Methemoglobinemia - A Case Report

ABSTRACT
Methemoglobinemia arising from the use of local anesthetics, such as benzocaine, prilocaine and lidocaine, is a potential complication in the dental operatory. Its recognition is critical, because failure to treat the condition can result in death. Occurrences during intubation have been reported in the medical literature, but methemoglobinemia has not been widely discussed in dentistry.

CASE REPORT
A forty-seven year old, white, male physician presented to the dental clinic at the University of Maryland Medical Systems. He stated, "The use of local anesthetics causes my blood to turn chocolate brown, it is in my medical record." His medical history included hepatitis, hyperension, and difficulty of intubation (secondary to anatomy). He was taking Prozac for an obsessive-compulsive disorder. On December 28, 1990 he was admitted to the hospital for elective surgical removal of his third molars.

Prior to intubation vital signs were: blood pressure-170/112 mm/Hg, pulse-110/minute, respiration-24/minute. Hemoglobin tested 14 g/dL. Oxygen saturation and pulse oxymetry levels were 99%. The lungs were clear and there was a normal flow murmur over the left sternal border. The abdomen was unremarkable and the extremities were cyanotic with pulses were present.

Before and during intubation the following medications were used: midazolam HCl, glycopyrrolate, Droperidol, Fentanyl, lidocaine, ceta­caine, surital and Neosynephrine. During intubation the patient became cyanotic. His O 2 saturation dropped to 74%. During and after attempted intubation chest radiographs were normal.

During surgery laboratory data was as follows: hemoglobin-11.7 g/dL with oxyhemoglobin-64.5%, carboxyhemoglobin 1.7% and methemoglobin-33.2%. The blood gases were pH -7.59, pCO 2 -24, pO 2 -584, on a FiO 2 of 100%.

The immediate assessment was that the cyanosis was secondary to methemoglobin reductase deficiency or toxic methemoglobinemia. Blood samples taken a week later indicated it was most likely the latter. It was decided that the condition probably had been caused by the combination of medications, including large doses of local anesthetics, that had been given.

DISCUSSION
Methemoglobinemia occurs when levels of methemoglobin exceed the normal one to two percent of the total hemoglobin. This results in a cyanotic-like state in the absence of cardiac or respiratory abnormalities.

Methemoglobin is a derivative of hemoglobin in which the ferrous (Fe++) portion of the heme complex has been oxidized to the ferric (Fe+++) state, and then is bound to either a water molecule or a hydroxyl group. This additional charge causes the ferric molecule to repel oxygen.1,2,3 As a consequence, the hemoglobin molecule is incapable of effectively transporting and releasing oxygen to the tissues. Therefore, the oxygen-hemoglobin dissociation curve of the normal oxyhemoglobin molecule is shifted to the left by methemoglobinemia.4

Normally, the methemoglobin form comprises 1-2% of total hemoglobin. Low concentrations of methemoglobin exist in red blood cells mainly due to the following chemicals in those cells: NADH-cytochrome b5 reductase, NADPH-methemoglobin reductase, glutathione reductase and ascorbic acid. It has been shown that cytochrome b5 reductase enzyme catalyzes the transfer of electrons from NADH to cytochrome b5 which, in turn, reduces methemoglobin (Fe+++) to hemoglobin (Fe++). Moreover, NADPH methemoglobin reductase is a flavin reductase which reduces flavin in the presence of glutathione which directly reduces methemoglobin to hemoglobin non-enzymatically.5

Methemoglobinemia can be hereditary, but it is more commonly acquired from drugs and chemicals that are derivatives of nitriles or aniline. This includes virtually all of the commonly used local anesthetics. Acquired methemoglobinemia occurs when the rate of formation of methemoglobin exceeds the rate of reduction as a result of exposure...
sure to certain substances. The following list of substances that have the potential to induce methemoglobinemia was compiled from several sources in the literature: benzocaine, prilocaine, lidocaine, nitroglycerin, phenytoin, silver nitrate, sulfonamide, amyl nitrate, aniline dyes, dapsone, miconazole nitrate, acetaminophen, nitrofurans, phenacetin, methylene blue.

The dental application is apparent. In addition, topical anesthetics like benzocaine are used for pain relief in oral mucositis following radiation therapy. Miconazole nitrate is a topical antifungal agent which sometimes is used to treat candida infections of the oral mucosa and is applied to dentures. S.F. Malamed states that prilocaine should not be used on patients taking acetaminophen or phenacetin since they induce methemoglobin formation.

Hereditary methemoglobinemia can be caused by a congenital defect in the structure of hemoglobin or a deficiency in the enzyme process that controls the daily production of ferric ions. The hereditary form of methemoglobinemia is much less frequent than acquired methemoglobinemia.

**DIAGNOSIS**
Normal individuals have a methemoglobin level of 1-2% of total hemoglobin. Higher levels result in signs and symptoms as shown in the chart below.

<table>
<thead>
<tr>
<th>Methemoglobin Level</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2%</td>
<td>Normal</td>
</tr>
<tr>
<td>15%</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>20%</td>
<td>Dizziness, altered mental state, dyspnea, Fatigue, headache and syncope</td>
</tr>
<tr>
<td>55%</td>
<td>Arrhythmia, seizures, coma</td>
</tr>
<tr>
<td>70%</td>
<td>Death</td>
</tr>
</tbody>
</table>

The diagnosis of methemoglobinemia is suggested by cyanosis that is not relieved by 100% oxygen when delivered via mask in the presence of adequate ventilation and good circulation. A chocolate brown hue is the characteristic hematological finding. The diagnosis is confirmed by laboratory spectrophotometric analysis of the blood. The methemoglobin level is determined by use of arterial blood gas analysis.

**TREATMENT**
The immediate treatment of methemoglobin begins with basic life support, general supportive care, including oxygen, and control of the airway if necessary. The ultimate treatment of choice is methylene blue given intravenously at a dose of 1-2 mg/kg.

Methylene blue acts as a cofactor in transferring electrons from NADPH to the ferric ion and results in the conversion of methemoglobin to hemoglobin. It is important to note that methylene blue in excess of 7 mg/kg causes dyspnea, chest pain, restlessness, tremor, dysuria and methemoglobinemia. Moreover, methylene blue is contraindicated in patients with hereditary methemoglobinemia and hemolytic anemia.

In addition, ascorbic acid is mainly used in patients with hereditary methemoglobinemia. However, in cases of life threatening refractory methemoglobinemia, exchange transfusion and hyperbaric oxygen are used to increase oxygen concentration in the blood.

**DENTAL CONSIDERATIONS**
When patients present with a history of methemoglobinemia, the dentist must obtain a detailed history to determine the type (acquired or hereditary). If it is acquired, the offending substances need to be identified and their effect on the patient must be learned. If the provoking substance was a local anesthetic, the dentist should determine if it was an ester, that usually cross-reacts or an amide, which usually does not cross-react. If the patient is unable to provide information, a consultation can be obtained from the patient's physician. Previous dentists can be contacted to learn if they had any problems with the patient.

A 1% solution of dyphenhydramine (Benadryl) with 1:100,000 epinephrine can be used as local anesthetic for patients who are unable to have either amide or ester local anesthetics. The duration of Benadryl as a local anesthetic is approximately 30-minutes. It can be used for infiltration or block injection. The side effects associated with Benadryl are burning sensation, swelling and erythema. It is important to note that there are conflicting opinions among dentists as to the effectiveness of using Benadryl as a local anesthetic. Another approach is to use general anesthesia, as was done in the above case report.

**CONCLUSION**
Methemoglobinemia is rare in dentistry because the substances that induce it are rarely given in the combinations and quantities that cause the condition. Because it is possible that a dental patient who is taking nitroglycerin or dapsone may receive multiple injections of local anesthesia the potential hazard of methemoglobinemia may exist in the dental operatory. Therefore it necessary that the dentist be knowl-
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References


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