Potential Interference by Hydroxocobalamin on Cooximetry Hemoglobin Measurements During Cyanide and Smoke Inhalation Treatments

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Study objective: Concentrated aqueous solutions of hydroxocobalamin (OHCoB) are administered intravenously for cyanide poisoning victims, many of whom also have concurrent smoke inhalation. Because of its intense light absorbance in visible wavelengths (absorption peak at 532 nm), we investigate potential interference effects of OHCoB on total hemoglobin concentration (tHb), carboxyhemoglobin (COHb), methemoglobin (MetHb), and oxyhemoglobin (Hb-O2) cooximetry measurement values in blood.

Methods: In vivo cooximetry measurements were conducted with 3 specific pathogen-free white New Zealand rabbits (3.80±0.21 kg) during the intravenous infusion of OHCoB (625 mg during a 100-minute period). Resultant changes in tHb, Hb-O2, COHb, and MetHb values were measured and correlated with respect to estimated in vivo OHCoB concentrations. In vitro measurements were conducted with rabbit blood to confirm in vivo measurements.

Results: The introduction of OHCoB clearly interfered with the cooximetry measurements of each of the hemoglobin component fractions in whole blood and resulted in altered measurement values from the baseline values. The presence of OHCoB in blood interferes with cooximetry measurements of COHb, MetHb, and Hb-O2. The increase in measured COHb fraction with increasing concentrations of OHCoB was most notable.

Conclusion: The presence of OHCoB in blood interferes with cooximetry measurements of COHb, MetHb, and Hb-O2. These effects need to be considered during OHCoB treatment of cyanide poisoning, particularly in smoke inhalation victims with potential for concurrent carbon monoxide exposure, because it may lead to potentially erroneous reported COHb levels. [Ann Emerg Med. 2007;49:802-805.]

SEE EDITORIAL, P. 814.

INTRODUCTION

Hydroxocobalamin (OHCoB) has been proposed as an alternative antidote to the well-known cyanide antidote kit for cyanide poisoning associated with smoke inhalation and other types of cyanide exposure and has been used successfully in Europe, with a better risk:benefit ratio than a cyanide antidote kit.1-3 OHCoB combines with cyanide to form essentially nontoxic cyanocobalamin (vitamin B12), which is excreted in the urine. The conventional cyanide antidote kit approved for use in the United States involves induction of methemoglobinemia with nitrates (amyl nitrite or sodium nitrite) because the methemoglobin (MetHb) binds CN more avidly than cytochrome c oxidase, which allows improved tissue oxygenation by unblocking the electron transport chain effects of CN but does reduce functional circulating hemoglobin because the MetHb that is formed is not effective in oxygen

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Editor’s Capsule Summary

What is already known on this topic
Hydroxocobalamin (OHCob) (an antidote for cyanide poisoning) is used in Europe and has advantages over agents currently available in the United States. Because of its intense color, OHCob may interfere with laboratory analyses based on light absorption.

What question this study addressed
Whether OHCob interferes with spectrophotometric measurements of carboxyhemoglobin, methemoglobin, and oxyhemoglobin.

What this study adds to our knowledge
In this rabbit model, OHCob altered spectrophotometric measurements of hemoglobin fractions.

How this might change clinical practice
Because cyanide poisoning is often due to fire, it frequently coexists with carbon monoxide poisoning. Those planning to use OHCob must consider alternate means of measuring hemoglobin fractions because cooximetry is likely to be inaccurate.


to examine the influence of light absorption by OHCob on cooximetry readings at different OHCob concentrations.

MATERIALS AND METHODS

Specific molar extinction coefficients of OHCob at visible and near-infrared wavelength ranges (450 nm to approximately 1000 nm) were measured using a spectrophotometer (Beckman DU650; Beckman Instruments Inc., Fullerton, CA) to compare the absorption spectra of OHCob with relevant hemoglobin species from the literature.

In vivo studies were conducted with 3 specific pathogen-free New Zealand white rabbits (Western Oregon Rabbit Supply, Philomath, OR), weighing 3.80±0.21 kg. The animals were anesthetized, intubated, and mechanically ventilated. Blunt dissection was performed to isolate the femoral artery and vein on the left thigh for the blood sampling and OHCob infusion, respectively. Seven hundred fifty milligrams of OHCob were dissolved in 60 mL of normal saline solution, and the solution was infused at 0.5 mL/minute. The total infused volume was 50 mL. A total of 625 mg of OHCob was infused during a 100-minute period. As a result, the average dose was 165 mg/kg, and infusion rate was 6.25 mg/minute. The in vivo concentration of OHCob was estimated with a 2-compartment open model for the constant intravenous infusion and pharmacokinetic data from the literature. Blood samples were taken 3 times (40, 80, and 100 minutes [rabbit 1] and 30, 60, and 100 minutes [rabbits 2 and 3] after OHCob infusion started) and cooximetry measurements were performed. On-site cooximetry measurements (AVOXimeter 4000; AVOX Systems, San Antonio, TX) were conducted to measure Hb-O2, COHb, MetHb fractions, and total hemoglobin concentration (tHb).

The cooximeter was calibrated specifically with rabbit blood by the manufacturer for the research purposes of these studies.

In an attempt to isolate the effect on cooximetry results from the infusion of OHCob and evaluate the dose effect of OHCob on cooximetry readings, in vitro measurements using whole blood were conducted at different OHCob concentrations from low to high ranges. The whole blood was acquired from the femoral artery of a different rabbit under the same anesthetic protocol and ventilation settings as those used in the in vivo studies. Twelve milligrams of OHCob was mixed with 5 mL of the rabbit whole blood to make a 1.784 mM concentration solution, and it was further diluted with whole blood to 0.892 mM and 0.382 mM.

RESULTS

Specific molar extinction coefficients shown in Figure 1 clearly demonstrate that spectral overlap exists between OHCob (solid line) and hemoglobin species in visible and near-infrared wavelength ranges. This spectral overlap may lead to erroneous cooximetry measurements.

The cooximetry reports tHb (g/dL) and the absolute fractional percentages of Hb-O2, COHb, and MetHb in tHb. The baseline cooximetry values of the in vivo arterial whole blood were 14.37 g/dL (tHb), 99.03% (Hb-O2), 0.80%
(COHb), and 0.63% (MetHb), respectively. With increasing concentration of OHCob in the whole blood, tHb, MetHb percentage, and COHb percentage values increased, whereas Hb-O2 percentage decreased. The correlation coefficient values between estimated in vivo OHCob concentrations and changes in cooximetry values for tHb, Hb-O2 percentage, COHb percentage, and MetHb percentage are 0.56, 0.701, 0.725, and 0.697, respectively. The change in COHb percentage was most noticeable at the end of OHCob infusion (6.63 ± 1.70%, mean ± SD). Figure 2 shows the relationship between the estimated in vivo OHCob concentration and changes in COHb percentage values.

The effect of OHCob on cooximetry values during in vitro blood measurements is illustrated in Figure 3. The baseline cooximetry values of the arterial whole blood were 14.32 g/dL (tHb), 99.25% (Hb-O2), 0.35% (COHb), and 0.05% (MetHb), respectively, before OHCob infusion. With increasing concentration of OHCob in the whole blood, a similar pattern was observed during in vitro measurements and in vivo measurements, and noticeable changes were observed in Hb-O2 percentage and COHb percentage, up to −7.9% and 14.7%, respectively. These results demonstrate the close relationship between increasing OHCob concentration and artifactual changes in cooximetry values observed during in vivo measurements.

LIMITATIONS

Because the pharmacokinetic measurement of whole blood OHCob for the rabbit was not available, the in vivo concentration of OHCob was estimated for these studies with a 2-compartment open model based on published experimental results of pharmacokinetics in dogs. Also, our model used a slow continuous intravenous infusion rather than a bolus infusion. Bolus injections could lead to even greater measured interferences if blood is withdrawn near peak concentration times. Differences in animal species and possible variation in pharmacokinetic data can potentially affect the estimation of OHCob concentration used in this evaluation.

DISCUSSION

Our results from both in vitro and in vivo cooximetry measurements of blood containing OHCob show that artifactual changes in measured hemoglobin fractions should be
considered when OHCoB is used to treat cyanide poisoning and smoke inhalation. The increase in measured COHb percentage values caused by the spectral interference by OHCoB is of concern because of simultaneous occurrence of cyanide and carbon monoxide poisoning in fire victims because cooximetry is the primary tool to diagnose and monitor COHb levels. Because the peak plasma levels of OHCoB have been reported to range from 356 to 1286 mg/L (0.267 to 0.956mM),10 we believe that measurement error effects may be clinically relevant. From the experimental results, the interference caused by OHCoB absorption spectrum on cooximetry might reach clinically important levels in some special cases, such as during continuous OHCoB infusion, blood sampling obtained shortly after bolus injection, or immediately upstream from the OHCoB bolus or infusion site (if venous samples are used).

In Retrospect

Our measurement results could have been strengthened if multiple cooximeters had been used and the in vivo concentration of OHCoB had been independently determined with other techniques rather than pharmacokinetic estimations used in this study. Despite that our data were measured with a single cooximeter, similar results are expected because similar visible wavelengths within this range are used in most commonly available cooximetry devices, and the broad absorption peaks of OHCoB would induce similar confounding effects. In addition, these studies were performed in animals with normal COHb levels. Future studies should be conducted in the presence of increased COHb levels to confirm the potential interference under these conditions.

In summary, even though this animal model evaluated animals throughout the limited range of normal COHB and MetHb and may not fully represent human clinical situations with truly increased COHb and MetHb levels, the presence of OHCoB in blood nevertheless interferes with cooximetry measurements of COHb, MetHb, and Hb-O2. These potential effects need to be considered during OHCoB treatment of cyanide poisoning, particularly in smoke inhalation victims with potential for concurrent carbon monoxide exposure.

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