Smoke Inhalation Injury in the Pregnant Patient. A literature review of the evidence and current best practices in the setting of a classic case.

Ensign Joseph D. Roderique M.A., Abel A. Gebre-Giorgis, M.D., Dane H. Stewart, Michael J. Feldman, M.D., Andrea L. Pozez, M.D.
The Evan-Haynes Burn Center, VCU Health Systems, Richmond Virginia.

1. Introduction

Smoke inhalation injury occurs infrequently in pregnant women, making the diagnosis, treatment, and management of this patient group challenging. One must be aware of the effects of carbon monoxide (CO) and cyanide (CN) poisoning on both the mother and the fetus. The size, age of the fetus, and the degree of poisoning allows for tremendous variability in the toxicity of CO, CN, and their respective treatment options. Furthermore, the pathophysiology of smoke inhalation injury in the unborn infant differs from the pathophysiology of the mother (1,2,3,4,5,6). Under steady state conditions, CO levels can reach 15% higher concentrations in the fetal circulation than in the maternal circulation (6). In addition, the fetus is more sensitive to the effects of CO, and is less likely to eliminate it from its circulation, even with adequate treatment (1,2,3,4,5,6). CN poisoning likewise carries greater risk to the fetus than the mother. In addition, animal studies have shown that combined CO and CN poisoning are more lethal than either one alone and at lower concentrations, and that this effect is further enhanced in the setting of low Oxygen levels such as occurs in structural fires (7).

We review the case of a 32 yr old female who was at 36 weeks of gestation (G2P1001) and admitted to the Burn Center after a house fire. She presented with cough and shortness of breath on admission. Examination revealed singed nasal hair and carbonaceous sputum. Inhalation injury was confirmed via bronchoscopy. She also had 3% Total Body Surface Area (TBSA) partial thickness flame burns involving her face, hands, and right foot. Initial treatment of her inhalation injury included 5 grams of intravenous Hydroxocobalamin (Cyanokit®) administered in the field by EMS. She was intubated, and received 6 hours of 100% oxygen therapy. Her initial Carboxyhemoglobin level was 1.7%, which rose to 3.0% at 5 hours post admission returning to the lowest value of 1.1 on hospital day 2. Of note, her cervix was fully closed and there was a non-distressed viable fetus on initial presentation.

2. Inhalation Injury

In the United States alone, smoke inhalation accounts for as many as 20,000 injuries every year (8). Moreover, deaths from smoke inhalation actually outnumber deaths from burns (8). However, there is a paucity of information regarding what percent of these injuries involve pregnant patients.

Inhalation injury is a complex process that arises from a variety of insults produced in a fire. Heat produced during a fire can injure the upper airway, and particulate matter generated from combustion can clog or irritate the airways. In addition, smoke inhalation has three primary asphixiant components (9). First, in the

setting of a structural fire in an enclosed space, there is an overall reduction in the partial pressure of oxygen in the structure, as oxygen is rapidly consumed by the fire. Second, there is production of CO as a result of the incomplete combustion of organic materials. Third, there is production of CN gas as a direct result of the combustion of synthetic materials, as well as natural materials like silk and wool. While any one of these toxicities can occur on its own depending upon the nature of the situation, it should be assumed that all three have occurred when a patient has been involved in a modern structural fire, even when there is no other evidence of injury (10). We will focus here on the asphixiant nature of the injury and appropriate treatments, as it applies to the pregnant patient and her child.

3. Cyanide

CN is a single Carbon triple bonded to a Nitrogen, and may be encountered either alone, or as part of an organic or inorganic compound. CN can therefore exist as a solid salt, or as a liquid or gas. CN has many different sources. However, in Western countries, smoke inhalation from structural fires is the most common cause of CN poisoning, (11), and a prospective study by Smith and colleagues indicated that CN poisoning can contribute independently and markedly to illness and death in smoke inhalation (12,13). In a structural fire, CN gas is produced from the combustion of most modern synthetic polymers, as well as some natural materials like wool, and silk. These materials contain carbon and nitrogen and produce CN gas when sufficiently heated (9,14,15). Accurate epidemiologic data on the incidence of CN toxicity in general, and especially in the setting of inhalation injury is scarce (16). The problem with this data is that lab values for CN are often not recorded or even obtained since this process can take days depending on the lab (12). Furthermore, most providers will administer treatment on an empiric basis since CN is so rapidly fatal, rendering a lab diagnosis unnecessary. Therefore we can assume that the occurrence of CN toxicity in the setting of smoke inhalation is much higher than what the statistics would indicate. This is supported by several prospective trials in which CN levels were measured in patients with smoke inhalation (12,13). However, to our knowledge, little information exists regarding the pathophysiology, diagnosis, or treatment of cyanide poisoning in the pregnant patient.

3.1 Pathophysiology of Cynanide

CN is rapidly fatal because it diffuses into tissues and binds to targets within seconds, the most rapid onset being seen with inhaled exposure (15,17). The primary mechanism of CN toxicity is its affect on aerobic cell metabolism. CN reversibly binds to the cytochrome oxidase a3 within the mitochondria causing intracellular hypoxia. CN completely stops oxidative phosphorylation in the cell by binding to the ferric ion at the terminal enzyme in the Krebs cycle (12,15). The Electron Transport Chain is stopped, and as a result the cell is unable to produce ATP (13). Thus, even in a high oxygen environment, cells are unable to use oxygen for ATP synthesis, resulting in a shift of the cell's metabolism to anaerobic metabolism, and lactate formation and ultimately a high- anion-gap metabolic acidosis ensue (12,15). The inability of the cells to use oxygen also leads to an accumulation of oxygen in the venous supply. Therefore, while arterial blood gases may be normal, a venous blood gas will show abnormally elevated oxygen levels resulting in a reduced arteriovenous oxygen saturation difference (<10 mm Hg)(13). Some CN also binds to the ferric form of hemoglobin making this type of hemoglobin incapable of transporting oxygen (12). In fact, CN binds preferentially to the ferric form of hemoglobin, a fact used by Chen and Rose to create the CN Antidote Kit (15,18). The normal physiologic mechanism of CN excretion is formation of thiocyanate by the liver. CN is converted to thiocyanate by hepatic Rhodanese and is then renally excreted (15,17). Unfortunately this mechanism is quickly overwhelmed by high doses of CN in the acute setting and in patients with kidney disease or decreased Creatine Clearance (17).

3.2 Diagnosis of CN poisoning

Serum CN concentrations of as little as 0.5 mg/L are associated with acute CN poisoning (11). As was stated earlier, however, this value is of little clinical value because of CN's rapid onset and mechanism of action. Moreover, serum CN concentrations are not predictive of disease severity in an individual. Borron and

colleagues noted that serum lactate may be a better predictor of disease severity, as well as assist in rapid assessment of a patient when CN toxicity is suspected (11). According to this study, serum lactate levels greater than 8 mmol/L were associated with acute poisoning (11). However, one should keep in mind that lactic acidosis is not specific to CN poisoning, and since CO binds to myoglobin as well as hemoglobin this can be a confounding factor in the setting of smoke inhalation (11).

3.3 Treatment Options: Cyanide Antidote Kit and Hydroxocobalamin

Acute CN toxicity is a life-threatening condition, but can be corrected when it is quickly recognized and immediately treated with the appropriate medications. Delaying administration of medical treatment allows time for hypoxic brain injury, cardiovascular compromise, and death within minutes to hours (19,20). Before 2006, the "Cyanide Antidote Kit" (A kit containing amyl nitrite, sodium nitrite, and sodium thiosulfate) was the only option for treatment of acute CN toxicity in the United States. While this kit has saved many lives, unnecessary administration of the Cyanide Antidote Kit can harm the patient due to its high potential for toxicity and multiple drug interactions (11). The toxic potential of the Cyanide Antidote Kit meant that treatment for suspected CN toxicity could only be administered by a physician in the hospital setting. There are no direct tests for rapid confirmation of CN toxicity. While lab values such as plasma lactate and venous blood gas are suggestive, the diagnosis of acute CN poisoning must often be made empirically. Signs of inhalation injury especially in the setting of altered mental status are sufficient to make the presumptive diagnosis of acute CN poisoning. In this setting it is imperative that administration of medical treatment is not delayed. With FDA approval of Hydroxocobalamin (Cyanokit®) in 2006 in the United States, a treatment which was safe enough to be rapidly administered in the pre-hospital setting was finally available (14,15,19). In addition to prompt administration of either the Cyanide Antidote Kit or Hydroxocobalamin, the administration of 100% oxygen by non-rebreather mask or endotracheal tube is also indicated in acute poisoning since it may compete with CN for the cytochrome oxidase a3 binding sites (9).

3.3.1 Cyanide Antidote Kit

The Cyanide Antidote Kit has been used for decades in the United States for acute CN poisoning (15,18). This kit consists of 3 separate medications that must be given in a very specific sequence in order to be effective: amyl nitrite, sodium nitrite, and sodium thiosulfate. Amyl nitrite is administered via inhalation over 15 to 30 seconds while sodium nitrite is administered intravenously over 3 to 5 minutes. These nitrites oxidize the iron in hemoglobin, thereby forming methemoglobin (15). CN appears to bind preferentially to the ferric ion of methemoglobin rather than to the ferric ion of the cytochrome oxidase a3 in the mitochondrial membrane. Since CN is reversibly bound to cytochrome oxidase, methemoglobin is effectively able to extract CN from the mitochondria and reverse its toxic effects on the electron transport chain. The cells are once again able to generate ATP, and the production of lactic acid decreases to more normal levels. The third and final drug of the Cyanide Antidote Kit, sodium thiosulfate, is then administered intravenously over 30 minutes. Sodium thiosulfate acts as a sulfhydryl donor (15). Unbound, extracellular CN binds the sulfhydryl group of thiosulfate forming thyocyanate which is then excreted by the kidneys (15). Unless the 2 nitrites are administered first, the administration of sodium thiosulfate will have little to no effect. Unless CN is drawn out of the mitochondria by the formation of methemoglobin, the sodium thiosulfate will be unable to cause the formation of thiocyanate extracellulary, and will instead merely function as a sulhydryl donor to the hepatic rhodanese enzyme. This is insufficient for alleviating acute CN toxicity.

3.3.2 Hydroxocobalamin

Although used widely in Europe for almost 30 years, Hydroxocobalamin (Cyanokit®) did not receive FDA

approval for the treatment of acute CN poisoning until December 2006 (21,22). “The starting dose of hydroxocobalamin for adults is 5 g (i.e., both 2.5 g vials) administered as an intravenous infusion over 15 minutes (approximately 15 mL/min), i.e., 7.5 minutes/vial. Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by intravenous infusion for a total dose of 10 g. The rate of infusion for the second dose may range from 15 minutes (for patients in extremis) to two hours, as clinically indicated. Each 2.5 g vial of hydroxocobalamin for injection is to be reconstituted with 100 mL of diluent (not provided with Cyanokit®) using the supplied sterile transfer spike. The recommended diluent is 0.9% Sodium Chloride injection (0.9% NaCl). Lactated Ringers injection and 5% Dextrose injection (D5W) have also been found to be compatible with hydroxocobalamin and may be used if 0.9% NaCl is not readily available.

To our knowledge, there are no adequate or well controlled studies of hydroxocobalamin in pregnant women, and should thus be used only if the potential benefits are deemed to be greater than the potential risks to the fetus (23). In studies performed on rats and rabbits it was demonstrated that when hydroxocobalamin was administered in high doses during organogenesis, there was an increased number of embryofetal resorptions and fewer live fetuses. In rats, fetal weight was decreased, and incomplete skeletal ossification occurred in both. There was a dose dependent increase in anomalies of soft and skeletal tissue in rabbit litters and fetuses (23).

Unlike the CN antidote kit, Hydroxocobalamin does not depend upon the formation of methemoglobin for its efficacy, but directly binds CN and then uses both hepatic and renal mechanisms to excrete it from the body. Hyrdoxocobalamin works first by binding with CN to form nontoxic Cyanocobalamin (vitamin B12) which can be renally excreted. Second, Cyanocobalamin can slowly release CN in the liver to allow hepatic rhodanese to convert it to Thiocynate which can also be renally excreted (24). Like methemoglobin, CN has a greater affinity for Hydroxocobalamin than for the cytochrome oxidase a3 within the mitochondria. However, because Hydroxocobalamin does not form methemoglobin, it can be safely used to without compromising the oxygen-carrying capacity of hemoglobin (12). This feature is especially important for pregnant patients and those with concomitant CO poisoning whose Oxygen-binding capacity is already reduced. The safety and efficacy of this treatment has been confirmed by several studies, and supported by evidence from Europe where it has been in use for nearly 3 decades (12,25,26,27).

The most common side effects are reddening of the skin and urine (25). This phenomenon is due to the color of the drug itself, and typically resolves in 2-3 days. Because of its red color, it can also interfere with several lab tests, including: bilirubin, creatinine, magnesium, serum iron, serum aspartate aminotransferase, carboxyhemoglobin, methemoglobin, and oxyhemoglobin. However, it is important to note here that this interference is minimal and has not been associated with any clinically meaningful changes (14,28). Another important side effect of administration is a transient increase in blood pressure. Some studies have indicated that this is due to Hydroxocobalamin’s inhibition of Nitric Oxide synthase, as well as direct clearing of Nitric Oxide from the blood (25). However, this effect is not pathological, and is generally considered beneficial, especially in those patients who become hypotensive due to the toxic effects of CN. This transient increase in blood pressure should not be treated, but close observation is recommended (20,25). One important potential problem is in patients requiring hemodyalysis. An interesting case report noted that the red color of hydroxocobalamin triggered an alarm on the dialysis machine, causing it to shut down. It appears that the compound binds to the dialysis membrane, staining it red and causing the machine to perceive that blood is being lost through the membrane. This is apparently something which cannot be overridden, and may prevent hemodyalysis from occuring until the hydroxocobalamin has been sufficiently flushed from the system. (29)

4. Carbon Monoxide

CO works by many of the same pathways as CN, but has a different preference. Like CN, CO inhibits transport, delivery, and utilization of Oxygen. Unlike CN, CO's primary and preferred mechanism of toxicity is interference with Oxygen delivery by binding to both hemoglobin and myoglobin. However, CO also binds to and inhibits cytochrome oxidase a3 and cytochrome P-450. There are additional studies that suggest other mechanisms of CO mediated toxicity, including reoxygenation and reperfusion injury (30). CO also causes lipid peroxidation and the production of free oxygen radicals (31,32).

4.1 Pathophysiology of Carbon Monoxide in the Fetus:

The pathophysiology of CO in the fetus is more insidious and can have extremely detrimental consequences even when the mother appears healthy. CO appears to pass through the placenta by both passive and facilitated diffusion (1,3,4,5,6). CO diffusion capacity across the placenta increases proportionally with gestational age and fetal weight (5). This is attributable to the rate of placental blood flow and maternal hemoglobin concentration (33). The levels of carboxyhemoglobin exhibit a delayed accumulation in the fetal circulation which is attributable to the slow dissociation of CO from maternal hemoglobin (33,34). Fetal tissue hypoxia occurs through two mechanisms: decreased Oxygen diffusion into the fetal circulation and by direct toxicity as CO crosses the placental membrane. Carboxyhemoglobin in the maternal circulation dramatically increases the binding affinity of hemoglobin for Oxygen (a left-shift of the dissociation curve) while simultaneously displacing Oxygen from available binding sites on the hemoglobin molecule. Together, these effects cause a dramatic decrease in Oxygen transport across the placenta (33). The percent saturation of Oxygen in the fetal circulation is diminished and the fetus is unable to increase cardiac output to compensate for this decrease in oxygen saturation (6). Even when CO has not yet crossed the placenta the fetus is already suffering from hypoxia due to the diminished levels of Oxygen present in the maternal blood (33,35). Ultimately, CO will cross the placental barrier and combine with fetal hemoglobin. Possibly due to the structural differences of fetal hemoglobin, the carboxyhemoglobin levels in the fetus are approximately 10%–15% higher than in the maternal circulation (1,6). Both accumulation and elimination are slower in the fetus with maximal fetal concentrations of CO occurring about four hours post exposure (6).

It is therefore no surprise that the fetal morbidity and mortality associated with acute CO poisoning is significant. Besides stillbirth and fetal distress, some studies have indicated an association of CO with potential teratogenic effects, although these results remain controversial (36). In the case presented in this paper, as the inhalation injury was experienced during the later stages of gestation, the risk of teratogenic effects was significantly low. Although CO exposure may result in hypoxic injury during any trimester, the fetal brain seems to be most sensitive during late gestation when the bulk of brain development is occurring (37).

Unfortunately, fetal death can still occur even when the mother appears healthy (4,5,6,38). The severity of damage depends on the degree and duration of hypoxia or asphyxia. Moreover, the maternal carboxyhemoglobin level is only helpful in confirming exposure and does not predict outcomes. While more severely elevated CO levels tend to be associated with less favorable outcomes, a Since CO tends to concentrate in the fetus, the maternal carboxyhemoglobin is not a reliable indicator of fetal hemoglobin and there are numerous anecdotal reports of cases where the fetus suffered an undesirable outcome despite minimal symptoms in the mother and apparently unconcerning carboxyhemoglobin levels (34,35). This is one of many reasons why smoking tobacco during pregnancy is so harmful to the fetus.

4.2 Treatment options for Carbon Monoxide Toxicity

On room air, the half-life of carboxyhemoglobin is about 5 hours. 100% Oxygen delivered through a non-rebreather mask can reduce the half-life of carboxyhemoglobin to about 1 hour (39). Reducing maternal carboxyhemoglobin is currently the only method of reducing fetal carboxyhemoglobin levels, short of delivering the fetus (1).

Besides normobaric oxygen, the only other available treatment option for CO poisoning is hyperbaric oxygen therapy (HbOt). The utility of this therapy remains a hotly debated subject, and at the time of publication there were no established guidelines for its use beyond institution specific policies. The reason that HbOt continues to be researched and discussed is due to the complex and prolonged nature of CO poisoning. Normobaric oxygen is capable of a relatively rapid reduction in the carboxyhemoglobin levels in patients, as noted above. However, many patients experience prolonged neurologic sequelae (PNS) for months or years after exposure, even when appropriate traditional therapy is quickly delivered. The precise mechanism and severity of these sequelae has unfortunately remained elusive (39,40).

It is very difficult to establish an accurate pre-exposure baseline of neurologic functioning in patients exposed to CO. This makes it difficult to establish the nature and severity of the changes experienced by patients following exposure to CO. Furthermore, the accuracy of neuropsychologic testing used in evaluating patients post-exposure, is likewise often called into question. Many older studies appear to have been either prospective or retrospective studies which carry little weight for making treatment recommendations (41). There have been some excellent randomized trials which have been performed in recent years (40). These have appeared to show benefit in using HbO therapy, however the studies have not been multicenter trials and thus lack generalizability. Moreover, these studies have varied in their selection of patients, and treatments, making attempts at Meta-Analysis difficult. A recent meta-analysis indicated that the use of HbOt could not be recommended based on any of these randomized trials for the reasons just indicated (39).

The other challenge facing HbOt is a lack of good understanding of the pathophysiology behind these prolonged neurologic sequelae. Several smaller in vitro and animal studies appear to indicate that the cytochrome oxidase system remains inhibited even when carboxyhemoglobin levels drop to undetectable levels (30,31,39,41). This means that neurons and other cells in the body are incapable of producing ATP even in a high oxygen environment. The current theory is that HbOt is somehow able to overcome this inhibition reducing delayed neuronal death. Other possibilities include Lipid peroxidation, which damages cell membranes and possibly the myelin sheath (3,4, 31,32,). Since this reaction is capable of self-propagation, there is the concern that damage continues even when the patient no longer appears to have carbon monoxide poisoning. Again, the theory is that HbOt is able to stop this progression and thereby reduce he prolonged neurologic sequelae reported by so many patients (39,41). Some authors have additionally proposed that use of HbOt in persons with smoke inhalation injury, versus pure CO poisoning (as in a suicide attempt) may be detrimental since there were concerns that HbOt might raise the CN levels in whole blood even as it decreased CO levels. A recent study appears to show that these concerns are unfounded (42). Nevertheless, HbOt continues to face major obstacles.

Until a large multicenter randomized control trial can be performed, and until the mechanisms for prolonged neurologic sequelae can be elucidated, the use of HbOt will remain controversial and unproven to the medical community at large (39). Even if these studies are done, and HbOt is proven effective and worthwhile, there remain significant hurdles to it use. Protocols for dosage of HbO and transfer of patients to large centers equipped with such technology would also need to be established, and could take years to develop even if HbOt were proven. Perhaps, through a better understanding of the precise pathophysiology

of PNS in CO poisoning we will be able to develop targeted adjunct medical therapies capable of preventing these processes, without the need for use of HbOt.

5. Case Summary:

On hospital day 4, post extubation, our patient underwent spontaneous labor and subsequently delivered a 2.7kg, male child, with a normal APGAR score. On delivery it was noted that the amniotic fluid as well as the baby's urine was stained bright pink by the Hydroxocobalamin. The initial fetal Carboxyhemoglobin level was 8.1% and fetal CN level was undetectable. The infant was admitted and observed in the Neonatal Intensive Care Unit for the first 24 hours after birth. He was placed on 100% O2 NRB. CO levels were undetectable after 72 hours and both patients were discharged to home without further complications. At the time of submission of this article followup appointments over a period of 5 months showed a very healthy male child with no obvious anatomical or developmental defects. To date, the child has met all developmental milestones.

Currently, the only treatment available for CO poisoning in the fetus is administration of 100% oxygen therapy to the mother, or use of a hyperbaric chamber, a topic which remains a controversial subject. However, in a smoke inhalation patient, CO is rarely the sole toxin and is often found in combination with CN poisoning. As was demonstrated in animal studies, CN drastically increases the toxicity of CO by lowering its LD50, and thus it may be considered that treating the CN poisoning is also an indirect treatment for the CO toxicity (7). Hydroxocobalamin is the only antidote safe enough to use in a pregnant patient, and its ability to cross the placental barrier is well documented and is illustrated in our case. While the absolute safety of Hydroxocobalamin in pregnancy has yet to be established, the toxic effects of combined CN and CO poisoning are well understood and documented. The diagnosis of inhalation injury is unfortunately one which must be made empirically, since failure to do so can result in serious and rapidly fatal consequences.

6. Conclusion:

The literature shows that Hydroxocobalamin crosses the placental barrier. Combining this knowledge with a proper understanding of the pathophysiology of smoke inhalation injury encourages us to inquire whether use of Hydroxocobalamin may be considered a viable treatment option not only for the mother, but for the fetus as well. Since CO and CN have synergistic effects when both are present in the bloodstream, the prompt administration of Hydroxocobalamin not only eliminates the direct effects of CN, but also removes its synergistic effects on CO. This means that following administration of Hydroxocobalamin, a higher concentration of CO would be necessary to achieve lethal effects in someone with combined CO and CN toxicity. It should be assumed that both CN and CO are present in all modern structural fires and that any person presenting with signs of smoke inhalation injury has at least some level of intoxication from these substances. Since these two toxins concentrate at even higher levels in the fetus than the mother, prompt administration of Hydroxocobalamin along with 100% oxygen therapy are vital interventions for saving the life of not only the mother but the fetus as well. Such conclusions are supported by empiric evidence and logic, based upon a sound understanding of the basic mechanisms of this disease and its treatments. Our review of the literature has shown that Hydroxocobalamin is at least as effective as the "Cyanide Antidote Kit", in reducing whole blood cyanide levels. It has also shown that the Cyanide Antidote Kit has many drug interactions and is contraindicated for use in patients with smoke inhalation, and in pregnant women or women who could be pregnant. At this time, according to the FDA, there are no known drug interactions and no contraindications to the use of Hydroxocobalamin (43). Finally, our review has shown that the best outcomes are produced when treatment for smoke inhalation is administered early. Of the current treatment options, only 100% Oxygen and IV administration of Hydroxocobalamin are safe enough to be administered in the field. Currently the FDA recommends that Hydroxocobalamin be administered without delay in any case where smoke inhalation or cyanide toxicity is clinically suspected (43).

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