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## Methemoglobinemia Associated with Benzocaine-containing Lubricant

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We report a case of a high concentration of methemoglobinemia associated with the use of a benzocaine containing anesthetic lubricant on an esophageal stethoscope in a premature infant.

### REPORT OF A CASE

A 1,340-g baby boy was born at an estimated gestational age of 30-32 weeks by spontaneous vaginal delivery at an outlying hospital. Apgar scores were 5 and 7 at 1 and 5 min, respectively. Although the child appeared well oxygenated, moderate respiratory distress was evident and he was transferred immediately to our facility.

He was admitted to the intensive care nursery (ICN) with a diagnosis of prematurity and respiratory distress syndrome. He was acyanotic, with clear breath sounds bilaterally; his respiratory rate was 99/min, with moderate to deep subcostal retractions, and bowel sounds were hypoactive. Other aspects of the physical examination were unremarkable for a premature infant.

Chest roentgenogram showed bilateral overexpansion, increased pulmonary blood flow, and an infiltrate present in the dependent portion of the left lower lobe. Analysis of arterial blood gases with a  $FI_{O_2}$  of 0.24 via an oxyhood were  $pH_a$  7.36- $Pa_{CO_2}$  38.5 mmHg,  $Pa_{O_2}$  65 mmHg, Hgb 14.9 g/dl.

Respiratory efficiency improved over the first five hospital days, but by the fifth hospital day the child developed a necrotizing enterocolitis. After administration of methicillin, ampicillin, and gentamicin, an exploratory laparotomy was scheduled on hospital day 6. Anesthesia was accomplished with halothane,  $N_2O$ , *d*-tubocurarine, and endotracheal intubation.

Extensive hemorrhage in the wall of the small and large bowel necessitated bowel resection. As much of the bowel as possible was spared, and laparotomy was to be repeated in 48 h to determine if more bowel had to be excised. The patient tolerated the procedure and anesthesia well with no evidence of cyanosis and was returned to ICN in stable condition.

On the eighth hospital day, laparotomy was performed again under identical anesthesia, except that the esophageal stethoscope, this time, was lubricated accidentally with anesthetic lubricant containing 20% benzocaine.‡ An estimated 0.5 g of the lubricant (100 mg ethyl aminobenzoate) was applied to the stethoscope.

No immediate postoperative or anesthetic complications were apparent. However, on return to ICN, the child became cyanotic with a  $FI_{O_2}$  of 0.25 and ventilator settings including a rate of 20 breaths/min, inspiratory pressure of 30 cm  $H_2O$ , and PEEP of 4cm $H_2O$ .  $FI_{O_2}$  was increased to 1.0 and the rate increased to 40 breaths/min with no improvement. The endotracheal tube was replaced, and analysis of arterial blood gases revealed at  $pH_a$  7.50  $Pa_{CO_2}$  14.7 mmHg,  $Pa_{O_2}$  201.5 mmHg, Hgb 14.2 g/dl.

Methemoglobinemia was suspected with a methemoglobin content ultimately found to be 83%.

The child immediately was given 2 mg methylene blue iv. Packed erythrocytes, 13 ml, which already had been typed and cross-matched for surgery also were transfused to add additional functioning hemoglobin to the blood. The methemoglobin level at this point was reduced to 40%.

An exchange transfusion of 201 ml of fresh whole blood was completed over 2 h. After this, no methemoglobin could be detected. The  $FI_{O_2}$  and respiratory rate then were decreased and the infant began spontaneous respiration. On the tenth hospital day no trace of methemoglobinemia was found.

After an extended hospital stay, he was discharged in stable condition and since has had closure of the ileostomy and is doing well.

### DISCUSSION

Methemoglobin is an abnormal oxidation product of hemoglobin in which the Fe moiety is in the ferric state and is unable to bind and transport elemental oxygen. Benzocaine (ethyl aminobenzoate) has been associated with acute methemoglobinemia in infants by several routes of exposure. Offending agents reported include dermatologic ointments,<sup>1</sup> rectal suppositories,<sup>2</sup> and an anesthetic lubricant used for the insertion of a rectal temperature probe.<sup>3</sup> This same benzocaine-containing product (Americaine Anesthetic Lubricant) was implicated in a case of methemoglobinemia after endotracheal intubation in a child of 38 months.<sup>4</sup> Our experience indicates that benzocaine, applied topically to the pharyngeal mucosa, can induce the formation of high levels of methemoglobin, and its use should be avoided in infants and small children.

In the normal adult erythrocyte, methemoglobin is produced continuously by various oxidizing agents but is reduced quickly to normal hemoglobin by an NADH-dependent methemoglobin reductase. In the adult, agents that accelerate the oxidation of hemoglobin to methemoglobin must be present in large amounts to overwhelm this system and produce clinically significant methemoglobinemia.<sup>5</sup> Infants, however, have a physiologic deficit of the enzyme and are at a much higher risk when exposed to an oxidant stress.<sup>6</sup>

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‡ Americaine Anesthetic Lubricant (Arnar-Stone Laboratories): Ethyl aminobenzoate 20% and benzethonium chloride 0.17%, in a water-soluble base.

Methemoglobinemia should be considered a possibility in any cyanosis without apparent cardiovascular or pulmonary etiology, especially if the cyanosis appears out of proportion to other signs and symptoms of hypoxia. Methemoglobin is a dark pigment, and the color of blood with high levels will appear chocolate brown and will not change upon agitation with room air. As in our case,  $P_{aO_2}$  may be high, even though the blood's total  $O_2$ -carrying capacity is decreased markedly causing tissue hypoxia.

The lethal blood level of methemoglobin is probably between 70 and 90%.<sup>6-8</sup> One case proved to be fatal at a level of 74% and a hemoglobin concentration of 8.7 g/dl.<sup>9</sup> Undoubtedly, the lethal level is dependent on other factors such as duration of methemoglobinemia before treatment, the general physical condition of the patient, and the hemoglobin concentration. The amount of functioning hemoglobin present in g/dl is figured by subtracting the nonfunctional methemoglobin from the total hemoglobin concentration. We call this the "effective hemoglobin concentration" and believe it gives a more accurate indication of the severity of the problem than does a simple methemoglobin percentage. By this method, the patient mentioned above had an "effective hemoglobin concentration" of 2.3 g/dl ( $8.7 \text{ g/dl} - [0.74] [8.7 \text{ g/dl}]$ ), and our patient had essentially the same level at 2.4 g/dl. The fact that this low a level of functioning hemoglobin was sustained without obvious sequelae of hypoxia is fortunate and is probably due to the rapidity with which the situation was reversed and to the high  $FI_{O_2}$  that the infant was given throughout the episode.

Specific therapy in methemoglobinemia is aimed at restoring the  $O_2$ -carrying capacity of the blood. Methylene blue in an iv dose of 1-2 mg/kg acts rapidly *in vivo* as an electron carrier in the reduction of methemoglobin

to normal hemoglobin. Blood transfusion is another rapid and simple measure that may be necessary to provide additional functioning hemoglobin to the bloodstream. As in our case, exchange transfusion may be considered when high levels of methemoglobin are present in an infant.<sup>10</sup>

Acute methemoglobinemia can be a serious, even life-threatening, reaction to the use of benzocaine-containing products in infants and small children. It can be diagnosed with relative certainty without time-consuming laboratory studies, and, in most cases, can be effectively treated with methylene blue and/or blood transfusion. Even if methemoglobin levels are very high, prognosis appears excellent if the problem is recognized early and therapy begun quickly.

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## Temperature-related T-Wave Changes during Thoracotomy

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Electrocardiographic changes due to whole body hypothermia<sup>1,2</sup> and hyperthermia<sup>3,4</sup> are well known. Much less appreciated are electrocardiographic (EKG) changes

in animals due to heating and cooling of the epicardial surface of the heart.<sup>5-8</sup> The only possible clinical paradigm of these latter animal experiments is to bathe the heart

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