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CASE REPORT / *OLGU SUNUMU*

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Toxic Methemoglobinemia Caused by Prilocaine: Presentation of Two Cases

Prilokaine Bağlı Toksik Methemaglobinemi: İki Olgu Takdimi

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ABSTRACT Prilocaine is a local anesthetic agent used in many areas, but it may cause the methemoglobinemia, a life-threatening side effect. As a result, hypoxia may develop in the tissues. In this study, two toxic methemoglobinemia cases are presented since they develop depending on the local prilocaine used during the invasive intervention by radiology. Methemoglobinemia is a serious hematological disease and occurs when iron in hemoglobin is oxidized and becomes trivalent (Fe+++). Methemoglobinemia should be brought to mind in the differential diagnosis in the case of determining nonconcurrence or cyanosis between PaO_2 and SaO_2 values after using a local anesthetic. In such circumstances, it is appropriate to monitor patients in fully equipped intensive care units in terms of problems that may develop. Methylene blue and ascorbic acid were successfully used in treatment. In this paper, two cases are presented since methemoglobinemia developed depending on the use of prilocaine for local anesthesia and they were treated by intravenous methylene blue and/or ascorbic acid.
Keywords: Interventional radiography, methemoglobinemia, prilocaine, methylene blue, ascorbic acid

ÖZ Prilokain, pek çok alanda kullanılan lokal anestetik bir ajandır, ancak hayatı tehdit edebilen bir yan etki olan methemoglobinemiye neden olabilmektedir. Bunun sonucunda dokularda hipoksi gelişebilir. Bu çalışmada radyoloji tarafından girişimsel işlem sırasında kullanılan lokal prilokaine bağlı gelişen iki toksik methemoglobinemi olgusu sunulmuştur. Methemoglobinemi ciddi bir hematolojik hastalık olup hemoglobindeki demirin okside olup, üç değerli (Fe+++) duruma geçmesiyle oluşur. Lokal anestezik kullanımından sonra, PaO_2 ile SaO_2 değerleri arasında uyumsuzluk veya siyanoz saptanması halinde ayırıcı tanıda methemoglobinemi akla getirilmelidir. Böyle durumlarda hastaların gelişebilecek problemler açısından tam donanımlı yoğun bakım ünitelerinde izlenmesi uygundur. Tedavide metilen mavisi ve askorbik asit başarıyla kullanılmaktadır. Bu yazıda lokal anestezi amacıyla prilokain kullanımına bağlı methemoglobinemi gelişen ve intravenöz metilen mavisi ve/veya askorbik asit ile tedavi edilen iki olgu sunulmuştur.
Anahtar Kelimeler: Girişimsel işlemler, methemoglobinemi, prilokain, metilen mavisi, askorbik asit

Introduction

Methemoglobinemia is a severe haematologic disease (1). The iron found in hemoglobin is bivalent under normal circumstances (Fe++). Methemoglobinemia occurs by oxidizing of iron in the hemoglobin and becoming triad (Fe+++). Methemoglobin (MetHb) level in blood is below 1% under normal circumstances and if it exceeds 10-15%, cyanosis develops. While systemic symptoms such as weakness, tachycardia, respiratory distress, nausea, and vomiting develop as a result of tissue hypoxia if the level exceeds 35%; lethargy, stupor, and syncope occurs when it is above 55%. If the level is above 70% and when methemoglobinemia is not treated, it is fatal (2). Prilocaine is one of the local anesthetics making methemoglobinemia (3). In this article, the literature related to diagnosis and treatment approaches was aimed to review in methemoglobinemia cases in company with two cases, for which prilocaine was administered before the invasive operation in radiology clinic, in which acute methemoglobinemia developed and which were treated.

Case Reports

Case 1

A woman at the age of 54, who had liver metastasis and diagnosed by breast cancer (ca), was operated in the oncology unit due to microwave ablation. The patient was then accepted by the anesthesia intensive care since there was cyanosis on hands and legs and around the mouth after 4-5 hours from ablation operation made by invasive radiology. The patient was dyspneic, cyanotic and agitated in physical examination. Her blood pressure was 96/55 mmHg, heart apex beat was 116/min, respiratory rate was 40/min, fewer 36.4 °C and lung and cardiac auscultation were ordinary. The patient's cyanosis did not get better after giving oxygen as 6 L/min with a nasal cannula since her oxygen saturation was 85%. Her pH was 7.47, PaO_2 was 141.3 mmHg, pCO_2 was 31.2 mmHg and MetHb level was 31.4% in venous blood gas measured. Her hemoglobin was 11.2 g/dL and leukocyte count was 10.100/mm^3 in complete blood count and her polymorphonuclear leukocyte (PMNL) was 68%, lymphocyte was 30% and monocyte was 2% in the peripheral blood smear. With these findings, methemoglobinemia was considered in the patient. At the 8th hour of her hospitalization, methylene blue was given to the patient by intravenous (IV) route at a dose of 1 mg/kg in 5 minutes as a slow push, as a single dose.

Blood MetHb level of the patient, whose cyanosis regressed after methylene blue treatment, was determined as 0.9%. The patient, who was followed up in the unit for observation for 24 hours, was referred to the oncology unit after obtaining her consent for this case report, as her vital signs were stable and cyanosis did not develop in the follow-up.

Case 2

A female patient at the age of 69 diagnosed by cholangiocellular ca was hospitalized in the oncology unit for chemotherapy plan. The patient, whose biliary stent operation was made by invasive radiology in company with local anesthesia, was accepted by the intensive care unit since there was cyanosis on lips, tachypnea, and respiratory distress after 5-6 hours from the operation. Her blood pressure was 121/57 mmHg, heart apex beat was 91/min, respiratory rate was 33/min, fewer 36.4 °C and she was cyanotic in her hospitalization. The patient's cyanosis did not get better after giving oxygen as 5 l/min with a nasal cannula since her oxygen saturation was 89%. Her pH was 7.48, PaO_2 was 104 mmHg, pCO_2 was 33.9 mmHg and MetHb level was 21.9% in venous blood gas measured. Her hemoglobin was 11.9 g/dL and leukocyte count was 4.500/mm^3 in complete blood count and her PMNL was 80% and lymphocyte was 20% in the peripheral blood smear. With these findings, the patient was diagnosed with methemoglobinemia at the 2nd hour of hospitalization, but methylene blue could not be obtained from the hospital pharmacy. Therefore, the patient was given 1000 mg/day ascorbic acid in 5% dextrose intravenously as a single dose over 2 hours. The patient, whose cyanosis regressed within 24 hours, MetHb level of 0.2%, and consent was obtained for this case report, was transferred to the oncology clinic. Thus, it was observed that the efficacy of methylene blue or 1000 mg ascoric acid applications was similar and sufficient.

Discussion

Methemoglobinemia generally develops with toxic reasons in adults. Drugs take an important place for these reasons. Methemoglobinemia may be seen depending on local anesthetic drugs, but cases depending on prilocaine are rare in adults (4). Prilocaine's injectable form (Citanest®) and prilocaine-lidocaine cream (EMLA®) are used in practical application. In our article, two cases were referred since they hospitalized in the oncology unit and transferred to the intensive care unit by methemoglobinemia pre-diagnosis. Shortness of breath, cyanosis on lips and low saturation were detected in the patients after a few hours from local prilocaine given during administered invasive operation. Methemoglobinemia pre-diagnosis was thought and the diagnosis was verified by arterial blood gas analysis in the patients who did not have such symptom previously and had local anesthetic drug usage history in anamnesis. If MetHb level is lower than 20% in acquired methemoglobinemia, recovery is generally seen upon discontinuing causing drug. Close follow up and support treatment of the patients are acceptable approach since they do not have an additional disease, whose general condition is good and whom cardiac, pulmonary or neurologic findings do not develop (5). However, there is a consensus on the elimination of toxic substance or drug, support treatment and giving more aggressive treatments such as ascorbic acid and methylene blue in the cases, which are symptomatic or of which MetHb level quickly increases. In general, methylene blue

and treatment are required in the cases, of which MetHb level is higher than 30% (5). NADPH-MetHb reductase enzyme system quickly activates by methylene blue that is given intravenously and slowly with the dose of 1-2 mg/kg in these patients (6). Response to the treatment should be quantitatively evaluated upon reducing MetHb level or returning to normal in 1-2 hours besides clinical findings. Conversion of MetHb into hemoglobin starts within 15-60 minutes in the patients to whom methylene blue is given (5). But, it should not be forgotten that methylene blue may rarely be the reason of methemoglobinemia (7). For example, in a case report study that had a place in the literature in 2008 and belongs to McRobb and Holt (8) it was determined that methemoglobinemia developed in the patient for whom methylene blue was used and whose hypoxias deepened during cardiac surgery.

1 mg/kg from 1% methylene blue solution was intravenously administered to the first case in treatment for 5 minutes as a slow push. It is known that dextrose treatment increases NADH production through glycolysis and participates in patient's MetHb clearance with NADH-diaphoresis enzyme (7). 100% oxygen and 5% dextrose treatment were concomitantly given to the patient and a quick decrease was determined in MetHb level within two hours.

The primary drug is methylene blue in toxic methemoglobinemia treatment; however, the ascorbic acid infusion may be preferred when it may not be supplied. Ascorbic acid degrades MetHb as in vitro in a non-enzymatic way. Usage of ascorbic acid in methemoglobinemia treatment is thought since it decreases methemoglobin level as *in vitro* in animal and human erythrocytes (9). It also showed a correlation to clinical response with clinical response to IV methylene blue treatment in the literature (10).

In conclusion, prilocaine from local anesthetics may cause acquired methemoglobinemia in adults. Methemoglobinemia pre-diagnosis should be brought to mind in the cases of cyanosis and desaturation. Ascorbic acid or methylene blue administration is lifesaving in early and effective ways. IV methylene blue primarily used in treatment is hard-to-get in our country's conditions. General support treatment was immediately made, methylene blue was given when supplied and ascorbic acid treatment was administered without delay when it could not be supplied in two cases in this article. This drug should be compulsorily kept available in certain centers since it is of vital importance. It is also brought to mind that ascorbic acid was effectively used when it could not be supplied.

Ethics

Informed Consent: The necessary permission and informed consent were obtained from the legal representatives of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.B., Concept: H.S., Design: Y.B., H.S., Data Collection and/or Processing: Y.B., Analysis and/or Interpretation: H.S., Literature Search: Y.B., H.S., Writing: Y.B.

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