An unusual complication after permanent pacemaker implantation: Methemoglobinemia

Kalıcı kalp pili yerleştirilmesi sonrası görülen sıradışı bir komplikasyon: Methemoglobinemi

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Summary– Permanent pacemaker implantation (PPI) is usually a very safe procedure with a low complication risk. It is a relatively straightforward process carried out under local anesthetic. This case report presents an 80-year-old male patient who required a permanent pacemaker due to complete atrioventricular (AV) block, and who developed cyanosis and was diagnosed with methemoglobinemia after the pacemaker insertion procedure, in which the local anesthetic prilocaine was administered. To our knowledge, this is the first case in the literature to describe methemoglobinemia developing after PPI.

Özet– Kalıcı kalp pili yerleştirilmesi (KKPY) komplikasyonları az olan, çok güvenilir bir işlemdir. Lokal anestezi altında yapılır ve nispeten karmaşık olmayan bir süreçtir. Bu olguda, tam atriyoventriküler blok nedeniyle KKPY'ye ihtiyaç duyulan ve işlem sonrası lokal anestezi ajanı prilokaine bağlı olağan dışı bir komplikasyon olan methemoglobinemi gelişen 80 yaşında erkek bir hasta sunuldu. Bildiğimiz kadarıyla bu olgu KKPY sonrası gelişen methemoglobinemi ile ilgili literatürdeki ilk olgudur.

Methemoglobinemia is an uncommon,[1,2] but potentially fatal hemoglobinopathy. It leads to rapid oxygen desaturation, and therefore requires prompt recognition and treatment. This condition is often reported in the perioperative period of procedures in which a local anesthetic is applied.

We report a case of an 80-year-old male patient who developed cyanosis soon after undergoing permanent pacemaker implantation and was diagnosed with methemoglobinemia due to prilocaine use during pacemaker insertion.

CASE REPORT

An 80-year-old man presented to the emergency department with lightheadedness and confusion. His medical history revealed coronary artery bypass surgery, heart failure, diabetes mellitus, hypertension, chronic kidney disease (glomerular filtration rate: 23.3 ml/min/1.73 m²) and Alzheimer's disease. Electrocardiography (ECG) showed complete atrioventricular (AV) block and a heart rate of 27 beats/min. Transthoracic echocardiography showed severe mitral regurgitation, mild tricuspid regurgitation, pulmonary hypertension (systolic pulmonary arterial pressure: 60 mmHg) and a left ventricular ejection fraction of 40%. In the absence of a temporary cause such as drugs, mad honey disease or electrolyte disorders leading to complete AV block, PPI was planned. The procedure was explained to the patient and his family, and written informed consent obtained. He was then taken to the catheterization laboratory and a VDD pacemaker (Identity ADx VDR, St. Jude Medical, Sylmar, CA,

Abbreviations:

AV	*Atrioventricular*
CAD	*Coronary artery disease*
CKD	*Chronic kidney disease*
COPD	*Chronic obstructive pulmonary disease*
ECG	*Electrocardiography*
HF	*Heart failure*
IV	*Intravenous*
Meth-hb	*Methemoglobin*
SaO_2	*Oxygen saturation*
VHD	*Valvular heart disease*

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USA) with a 1368/58 cm AV plus lead prepared for implantation through the left subclavian vein. Prior to the procedure, a local anesthetic was given to the patient to numb the left pectoral fossa.

Prilocaine (Priloc 2%, Vem, Tekirdağ, Turkey) was used as local anesthetic. A bottle of Priloc (20 mL) contains 400 mg of prilocaine hydrochloride. 600 mg of subcutaneous prilocaine was injected into the left pectoral fossa for anesthesia. However, insertion of the leads into the left subclavian vein failed because of a venous anomaly—the absence of vessels of adequate caliber and difficulty in subclavian vein puncture. Therefore, the right pectoral fossa was punctured immediately after injection of a further 800 mg of prilocaine into the area. The pacemaker was then successfully implanted. The duration of the entire procedure was 30 minutes and a total of 1400 mg prilocaine was used.

Approximately 30 minutes post-procedure, the patient began to develop cyanosis. On physical examination, systolic blood pressure was 125 mmHg, and heart rate 66 beats/min. Body temperature was 36.2 ºC and pulse oximetry measured oxygen saturation (SaO_2) was 88%. ECG showed paced rhythm and heart rate of 67 beats/min. In general, he appeared well and had a normal level of alertness and interaction. There was cyanosis around the lips and mucosa. He was noted to have central cyanosis and the remainder of his physical examination was normal. Despite 100% O_2 treatment by mask, the central cyanosis persisted.

Analysis of arterial blood samples showed that on admission pH was 7.33, pCO_2 23.7 mmHg, pO_2 78.3 mmHg, SaO_2 94%, and HCO_3- 12.3 mmol/L; and methemoglobin (Meth-hb) level was 24.9%. Hemoglobin was 7.6 g/dL, white blood cell count 9200/mm^3 and platelet count 158.000/mm^3. Serum electrolytes, liver function test, and postero-anterior chest X-ray study were normal.

After all evaluations, an absolute diagnosis of methemoglobinemia was confirmed. The patient was treated with intravenous (IV) infusion of 1–2 mg/kg methylene blue 1% over 3–10 minutes. With cyanosis persisting for 1 hour, an additional dose of methylene blue was given. Cyanosis was resolved and disappeared entirely after 6 hours. After treatment, blood methemoglobin concentration was measured over several hours and a gradual decrease was observed: from 24.9% to 21.4% at 2 h, to 6.4% at 8 hours and 2.9 % at 20 h. However, the following day, the patient's blood creatinine level was seen to have increased from 2.45 mg/dL to 3.0 mg/dL and urine output had decreased. Creatinine levels continued to increase gradually and oliguria developed. On the 4th day, the patient was taken to hemodialysis. The reason for this progressive renal failure was considered to be the methylene blue. At follow-ups, renal function improved and the patient was discharged.

DISCUSSION

Indications and technologies of cardiac pacing continue to evolve and have resulted in a rapid increase in the number of pacemaker implantations. This procedure is now considered minor surgery. In most cases, sedation, rather than general anesthesia, is utilized in order to numb the area over which the pulse generator will be placed. Although mostly a safe procedure, PPI may rarely lead to some known complications, such as pneumothorax/hemothorax, pocket hematoma, pacemaker system infection, diaphragmatic stimulation, and cardiac or venous perforation. However, an unusual complication after PPI, namely methemoglobinemia due to the use of prilocaine as local anesthetic prior to pacemaker insertion, has not been reported previously in the literature.

Methemoglobin levels increase when the mechanisms within the red blood cells are overwhelmed by oxidative stress with resulting oxidization of the ferrous ion (Fe^{2+}) of the heme group to the ferric state (Fe^{3+}). This conversion leads to reduced ability to release oxygen to tissues and thereby hypoxia. Mechanism against Meth-Hb is performed mainly by the enzyme systems cytochrome-b5 reductase and NADPH meth-Hb reductase within the red cell, and to a lesser extent by the ascorbic acid and glutathione enzyme systems. Impairment of these enzyme systems results in methemoglobinemia.[3,4]

Factors that predispose to drug-induced methemoglobinemia include excessive dose, a break in the normal mucosal barrier—which may increase systemic absorption—and the concomitant use of other drugs known to cause methemoglobinemia. Our patient received an excessive dose of prilocaine due to initial failure of leads transmission in the left subclavian vein and because the procedure was attended to with no interval after the first dose of prilocaine. Another

risk factor for developing drug-induced methemoglobinemia is concomitant illnesses such as cardiac and respiratory diseases.[3] Our patient also had chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), heart failure (HF) and valvular heart disease (VHD). Concentration of methemoglobin is reported as a percentage of total hemoglobin, and it affects the degree of functional anemia. Our patient had baseline anemia (hemoglobin level: 7.6 gr/dL), which put him at a higher risk of developing more symptoms of methemoglobinemia.

Methemoglobinemia is a rare and serious hematological disorder requiring emergency treatment. It can be caused by a genetic defect in erythrocyte metabolism, hemoglobin structure, or exposure to various drugs and toxins.[4] Local anesthetic drugs like lidocaine, bupivacaine and prilocaine are common oxidant drugs that cause methemoglobinemia. Many cases resulting from exposure to these drugs have been reported in the literature.[4–6] Methemoglobin physiological concentration in blood is between 0% and 2%. Cyanosis occurs if concentrations are greater than 10%, dyspnea, nausea, and tachycardia with those above 30%, and lethargy and stupor from concentrations above 55%.[4] Death can occur with those exceeding 70%. In the present case, methemoglobin concentration was 24.9%, and only cyanosis was present.

Diagnosis of methemoglobinemia may be challenging. One possible clue is the presence of a "saturation gap". The most commonly used laboratory measurements of blood oxygen levels are the pulse oximetry-derived SO_2 and the arterial blood gas-derived PO_2 and SO_2. However, neither of these is adequate for detecting or measuring metHb. Saturation gap occurs when there is a difference between the SO_2 measured by means of pulse oximetry (the lower value) and that calculated by means of arterial blood-gas analysis. Typically, this saturation gap is greater than 5% in cases of metHb.[7]

In methemoglobinemia due to drugs, the medication should be stopped and if possible, removed from the body.[8] Treatment must be considered when the concentration exceeds 20% in a symptomatic patient, as in our case, and 30% in an asymptomatic patient after acute exposure to an oxidant agent. Even in therapeutic doses, prilocaine can cause methemoglobinemia via its metabolite O-toluidin.[5] Methylene blue infusion is the first treatment modality. Methylene blue restores the iron in hemoglobin to its normal oxygen-carrying state by activating meth-Hb reduction using NADPH dehydrogenase.[7] It is administrated at a dose of 1–2 mg/kg IV slowly over 3–10 minutes. Improvement should occur within one hour, but if cyanosis persists, a second dose of methylene blue should be given.[3] Vitamin C can occasionally reduce cyanosis associated with chronic methemoglobinemia, but has no role in treatment of acute acquired methemoglobinemia. Ascorbic acid should be used in those with G6PD deficiency, since even therapeutic doses of methylene blue can lead to hemolysis of erythrocytes.[6]

Because complications related to methemoglobinemia and its treatment can be severe and life-threatening, it is necessary to be mindful of this disorder after PPI. Over a 2-year-period in our clinic, the reported patient is the only one among 172 receiving cardiac pacing to have experienced methemoglobinemia as a complication. With no other patients being administered prilocaine in excess of 500 mg, we attributed the complication in this case to the high doses (1400 mg).

This case indicates that a local anesthetic drug, prilocaine, commonly used in PPI may cause methemoglobinemia. Diagnosis should be considered in a patient on whom prilocaine, especially in high doses, is used during the procedure, and in whom baseline anemia, CKD, COPD, CAD, HF and VHD are present. While methylene blue is the standard treatment of choice, it should be noted that this treatment too may result in various complications, such as acute renal failure or even death. Therefore, the clinician must be familiar with this condition to ensure prompt diagnosis and effective treatment, and, in cases where additional doses of prilocaine are required, be mindful of leaving an adequate time interval, or postponing the procedure, to decrease the risk of methemoglobinemia.

Consent

Written informed consent was obtained from the patient for publication of this case report.

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