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All materials should be submitted to: Delaware Medical Journal, The Medical Society of Delaware, 900 Prides Crossing, Newark, Delaware 19713 or e-mailed to koj@medsocdel.org.
The Delaware Medical Journal (ISSN 0011-7781, USPS 152140) is published monthly by the Medical Society of Delaware at 900 Prides Crossing, Newark, DE 19713. Periodicals postage paid at Newark, Delaware, 19711 and additional entry offices. Copyright 2010 by the Medical Society of Delaware. Indexed in "Hospital Literature Index" and "Index Medicus." Available through University Microfilms. The Delaware Medical Journal does not hold itself responsible for statements made by any contributor or advertiser. Annual subscription rates are $30 for domestic and $45 for overseas. Single copies are $2.50. Advertising copy is accepted, subject to the approval of the Publication and Editorial Committee of the Medical Society of Delaware. For information about advertising, call the Journal office at (302) 366-1400. POSTMASTER: Address changes to 900 Prides Crossing, Newark, DE 19713.
“A Modest Proposal”
for Restructuring the Medical Society of Delaware

David M. Bercaw, M.D.

“I profess, in the sincerity of my heart, that I have not the least personal interest in endeavoring to promote this necessary work, having no other motive than the public good of my country.”

– Jonathan Swift, A Modest Proposal, 1729

In 2006 and 2007, in response to diminished membership engagement – especially at the county medical society level – the MSD House of Delegates adopted resolutions which established a Task Force to Study Governance & Activities of the County Medical Societies. The Task Force has met several times over these past years and its most recent proposal has now been accepted by the MSD Board of Trustees. It is planned for the proposal to be presented for a vote at the upcoming MSD House of Delegates in October. Acceptance of the Task Force’s proposal would pave the way for the most sweeping overhaul of MSD’s governance structure in its 222-year history. So how did this all come about?

The diminishing level of membership engagement in the county medical societies has been evident for years. Fewer members are stepping up into leadership roles, especially in Kent and Sussex Counties. Membership participation in the New Castle County Medical Society, while more robust, has still diminished significantly over the years. Multiple surveys demonstrated that physician members were mostly interested in social events and in continuing medical education. Under Delaware Law, the county societies are no longer permitted to participate in peer review and professional conduct processes, both of which had been duties established for the county medical societies under MSD Bylaws. Despite declining interest, the financial costs and administrative burdens of running the county societies have continued to escalate. It is time for a change.

The proposal from the Task Force would be to eliminate county medical societies as corporate structures with its officers and bylaws. The creation of less formal “districts” throughout the state, without corporate structure, but based upon smaller geographic areas would be developed. Examples of geographic districts could include:

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MSD President David M. Bercaw, M.D., is Vice Chair of the Christiana Care Health System Department of Family and Community Medicine and practices at the Family Medicine Center in Wilmington, Delaware.
President’s Page

- Eastern Sussex County
- Western Sussex County
- Milford area
- Dover area
- Middletown area
- Christiana/Newark area
- City of Wilmington/North Wilmington area
- Hockessin/Pike Creek area

MSD would assume responsibility for all programming, CME, social events, and other functions which were formerly conducted by the county societies. The districts, however, would serve as smaller, more cohesive member groupings which should result in improved member recruitment, leadership development, and grassroots engagement. Local leaders within each district would be identified to advise MSD on member engagement, leadership development, and advocacy issues.

Such sweeping changes can be accompanied by a more efficient and streamlined MSD governance in order to more effectively represent the needs of the membership [refer to charts on the next page]. The House of Delegates (which meets once each year and is currently comprised of 378 Delegates and Alternate Delegates) would be replaced by a Council (approximately 60 members who would meet at least twice yearly). Proposed members of the Council would include:
- Members of the Executive Board, (15) comprised of:
  - Officers (6)
  - AMA Representative (1)
- MSD Section Representatives (3)
- At-Large Representatives (4)
- Legislative Committee Representative (1)
- District Representatives (approximately 16 to 18 – two from each district)
- Specialty societies (approximately 25 – one from each American Board of Medical Specialties-recognized organization in Delaware)
- Practice type (8)

Having been involved in MSD leadership throughout the entire tenure of the Task Force, I have witnessed the process unfold and have taken part in the debates and deliberations of such a sweeping proposal. With tongue in cheek and a nod to Jonathan Swift, I fully support the “cannibalization” of the current county medical society system and the revamping, streamlining, and modernization of our entire MSD governance structure.

The MSD website, www.medicalsocietyofdelaware.org homepage contains a link to the full report: “A Proposal for Reorganizing the County Medical Society Structure and MSD Governance Structure.” Feel free to respond to MSD leadership via the link within the proposal. We look forward to hearing your thoughts.

David M. Bercaw, M.D.
President, Medical Society of Delaware

Save the Date

THE 222ND ANNUAL MEETING
of the
MEDICAL SOCIETY OF DELAWARE

SATURDAY, OCTOBER 22, 2011
House of Delegates Meeting at the MSD Conference Center
Inaugural Dinner Dance at the Wilmington Country Club
NATIONAL CANCER INSTITUTE CLINICAL TRIAL OF THE MONTH

CTSU S0777:
A Randomized Phase III Trial of CC-5-13 (lenalidomide, NSD-703813) and Low Dose Dexamethasone (LLD) versus Bortezomib (PS-341, NSC-681239), Lenalidomide, and Low Dose Dexamethasone (BLLD) for Induction, in Patients with Previously Untreated Multiple Myeloma without Intent for Immediate Autologous Stem Cell Transplant

The Objectives of the Trial are:
Primary Objective:
- The primary objective of this study is to compare progression-free survival (PFS) in patients with newly diagnosed myeloma treated with lenalidomide plus low dose dexamethasone versus bortezomib plus lenalidomide and low dose dexamethasone.

Secondary Objectives:
- Assess response using the new international response criteria.
- To bank specimens for future translational medicine research.
- Follow patients to assess overall survival and other long-term outcomes stratified by intent to transplant at progression.

Eligibility:
- Patients must have newly diagnosed multiple myeloma.
- Patients must have received no prior chemotherapy for this disease.
- Patients must have a Performance Status of 0 – 3.

Treatment:

Arm 1 – LLD: 6 cycles, each 28 days
Dexamethasone 40 mg/day PO days 1, 8, 15, 22
Lenalidomide 25 mg/day PO Daily at bedtime; days 1-21
Aspirin 325 mg/day PO Continuous

Arm 2 – BLLD: 8 cycles each 21 days
Dexamethasone 20 mg/day PO days 1, 2, 4, 5, 8, 9, 11, 12
Lenalidomide 25 mg/day PO Daily at bedtime; days 1-14
Bortezomib 1.3 mg/m2 IVP days 1, 4, 8, 11
Aspirin 325 mg/day PO Continuous

HSV prophylaxis per institutional standard.

For information regarding this clinical trial or if you would like to have the list of open protocols e-mailed to you, please call the Cancer Research Office at (302) 623-4450 or e-mail akee@christianacare.org.
Methemoglobinemia: A Systematic Review of the Pathophysiology, Detection, and Treatment

John Ashurst, D.O.¹ and Megan Wasson, D.O.²

Abstract

Methemoglobin is the oxidized form of hemoglobin which does not bind to oxygen efficiently. An increased level of methemoglobin can be attributed to congenital enzymatic defects, alterations in the hemoglobin molecule, or as a result of medications and toxins. The main clinical characteristic of the disease include cyanosis which is unresponsive to oxygen therapy and blood that is chocolate color when drawn. Co-oximetry is the gold standard for diagnosis but arterial blood gas paired with pulse oximetry and serum methemoglobin levels can confirm the diagnosis clinically. Treatment is aimed at removal of the offending agent, if medication induced, and is directed at aggressive oxygen therapy and treatment with the antidote, methylene blue.

Key words: Hypoxia, Congenital Methemoglobinemia, Drug-Induced Methemoglobinemia, Methylene Blue

INTRODUCTION

Methemoglobinemia is a clinical syndrome caused by either an increase of methemoglobin in the blood due to congenital changes in hemoglobin synthesis and metabolism or an acute adverse drug reaction. Methemoglobin is an oxidized form of hemoglobin in which the original ferrous atom is oxidized to a ferric atom. The ferric atom then causes an allosteric change in the heme portion of the oxidized hemoglobin molecule causing an increase in its oxygen affinity but a functional decrease in its oxygen binding capacity.¹ Physiologically, the newly formed methemoglobin shifts the oxygen dissociation curve of the oxidized hemoglobin to the left which hinders the release of oxygen in tissue.¹ Not only is the tissue hypoxia due to a leftward shift of the oxygen saturation curve but can also be related to the reduction of free hemoglobin to transport oxygen to the tissues (a relative anemia).¹ Clinically these two mechanisms will produce central cyanosis which is unresponsive to oxygen therapy.¹

The prevalence of the syndrome is difficult to determine due to the mild nature of many cases but must be within the differential of any patient with preoperative cyanosis, beginning a new medication, and any child living in an agricultural region. In this article, the pathophysiology, diagnosis, and management of hereditary and acquired methemoglobinemia will be discussed.

GENETIC DEFECT

Hereditary methemoglobinemia is a recessively inherited disorder which is attributed to the deficiency of the enzyme nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase.¹⁻⁵ Erythrocytes convert harmful methemoglobin into useful hemoglobin through their inherent cytochrome b5 reductase pathway.¹⁻⁵ However, the gene regulating the synthesis of NADH cytochrome b5 reductase has been localized to chromosome 22q13qter which has been noted to be involved in over 40 genetic mutations.¹⁻⁵ Due to these mutations, hereditary methemoglobinemia

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has been classified into two subtypes, erythrocyte (type I) and generalized (type II).1-5

In the type I form, only mature erythrocytes are affected due to a deficiency of the soluble form of the enzyme.1-5 Currently, type I is found worldwide but has been noted to be endemic in several population groups including the Athabasca and Navajo Native Americans in the United States and the Yakutusk in Siberia. Homozygous individuals present with a methemoglobin level varying between 10 percent and 35 percent.1 Due to the relatively low levels of methemoglobin present in the blood, patients present with central cyanosis and polycythemia while other symptoms of methemoglobinemia present only when the percentage exceeds 50 percent.1-5 Currently, the life expectancy of these individuals is not lower than the general population and potential pregnancies have not been complicated due to the disorder.1

Patients with the heterozygous form of hereditary type I methemoglobinemia typically have a cytochrome b5 reductase deficiency of approximately 50 percent as compared to the general population.1-5 Although there is an altered level of activity of the enzyme, it is sufficient in maintaining methemoglobin levels around one percent.1,5 However, conditions in which the body is placed under significant oxidative stress may induce an attack of acute or chronic methemoglobinemia. Hereditary type II methemoglobinemia is classified as a deficiency of the membrane bound form of cytochrome b5 reductase. Research has shown that type II methemoglobinemia occurs in all tissue types (including fibroblasts, lymphocytes, and cells from the central nervous system) because the enzyme deficiency is located in the outer mitochondrial membrane and the endoplasmic reticulum of all somatic cells.1-5 Currently type II is sporadic worldwide and presents with severe mental retardation, neurological impairment, and developmental abnormalities.1-5 Due to the severe nature of the neurological impairment which is unresponsive to methylene blue therapy, the life expectancy of the patients is severely diminished.1-5

Although two types of hereditary methemoglobinemia have been attributed to an enzyme defect, a third subtype has been distinguished as hemoglobin M and is attributed to abnormal variants of the hemoglobin molecule.1,6-8 In the majority of the cases, tyrosine replaces either the proximal or distal histidine in the alpha or beta chain of hemoglobin causing the formation of an iron-phenolate complex.1,6 This aberrant complex results in a diminished capacity of reducing the ferric form of iron into its divalent form of ferrous, ultimately leading to methemoglobinemia.1,6-8 Those patients affected with the alpha chain deficiency present with cyanosis at birth while those with the aberrant beta chain present with cyanosis later in life due to the conversion of fetal hemoglobin to adult hemoglobin.1,6-8 Hemoglobin M is inherited autosomal dominantly and does not affect the life expectancy of the affected individual.1

### DRUG INDUCED

Although several congenital forms of methemoglobinemia have been established, by far the most common cause is due to an acute drug reaction (Table 1).1,8-20 Over the years, numerous case reports have established that either the ingestion of or the exposure to skin and or mucous membranes can lead to an adverse reaction which causes methemoglobinemia.1,8-20 Most of the medications directly oxidize hemoglobin to methemoglobin, while others indirectly oxidize hemoglobin to methemoglobin by reducing free oxygen to a superoxide free radical.1,8-20

A major predisposition to the acquisition of drug induced methemoglobinemia would be the concurrent use of a hemoglobin oxidizing medication and having glucose 6 phosphate dehydrogenase (G6PD) deficiency. The nicotinamide adenine dinucleotide phosphate (NADPH) pathway, a second enzymatic system which reduces methemoglobin to hemoglobin, is directly dependent on both the activity of glutathione and glucose-6-phosphate dehydrogenase.17,21 However in those with a deficiency of G6PD, inherent levels of methemoglobin can not be efficiently reduced and an additive effect will be seen in the presence of increased hemoglobin oxidation.17,21

A second population group which must be closely monitored when given hemoglobin oxidizing agents would be those with liver cirrhosis.22
The red blood cells in those with cirrhosis are already under severe oxidative stress, especially in those where bleeding complications have arisen. Due to this, any increase in oxidative stress may lead to methemoglobinemia.22

Although patients with acquired methemoglobinemia due to toxin exposure can be severely ill when diagnosed, with appropriate treatment a full recovery is possible. Strict outpatient follow-up is recommended for those with acquired methemoglobinemia upon discharge from the hospital to ensure no recurrence of the disease process.

<table>
<thead>
<tr>
<th>Table 1: Drugs and toxins that can cause methemoglobinemia</th>
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<td>Bupivacaine hydrochloride</td>
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<td>Clofazimine</td>
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<td>Dimethyl sulfoxide</td>
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<td>Exhaust fumes</td>
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<td>Flutamide</td>
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<td>Lidocaine hydrochloride</td>
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<td>Methylene blue</td>
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<td>Nitrates</td>
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<td>Paraquat</td>
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<td>Phenazopyridine hydrochloride</td>
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<td>Prilocaine hydrochloride</td>
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<td>Rifampin</td>
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<td>Sodium valproate</td>
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<td>Sulfonamides</td>
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CLINICAL MANIFESTATIONS

The clinical manifestations of methemoglobinemia are directly related to the reduction in oxygen carrying capacity of hemoglobin which leads to hypoxia.1,8-12 Although the physiologic levels of methemoglobin range between 1-2 percent, when concentrations reach 10-15 percent central cyanosis is noted as well as a general grayish color of the skin.1,12-16 As levels reach 30 - 40 percent neurologic and cardiovascular symptoms are noted (headache, fatigue, tachycardia, weakness, and dizziness).1,14-20 Levels of 60 percent typically result in lethargy, convulsions, and coma.1,8-20 Some research has shown that the lethal level of methemoglobin is 70 percent, but survival has been reported when the methemoglobin concentration has reached 81 percent.1,8-20

However, many patients with lifelong methemoglobinemia are usually asymptomatic at relatively high levels. Although these patients can withstand these levels, patients exposed to drugs and toxins who abruptly develop the same concentration of methemoglobin may be severely symptomatic. Due to this, it has been proposed that not only the amount of methemoglobin in the blood but also the rapidity of methemoglobin formation will lead to a patient’s symptoms.1,8-20

A higher level of suspicion must be used when a patient has a co-morbidity. Patients with glucose 6 phosphate dehydrogenase deficiency have an increased risk of oxidation of hemoglobin to methemoglobin.21,23 Also, a form of idiopathic methemoglobinemia can occur in association with systemic acidosis in infants.24,25 Typically, this will occur in the first six months of life and is associated with dehydration and diarrhea.24,25 The disease process is exacerbated by the lower levels of functioning methemoglobin reductase enzyme found in infant’s blood.24,25

DIAGNOSIS AND MONITORING

Methemoglobinemia should be suspected in patients with central cyanosis and low oxygen saturations which are unresponsive to oxygen therapy.1,9-20 Currently in the clinical setting, arterial blood gas analysis paired with oxygen saturation by pulse oximetry and serum methemoglobin levels are now considered the definitive measures to make a diagnosis.1,9-20 However in an emergency setting, the presence of chocolate brown blood that does not turn red when exposed to atmospheric oxygen and a positive family history is indicative of methemoglobinemia.1,9-20,26
Typically in methemoglobinemia, arterial blood gas (ABG) will reveal a normal to elevated PO2 with low oxyhemoglobin saturation.\textsuperscript{1,9-20} Although arterial blood gasses (ABGs) are used in aiding in the diagnosis, new research has shown that ABGs should not be the sole diagnostic tool to assess the oxygen carrying capacity of methemoglobinemia.\textsuperscript{26,27} Currently, the conventional analyzers used for ABGs use a mathematical relationship for determining the value of hemoglobin saturation which is based solely upon the standard hemoglobin dissociation curve.\textsuperscript{26,27} Thus, in critically ill individuals or those with congenital methemoglobinemia the parameters that the machine sets will inaccurately measure the amount of saturated hemoglobin.\textsuperscript{26,27}

A low oxyhemoglobin detected by pulse oximetry can be pathognomonic for methemoglobinemia. Although pulse oximetry is one crucial tool in the diagnosis, it may also overestimate the true amount of saturated hemoglobin in the blood.\textsuperscript{7,8} A pulse oximeter is based on the fact that light absorption of both saturated hemoglobin and reduced hemoglobin will occur at the wavelengths of 660 nm and 940 nm.\textsuperscript{1,7,8,20,26,28-30} At these wave lengths, red and infrared light is absorbed in a 1-to-1 ratio.\textsuperscript{7} However, methemoglobin has two distinct peaks of absorption which lie at 630 nm and 960 nm.\textsuperscript{1,7,8,20,26,28-30} Due to the increasing levels of methemoglobin in the blood, the pulse oximeter will be insensitive to hypoxemia and would overestimate the degree of oxygen saturation. Further research has shown that when methemoglobin levels reach 30 percent or greater, oxygen saturation detected by a pulse oximeter would plateau at 85 percent and would be unchanged with oxygen therapy.\textsuperscript{7,8,20,26,28-30}

Although in a clinical setting arterial blood gas paired with pulse oximetry and a serum methemoglobin level will aid in the diagnosis of methemoglobinemia, in the research setting several other means for detection exist.\textsuperscript{20,26,28-30} The definitive means for detecting methemoglobinemia is by the use of a pulse co-oximeter. A pulse co-oximeter is an oversimplified spectrophotometer that measures the light absorbance of four different wavelengths in the blood.\textsuperscript{20,26,28-30} Due to the increased differentiation of wave lengths, a co-oximeter can distinctly measure the levels of hemoglobin, carboxyhemoglobin, oxyhemoglobin and methemoglobin in the blood.\textsuperscript{20,26,28-30} Further-more, the newer versions of co-oximeters can also detect sulfhemoglobin.\textsuperscript{20,26,28-30} However, due to the cost of these machines very few laboratories currently have them in use. Unfortunately, the presence of lipemic specimens and methylene blue in the blood will lead to elevated levels of methemoglobin.\textsuperscript{20,26,28-30} Thus, this method is not a reliable tool for following the trend of methemoglobin in a treated patient.\textsuperscript{20,26,28-30}

In those patients where sulfhemoglobin of the blood is suspected, the potassium cyanide test may aid in the diagnosis of methemoglobinemia.\textsuperscript{1,26,31} The methemoglobin in the blood will react with the cyanide to form cyanomethemoglobin.\textsuperscript{1,26,31} When a drop of this blood is placed on a swatch of white paper it will appear bright red.\textsuperscript{1,26,31} However, since sulfhemoglobin does not react with cyanide, there would be no change in color.\textsuperscript{1,26,31}

TREATMENT

Currently there is no cure for hereditary methemoglobinemia and these patients should avoid oxidizing medications at all costs.\textsuperscript{1-5} However, treatment can be aimed at the cosmetic defects (blue skin) of the disorder. It has been shown that 300 to 600 mg of ascorbic acid given three times a day orally is helpful in diminishing skin discoloration.\textsuperscript{2,3} Unfortunately, long term high dose management with ascorbic acid may result in the formation of sodium oxalate kidney stones.\textsuperscript{32}

Treatment of patients with drug induced methemoglobinemia should be guided by the severity of the symptoms initially. Secondly, treatment should be aimed at decreasing the amount of methemoglobin found in the blood.

When the patient’s symptomology is mild, treatment consists of removal of the offending agent as well as administration of high flow oxygen, observation, and serial evaluation with a co-oximeter.\textsuperscript{1,8-20} Typically, after removing the offending agent for 36 hours, the patient’s methemoglobin level will return to baseline. Research has shown that hyperoxic pulmonary ventilation can further accelerate the degradation of methemoglobin concentrations in those exposed to a lethal toxic ingestion.\textsuperscript{33}

When significant symptoms (dizziness, confusion, seizure, somnolence, headache etc.) are present methylene blue in association
with the aforementioned treatments should be conducted.1,8–20 Methylene blue is a thiazine dye which possesses dose-dependent antiseptic and oxidizing properties.1,8–20,34 Intravenously, methylene blue is oxidized into leukomethylene blue by accepting an electron from NADPH in the presence of NADPH-methemoglobin reductase.1,8–20,34 Leukomethylene blue then acts as an artificial electron acceptor to methemoglobin resulting in its conversion back to hemoglobin.1,8–21,34

The methylene blue dose is 1–2 mg/kg administered as a 1 percent solution over a five minute interval and should not exceed 7 mg/kg, because this agent in itself can be toxic and cause dyspnea, chest pain, and hemolysis.1,9–20 This dose may be repeated again at 1 mg/kg every 30 minutes as necessary.9–20 However, additional studies have shown that supplementing the methylene blue with activated charcoal will result in a lower dose of methylene blue being required to trigger a reversal of methemoglobinemia symptoms.36 Furthermore, IV dextrose should be given in conjunction with methylene blue.1,20 Dextrose is necessary to form NADPH through the hexose monophosphate shunt, which is crucial for methylene blue to be effective.1,20

Additionally, patients who have G6PD deficiency will not respond to methylene blue therapy.1,20 Patients with G6PD deficiency will not produce sufficient NADPH to reduce methylene blue to leukomethylene blue in the blood.1,20 Due to this, the relatively large doses of methylene blue used in treatment may result in higher levels of methylene blue rather than the oxidized leukomethylene blue. This then will result in hemolysis and a paradoxical methemoglobinemia in these patients.1,20 Current research has shown that the electron acceptor N-acetyl-cysteine can be used in these cases.1,35

Moreover, methylene blue therapy has not been FDA approved for the use in the pediatric population. Due to this, infants with idiopathic methemoglobinemia caused by metabolic acidosis should be treated with intravenous hydration and bicarbonate to reverse the acidosis.24,25 Furthermore, intravenous hydration should be accomplished by the use of 5 percent dextrose in water due to the increased need of NADPH for methemoglobin to be cleared.24,25 New research has also shown that methylene blue given intrasosseously will effectively lower the amount of methemoglobin in the blood.37

For those who fail original therapy with methylene blue or those who are severely symptomatic, exchange transfusion or hyperbaric oxygen therapy may be considered.1,38 Hyperbaric oxygen therapy will increase the amount of dissolved oxygen in the blood and will also bring the amount of carbon dioxide to the minimal limit that still allows metabolism to occur.33 Therefore, with hyperbaric oxygen therapy one can maintain oxygenation until exchange transfusion can be assembled.

Further experimental research has shown that the use of cimetidine and ketoconazole can be used in the long-term management of decreasing methemoglobin levels in those with an enzyme deficiency or those who need to be on oxidizing medications for long term management of chronic illnesses.39,40

**CONCLUSION**

Currently, methemoglobinemia is a syndrome with many unknowns. Prevalence, modes of diagnosis, treatments, and many of the causes have yet to been discovered. However, a high clinical suspicion must be maintained in all cases of severe cyanosis which is unresponsive to aggressive oxygen therapy. Once the diagnosis is made, aggressive treatment with methylene blue should be initiated, as well as clinical observation of a downward trend of methemoglobin levels in the blood.

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CASE STUDY

Licorice: A Patient’s Shocking Presentation

Mohammed Kaleel, MSIV,¹ Vinay Hosmane, M.D.,² Manish Garg, M.D., FACP³ and Wasif A. Qureshi, M.D., FACC, FSCAI⁴

Chronic licorice ingestion is a known, albeit rare, cause of pseudoaldosteronism. Pseudoaldosteronism should be suspected in patients presenting with alkalosis and uncorrectable hypokalemia, particularly when a low plasma aldosterone level can distinguish the syndrome from primary aldosteronism. History and physical should be thorough enough to evaluate for all possible etiologies, including licorice ingestion.

CASE REPORT

A 38-year old male presented to the Emergency Department after his Automatic Implantable Cardioverter Defibrillator (AICD) began firing the previous night, where it was found to have a delivered a total of six shocks. His significant past medical history included nonischemic cardiomyopathy with a left ventricular ejection fraction of 10 to 15 percent and Congestive Heart Failure (CHF) stage 3. He also had a past history of anoxic encephalopathy due to pulseless electrical activity several years prior, for which he received his AICD placement.

On presentation, he was found to have a serum potassium of 2.1 and was found to be alkalotic. He had no prior history of electrolyte abnormalities or alkalosis. He was also noted to be severely dehydrated, with a Blood Urea Nitrogen (BUN) of 103 and creatinine of 2.7. His current medications included the loop diuretic Bumetanide. Therefore,
diuretic overdose was suspected as the most likely etiology of his hypokalemia. He was given 4g IV of Potassium and Magnesium. His AICD continued to deliver several more shocks, due to ventricular fibrillation, by the time he was admitted to the ICU. Repeat labs in the ICU showed a potassium level of 2.3. He was further given 40 mEq of both K-Dur and K-Phos per oral. Further lab studies overnight still showed no improvement and he was further dosed with 200 mEq of K-Dur per oral. Several hours later, his potassium had improved marginally to 2.6. Nephrology was consulted and a history was elucidated of recent, heavy licorice ingestion. His potassium levels that night were finally found to be elevated at an acceptable value of 4.0. As the effects of his licorice ingestion began to wear off and his potassium levels stabilized, no further treatment was necessary. He was then strongly advised to avoid further licorice ingestion.

DISCUSSION

Mineralocorticoid excess can be caused by a wide range of different diseases that present with similar findings. These diseases include primary and secondary hyperaldosteronism, apparent mineralocorticoid excess syndrome, ectopic ACTH syndrome, licorice ingestion, carbenoloxone treatment, and, rarely, Liddle syndrome. The primary findings in these patients are hypertension, hypokalemia, and metabolic alkalosis. As treatment varies significantly based on the underlying disease, it is important to work-up patients presenting with these symptoms.

When evaluating the underlying etiology, plasma renin activity and plasma aldosterone levels are useful initial tests to help differentiate the various causes (Figure 1). When aldosterone is elevated, the cause can be narrowed down to primary or secondary hyperaldosteronism. These two causes can be further differentiated from each other by renin levels. In the presence of elevated aldosterone, low renin levels indicate primary hyperaldosteronism and high levels indicate secondary hyperaldosteronism. Furthermore, when aldosterone and renin levels are both low, the other mineralocorticoid excess syndromes are suspected.

Mineralocorticoid excess syndromes share in common an increased urinary cortisol to
cortisone ratio. In normal subjects, this ratio is between 0.3 to 0.5, as most of the physiologically active cortisol is converted to inactive cortisone by 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2). Thus, there is typically a higher urine concentration of inactive cortisone than there is of cortisol. However, when the enzyme 11-beta-HSD2 is not functioning, physiologically active cortisol remains unconverted. Active cortisol is then able to bind to mineralocorticoid receptors with the same affinity as aldosterone, causing a similar phenotypic presentation to hyperaldosteronism. Moreover, the inability to convert cortisol to cortisone results in a higher urinary cortisol to cortisone ratio.

Apparent mineralocorticoid excess (AME) syndrome is a congenital deficiency of 11-beta-HSD2 that is oftentimes transmitted as an autosomal recessive trait. Due to the congenital deficiency of this enzyme, patients suffering from AME syndrome often present with juvenile hypertension. Ectopic ACTH syndrome results in the production of excess cortisol and leads to mineralocorticoid excess through two suggested mechanisms. The excess cortisol can result in mineralocorticoid excess by either exceeding the metabolic capacity of 11-beta-HSD2 or by actually inhibiting the enzyme with high circulating levels of cortisol. Licorice and carbenoloxone exert their mineralocorticoid effects by acting to inhibit 11-beta-HSD2.

Licorice has been used for over a millennium as an herbal supplement, a natural sweetener, and as a mouth freshener. Earlier this century, it was found to have some beneficial effects in treating duodenal ulcers by Revers et al. This led to the formulation of the drug carbenoloxone, which is a synthetic derivative of licorice's active ingredient. In 1946, Revers first documented the adverse mineralocorticoid effects of licorice ingestion during the treatment of his patients. These effects have been strongly documented as common adverse effects of carbenoloxone, a drug currently licensed for use in the UK and Europe.

Licorice contains a compound called glycyrhizin (GL), responsible for the sweet taste, that is metabolized to the steroid glycyrrhetinic acid (GA) by Beta-D-glucoronidase. GA then acts to competitively inhibit 11-beta-HSD2 and reduce its gene expression. This results in the hyper-mineralocorticoid state observed with licorice ingestion, as 11-beta-HSD2 is no longer available to convert circulating cortisol.

While there is still speculation over which patients are more at risk than others for being susceptible to adverse effects, a few documented trials on licorice gives us a general consensus on its effects on normal subjects. The most popular study, performed in 1977 by Epstein et al, evaluated the effects of 100g to 200g of licorice daily on healthy subjects. The subjects were followed for one to four weeks and were observed for variations in blood pressure, body weight, plasma renin activity, aldosterone, angiotensin II, and electrolytes. The study was prematurely stopped in 43 percent of the patients because of adverse effects of hypokalemia and edema. Another 28 percent developed transient generalized edema but continued the study. All of his subjects showed signs of significant mineralocorticoidism in the forms of hypokalemia, sodium retention, and weight gain. The study demonstrated the considerable effects in healthy subjects of consuming a relatively small amount of 100 to 200g/day, in the form of just two or four confectionery twists respectively.

A study on licorice and GA by Van Gelderen et al in 2000 attempted to find a safe level of GA consumption at which no adverse effects were produced. Healthy female volunteers were selected to consume 0, 1, 2, and 4 mg of GA per kg of body weight for 12 weeks. It was found that effects were observed in patients receiving 4mg/kg but were essentially absent in patients receiving 2mg/kg or less daily, which led to his conclusion that 2mg/kg could be established as the safe daily level of consumption.

It has more recently been demonstrated that there is a direct linear dose-response relationship with licorice-induced rises in blood pressure. This was demonstrated in a 2001 study by Sigurjonsdottir et al. Once again, healthy subjects were selected and they consumed between 50 and 200 g/day for two to four weeks. The study found a systolic blood pressure increase of 3.1 to 14.4 mmHg with a strong dose-response relationship. The response was evident with doses as low as 50 g/day, with maximal effects observed after only two weeks of consumption. This study highlighted both the strength of the dose-response relation-
ship as well as the acuity of the response with relatively low levels of daily consumption.

In an effort to discover a susceptibility factor for some patients to have more severe adverse effects than others with similar amounts of licorice consumption, a recent 2010 study by Miettinen et al studied 30 volunteers with documented licorice-induced hypertension.12 The objective of the study was to determine whether these patients suffering adverse effects from licorice ingestion had any variations of the gene encoding 11-beta-HSD2, and thus rendering them more susceptible than the general population to licorice’s effects. All patients’ DNA samples were taken and screened for any genetic variations. No significant variations were found and the study suggested this does not represent a likely cause of susceptibility for most patients. However, variants of epithelial sodium channel subunits were found at a much higher incidence in the patient population with licorice-induced hypertension, suggesting this may lead to an increased susceptibility in some patients.

Mineralocorticoid excess has been known to result in a wide range of symptoms. The most common symptoms of mineralocorticoidism resulting from licorice use are hypertension and hypokalemia.13,14 However, a variety of presentations due to licorice consumption have been reported in the literature. Two such patients developed hypertensive encephalopathy as their initial presentation of mineralocorticoid excess resulting from licorice ingestion.15 There have been reports of patients presenting with fatigue, weakness, rhabdomyolysis, and even paralysis, who were discovered to have an underlying diagnosis of licorice-induced mineralocorticoidism.16-18 Furthermore, a few other reports describe cardiovascular complaints as a result of prolonged licorice ingestion. Crean et al reported on a patient who developed cardiac arrest due to licorice use.19 Two other case reports documented cases of licorice causing ventricular fibrillation and ventricular tachycardia in their patients.20,21

Although it is fairly common for patients to present with both hypertension and an incidental finding of hypokalemia, it is important for the clinician to keep possible syndromes in mind. This is especially important when considering uncorrectable hypokalemia or any of the other symptoms described above. Tools that can aid in the diagnosis include a urinary cortisol/cortisone ratio.1 While the normal ratio is 0.3 to 0.5, the ratio in mineralocorticoid excess reaches as high as 18 in adults.22,23 Urinary GA can also be measured, with normal values typically being less than 5 micrograms. However, for clinical practice, these diagnostic tests may not be practical. Thus, the most reasonable method of diagnosis is through a thorough history and physical exam.

If the history reveals heavy licorice use in a patient with compatible symptoms, simply ask them to remove licorice from their diet and observe them. This serves as both the diagnosis and treatment of the patient. In cases of severe or symptomatic hypokalemia, as in our case, correction is required through high dose potassium supplementation.

If the patient does not respond after several weeks of licorice removal from the diet, it is imperative to work the patient up for other causes of mineralocorticoid excess. Leitolf et al recently described a patient who presented with hypertension and hypokalemia and reported a history of heavy licorice consumption.24 Despite removing licorice from his diet, he continued to present with hypertension and hypokalemia. Further workup uncovered an adrenal adenoma for which the patient received an adrenalectomy. This highlights the importance of following up to ensure that removal of licorice from the diet corrects the symptoms.

It is also important for the clinician to educate patients on safe levels of licorice for prevention of symptoms. The European Union recommends 100mg/day as the upper limit for ingestion of glycyrrhizin, which is equivalent to the GA found in about 60-70g of licorice.13 However, as Van Gelder demonstrated, the mg of licorice per kg of body weight is a more accurate gauge of safety levels. Stoving et al recently reported on an anorexic patient who developed symptoms of mineralocorticoidism with only 20g of licorice use per day.25 It is particularly vital to educate patients on the potential harmful effects when they inquire about its benefits as an herbal remedy. Patients currently use licorice as a treatment for peptic ulcers, as a cough suppressant, and as an expectorant. Licorice fluid extracts contain approximately 10 to 20 percent glycyrrhizin and
CONCLUSION

This case demonstrates the value of a thorough history in the clinical evaluation of a patient presenting with symptoms of mineralocorticoid excess. Despite leading to potentially life-threatening complications, mineralocorticoid excess due to licorice use can be easily remedied with licorice cessation and potassium supplementation if the diagnosis is made in a timely manner. Thus, it is crucial for the clinician to keep licorice in mind as a possible cause of mineralocorticoid excess and investigate it thoroughly.

REFERENCES

**NEWSMAKERS**

**MSD Members**

**Mehdi Balakhani, DDS, M.D., FACS** was selected to serve on the Government Affairs Committee of the American Society of Plastic and Reconstructive Surgery. Dr. Balakhani practices Plastic Surgery in Newark.

**Daniel J. Meara, M.D., DMD** was selected to serve on the Research Education Committee for the American Cleft Palate-Craniofacial Association. Dr. Meara practices in the Department of Oral and Maxillofacial Surgery at Christiana Care.

**William S. Weintraub, M.D., FACC** was awarded the American College of Cardiology's 2011 Distinguished Service Award at the College's Annual Scientific Session in April. The award is in recognition of Dr. Weintraub's numerous contributions to medicine and the delivery of health care. He is the John H. Ammon Chair of Cardiology at Christiana Care and Director of the Christiana Care Center for Outcomes Research.

**Rafael Zaragoza, M.D. and Venerando Maximo, M.D.** led the 16th Annual Operation We Care Medical Mission to the Philippines. The project is an international project of the Dover Rotary Club. The 2011 mission was co-sponsored by the Gallipolis, Ohio Rotary Club and included 24 physicians. The team performed 97 major and 70 minor surgical procedures.

**Hospitals**

**Alfred I. duPont Hospital for Children** was ranked in eight of ten specialty areas among the best in the nation in the 2011-2012 edition of *Best Children's Hospitals* by *U.S. News & World Reports*. The hospital was ranked:

- 7th in Orthopedics;
- 17th in Gastroenterology;
- 24th in Pulmonology;
- 29th in Urology;
- 33rd in Cardiology and Heart Surgery;
- 41st in Neonatology;
- 44th in Nephrology; and
- 50th in Diabetes and Endocrinology.

The *Bayhealth Wound Care Center* has earned the Center of Distinction Award from Diversified Clinical Services for the second year in a row. The award recognizes wound care facilities with high patient satisfaction rates, exceptional healing results, and outstanding clinical outcomes for wound care management and related services.

**Beebe Medical Center** has received the American Heart Association/American Stroke Association's Get With the Guidelines Stroke Gold Plus Quality Achievement Award in recognition of the Medical Center's commitment and success in implementing excellent care for stroke patients.

**Christian Care's Department of Family and Community Medicine** has received recognition for patient-centered, highly coordinated care and use of long-term, patient-doctor relationships from the National Committee for Quality Assurance (NCQA). The Department's Family Medicine Center has sites at Foulk Road and the Wilmington Hospital Annex. It is the first practice in Delaware and one of 2,189 in the nation to achieve designation as a Physician Practice Connections Patient-Centered Medical Home from NCQA.

The cardiac surgery programs at *Christiana Care Health Systems's Center for Heart and Vascular Health and Beebe Medical Center* have earned the highest quality ranking from the Society of Thoracic Surgeons for the second consecutive year. Only 13.5 percent of 968 hospitals in the Society's cardiac surgery database received the three-star rating for 2010.

**Nanticoke Health Services** has been named to the 2011 Becker's Hospital Review list of Best Places to Work in Healthcare. Those selected provide a work environment that promotes teamwork, professional development, and quality patient care.
OBITUARY

Lawrence Martin Baker III, M.D.

Michael R. Zaragoza, M.D.

Dr. Lawrence M. Baker died May 25, 2011, in Chestertown, Maryland, at the age of 85. He practiced general and thoracic surgery at Kent General Hospital, now Bayhealth, in Dover from 1957-1993. After his retirement from medicine, he eventually moved to Chestertown with his wife Margot in 2000.

Dr. Baker was born July 8, 1925, in Franklin, Pennsylvania, and grew up in Coraopolis, Pennsylvania, outside of Pittsburgh. He served in the U.S. Army from 1943-1946 and spent time in Saipan in the Pacific in preparation for the expected invasion of Japan. Upon discharge from the military, he attended Harvard College and then received his medical degree from Harvard Medical School in 1951. He completed his internship at the Geisinger Memorial Hospital, Danville, Pennsylvania, in 1952, followed by his surgical residency at the Hospital of the University of Pennsylvania from 1952-1957.

He initially joined Dr. Henry Wilson as part of the first General Surgery practice in Dover. He later partnered with Dr. Arthur Zimmerman and Dr. Bruce Bolasny during his 37 year career in the area. A respected member of the medical staff and Dover community, Dr. Baker was a fellow of the American College of Surgeons, and a diplomate of the American Board of Surgery and the National Board of Medical Examiners. He served as Chief of the Department of Surgery at Kent General and was a long-standing member of the Applications Committee for the American College of Surgeons.

Dr. Baker is survived by his wife of 62 years, Margaret (Margot) Holliday Hoon Baker; four daughters, Christine Brockmeyer of Pittsburgh, Pennsylvania, Nancy Coffin of Greenwich, Connecticut, Marianne Kitchell of Seattle, Washington, and Barbara A. Baker, M.D. of Pewaukee, Wisconsin.; nine grandchildren and two great grandchildren; and his sister Elizabeth Kuci of Signal Mountain, Tennessee. He was preceded in death by his sister, Jean Marie Baker.

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LAWRENCE M. BAKER III, M.D.

Michael R. Zaragoza, M.D., is a Urologist who practices in Dover, Del., and a member of the Delaware Medical Journal Editorial Board.