 10 yaşında bir erkek çocuk sunuldu. Methemoglobin seviyesi %18.7 olarak ölçülen hasta askorbik asit ile başarıyla tedavi edildi.

Anahtar sözcükler: Askorbik asit; göğüs tüpü; methemoglobinemi; prilokain.

Methemoglobin is the oxidized form of hemoglobin that cannot bind and transport oxygen. It is characterized by increased quantities of ferric iron that contain more than 1-2% hemoglobin,[1] and cyanosis suggestive of hypoxia is the characteristic sign of this condition. Methemoglobinemia may occur due to inherited defects in erythrocyte metabolism or the structure of hemoglobin. In addition, it can also be present after exposure to different drugs and toxins.[2] Oxidants, such as local anesthetics, sulfonamides, and nitrates, may cause methemoglobinemia,[1,2] and although the local anesthetic prilocaine is generally safe and is often used in pediatric practice, it can cause life-threatening, toxic methemoglobinemia.[3]

Herein, we present a boy diagnosed with methemoglobinemia who was treated with prilocaine after a chest tube was inserted for empyema. This case offers evidence that a high degree of suspicion for methemoglobinemia should be maintained after chest tube insertion when cyanosis is present.

CASE REPORT

A 10-year-old boy weighing 30 kg was admitted to the hospital after suffering from chest pain, dyspnea, and fever for a week. Antibiotic treatment (amoxicillin/clavulanate) was started after he was diagnosed with an upper respiratory tract infection. The patient's complaints continued, and a chest X-ray revealed

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a pleural effusion on the left hemithorax at his second admission. He was then hospitalized, and thoracentesis detected empyema. A chest tube was then inserted after infiltrating the subcutaneous, intercostal and subpleural space with 7 mL of 2% prilocaine. A total amount of 50 mL purulent effusion was drained, and the oxygen saturation (OS) rate was 85% with pulse oximetry in room air and 2 liters per minute of oxygen being administered through a nasal catheter. Additionally, a physical examination showed no abnormalities except for the cyanosis. The patient's arterial blood gas analysis was within normal ranges (pH: 7.4, partial pressure of carbon dioxide (pCO_2): 32.7 mmHg, partial pressure of oxygen (pO_2): 67 mmHg and OS: 94.2%). Moreover, a chest X-ray revealed full lung expansion, and bedside echocardiography excluded the presence of a pulmonary embolism, pericardial effusion, or disturbances in the mechanical valves. Furthermore, the patient's hemoglobin levels (10.9 g/dL) were the same as they were upon admission, and his biochemical tests were normal except for a methemoglobin level of 18.7%.

A 5% dextrose solution and a single dose of ascorbic acid (100 mg/kg) were given intravenously with the diagnosis of methemoglobinemia, and the cyanosis completely disappeared after the second hour of treatment. Moreover, the methemoglobin levels decreased to 6.3% at the fourth hour and 1.8% at the 12th hour of treatment.

DISCUSSION

Normal concentrations of methemoglobin account for less than 1-2% of circulating hemoglobin.[4,5] In clinical settings, when the concentration reaches approximately 15%, cyanosis occurs, and when it exceeds 30%, nausea, shortness of breath, and tachycardia develop. Arrhythmia, circulatory failure, renal failure, and eventually mortality are observed when the methemoglobin concentration hits 70%.[2]

Drugs that may induce methemoglobinemia are widely used in many clinics, and in most cases, this disorder often goes unrecognized and is thus left untreated. Methemoglobinemia caused by local anesthetics was first reported by Scott[6] in 1964, and there have since been many other cases in the literature.[2-11] Guay[12] reported that the prilocaine, benzocaine, lidocaine and tetracaine might possibly cause this condition, and of these, the mechanism of prilocaine is understood the most. In these cases, one of the toluidine isomers, ortho-toluidine (o-toluidine), is responsible for the oxidation of hemoglobin to methemoglobin, Methemoglobin consists of hemoglobin in which one or more of the ferrous ions found in the four heme groups have been oxidized to become ferric ions (Fe3+). The presence of the ion(s) changes the molecular shape and function of the methemoglobin. After this aforementioned change, the molecule binds to a water molecule instead of oxygen. Methemoglobin has an increased affinity for its bound oxygen, and a decreased affinity for unbound when compared to hemoglobin. As a result tissue hypoxia develops due to less oxygen transportation and release to peripheral tissues and followed by a reduction of the affinity for carbon dioxide. Consequently, peripheral acidosis may occur as a result of carbon dioxide accumulation.[12]

After subcutaneous administration, peak plasma levels are generally reached after several hours, and toxicity is observed when plasma levels exceed 3 mg/L.[4] Vasters et al.[13] found that up to 15.4% methemoglobin may be present at three hours when 300-400 mg of prilocaine (2.6-7.4 mg/kg) is used in adults over the age of 18. However, the dosage amount, age, gender, and concentration of prilocaine used can explain only 36% of the cases of methemoglobinemia that have been reported.[13] Hence, the appearance of methemoglobinemia is unpredictable and varies widely among individuals.[13] We infiltrated 140 mg (4.6 mg/kg) of prilocaine, which we considered to be safe, before inserting the chest tube. From the cases in the literature, we determined that doses as low as 2.5 mg/kg in children, 1.3 mg/kg in the presence of additional oxidizing drugs, 3.2 mg/kg in adults with chronic renal failure, and 5.0 mg/kg in adults with no predisposing factor were sufficient to induce clinically symptomatic methemoglobinemia. Thus, as Guay[12] pointed, higher doses reaching up to 8 mg/kg which was recommended classically, should be reduced.

Besides prilocaine, benzocaine-related methemoglobinemia has also been reported in the literature, but surprisingly it is no longer recommended because it is not possible to predict who is at risk when this drug is used. No therapeutic window has even been defined in susceptible individuals, and even after a single dose of benzocaine spray, methemoglobinemia can develop. In addition, lidocaine may rarely induce methemoglobinemia. For patients receiving other oxidizing drugs such as nitrates, trimethoprim-sulfamethoxazole and dapsone and for patients with congenital methemoglobinemia, it is recommended that these drugs be replaced with other local anesthetics.[12]

Almost all patients with methemoglobinemia are anemic,[1,7] and this was also the case with our

patient who had a hemoglobin level of 10.9 mg/dL. Additionally, anemic patients may be more sensitive to symptoms of methemoglobinemia because of their lower functional hemoglobin reserve.

In our patient, the methemoglobinemia was considered to be part of the differential diagnosis of cyanosis, and its presence was easily diagnosed by measuring the methemoglobin level. If for some reason this measuring this is not possible, the saturation gap, which is the difference between the sulfur dioxide (SO_2) level measured by pulse oximetry and the SO_2 level calculated from the arterial blood gas analysis, can also be used to diagnose this blood disorder.[8] The saturation gap should be greater than 5% in cases of methemoglobinemia. Two other simple bedside tests have also been useful. One involves the inspection of the arterial blood sample to see if it has a characteristic chocolate-brown color that does not change when exposed to air, and the second is known as the "filter paper test" in which a drop of blood is placed on white filter paper. If the methemoglobin concentration is more than 10-15%, it will be brown, easily differentiating it from the normal blood color.[1,5,9]

To our knowledge, methemoglobinemia after a tube thoracostomy has been previously reported in only the single case report by Tunc et al.[14] However, we believe this situation is not the norm since the common dyspneic patient profile that thoracic surgeons face most likely overlaps with the symptoms of methemoglobinemia. Hence, a failure to diagnose this condition or a misdiagnosis is possible.

The treatment goals for this condition include the resolution of symptoms and the reversion to normal methemoglobin levels. When light hypoxia is present, general supportive therapy such as supplemental oxygen might be sufficient. Furthermore, improvement in patients with cyanosis is a poor marker for adequate treatment; therefore, the serial methemoglobin levels should be measured to ensure that the most effective treatment is used.[10] If obvious tissue hypoxia develops with high methemoglobin levels (>15%), the general consensus is that intravenous methylene blue should be given as a 1% solution (1-2 mg/kg) over a period of between five and 10 minutes. However, high doses should be avoided (>7 mg/kg) since they might overwhelm the ability of G6PD to produce adequate amounts of nicotinamide adenine dinucleotide phosphate (NADPH), which is required in the production of reduced methylene blue (leukomethylene blue). In turn, this could worsen the methemoglobinemia. Methylene blue is contraindicated when there is G6PD deficiency because it would worsen the condition.[1,5]

Ascorbic acid, a potent antioxidant and reduction agent, may also be used as an alternative treatment. Although under physiological conditions, ascorbic acid-induced methemoglobin reduction is less important than the reduction performed by the NADP-dependent methemoglobin reductase system. Nevertheless, under methemoglobinemic conditions, treatment with ascorbic acid is possible and even recommended because it is widely available, and the positive effect of the scavenging free radicals is beneficial.[1,11] In our patient, we used ascorbic acid intravenously (100 mg/kg) for two reasons. First, we could not measure the G6PD levels. Furthermore, the intravenous form of methylene blue was not readily available in our hospital at that time. In addition to the ascorbic acid, we used a 5% dextrose solution as a source of NADH in the red blood cells (RBC), and improvement in the cyanosis was observed during the first hour.

In conclusion acute toxic methemoglobinemia is not an infrequent complication of topical anesthesia, as evidenced by the literature. Our patient exhibited typical symptoms of methemoglobinemia: cyanosis and dyspnea. Thus, methemoglobinemia was suspected, and the diagnosis was easily made by measuring the methemoglobin levels in the blood. Our early recognition of this disorder and prompt management quickly resolved the symptoms and prevented possible morbidity or even mortality.

Methemoglobinemia can easily be missed in children due to the presence of accompanying respiratory problems. Therefore, a high level of suspicion is necessary in cases with unexplained cyanosis after local anesthesia that are unresponsive to oxygen therapy. When this occurs, the early recognition of methemoglobinemia can prevent tissue hypoxia. We also believe that intravenous ascorbic acid, the treatment of choice for our patient, should be readily available and that prilocaine, even at low doses, should be used with caution.

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