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Hypoglycemia Related to Hyperbaric Oxygen in *Hemophilus influenzae* Purpura Fulminans

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Bland, DK, Klooster MJ. Hypoglycemia related to hyperbaric oxygen in *Hemophilus influenzae* purpura fulminans. J Hyper Med 1988; 3(2):65–71.—We report a case of *Hemophilus influenzae* type b meningitis, septicemia, and purpura fulminans in a 9-mo.-old child where marked hypoglycemia occurred concurrently with hyperbaric oxygen (HBO) therapy. Blood glucose dropped from 148 to 43 mg/dl, and cerebrospinal fluid glucose decreased from 36 to 6 mg/dl. After cessation of HBO no further episodes of hypoglycemia occurred. We postulate that a depression of glucose utilization in this child was due to impaired oxygen availability in large volumes of ischemic tissue. HBO therapy to increase oxygen availability may have increased glucose utilization at a time when glucose supply was constant, resulting in depletion of hepatic glycogen and subsequent hypoglycemia. It seems prudent to recommend careful monitoring of blood glucose levels when critically ill children with large amounts of ischemic tissue are treated with HBO.

hyperbaric oxygen, hypoglycemia, Hemophilus influenzae, *purpura fulminans*

Introduction

Hyperbaric oxygen (HBO) therapy is generally not associated with fluctuations in blood glucose concentrations, although it has been anecdotally observed that some diabetics have reduced insulin requirements while receiving HBO (Minkiewitz K, personal communication). We describe the occurrence of significant hypoglycemia accompanied by a marked drop in cerebrospinal fluid glucose in a critically ill, 9-mo.-old child treated with HBO. We were unable to find another satisfactory explanation for the hypoglycemia, and attributed it to the HBO treatments.

Materials and Methods

Blood glucose concentrations were measured by pediatric intensive care nurses on capillary blood obtained by lancet skin puncture, placed on Chemstrip bG strips, and analyzed by an Accu-Chek II blood glucose monitor (Boehringer Mannheim, Indianapolis, IN). Other laboratory tests including

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spinal fluid glucose values were from the appropriate hospital laboratory. HBO treatments were administered in a Sechrist model 2500 B monoplace hyperbaric system (Sechrist Industries Inc, Los Angeles, CA).

Case Report

A 9-mo.-old male child, who was previously healthy apart from jaundice as a neonate and pneumonia, was treated with ampicillin as an outpatient 1 mo. before this illness.

On the evening before admission to the hospital his mother noted that his skin felt abnormally warm, and he was restless and irritable that night. Next morning, his mother noticed nothing unusual at first, but 30 min after first checking she observed that his skin was pale with perioral cyanosis. The child was taken immediately to the closest emergency room, where he was noted to have pale, mottled skin and mild intercostal retractions. Rectal temperature was 102°F, pulse 120 beats/min, and respirations 60/min. Chest examination revealed bilateral wheezes and crackles. Chest x-ray was reportedly normal; hemoglobin 12.4 g/dl; white blood cell count 13,800/cm with 20% polymorphous; 22% bands; and 3% metamyelocytes. Platelet count was 169,000/cm. Blood cultures were obtained. Random blood glucose performed in the laboratory was 98 mg/dl. Serum Na was 135 meq/liter, K 5.9 meq/liter, Cl 106 meq/liter, CO_2 16 meq/liter, blood urea nitrogen (BUN) 25 mg/dl, and creatinine 0.6 mg/dl. A nebulized bronchodilator treatment was administered, he was admitted to the hospital, and intravenous fluids including 50 ml of 5% albumin were administered, along with intravenous ampicillin, cefotaxime, and 8 meq $NaHCO_3$.

Over the next few hours his condition deteriorated. He was intubated, and mechanical ventilation was initiated for progressive respiratory distress. His temperature rose to 106°F, and urine output was nil. His skin was noted to be cold, clammy, and mottled. Our pediatric intensive care team transported the child to our institution. During transport the child became hypotensive, and intravenous fluid challenges were administered followed by a dopamine infusion for blood pressure support.

On arrival at this institution the child was noted to be very lethargic. Heart rate was 206 beats/min with a supraventricular rhythm. Respirations were controlled by bagging, and blood pressure was 70 to 80 mmHg systolic by Doppler on 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine infusion. His temperature was 98.5°F. His skin was mottled, pale, cool, and clammy, with petechiae on the neck, scrotum, and buttocks. The anterior fontanel was sunken and the neck supple. Pupils were equal and sluggishly reactive to light bilaterally. Heart, lung, and abdominal examinations were otherwise unremarkable. Deep tendon reflexes were sluggish-to-absent bilaterally. The initial impression was that of septic shock, probably meningococcemia.

Fluids were administered i.v., mechanical ventilation was started, and central venous and arterial lines were placed. Cultures were obtained and antibiotic

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therapy with ampicillin and cefotaxime continued. Coagulation studies were ordered and methylprednisolone, fresh frozen plasma, cryoprecipitate, and packed red blood cells were ordered. Digoxin was started for the supraventricular tachycardia. Lumbar puncture was performed. The fluid was cloudy, with no detectable glucose and a protein level of 970 mg/dl. Blood lactate was elevated at 17.1 mg/dl (Normal 3.0–12.0). Serum ionized calcium was found to be low, and calcium was added to the intravenous fluid. After initial ventilator adjustments the pH was 7.39, Pco_2 39 mmHg and Po_2 158 mmHg on 40% O_2, positive end expiratory pressure 4 cm H_2O, synchronous intermittent mandatory ventilation 25/min, and Vt 100 ml. Chest x-ray showed a diffuse alveolar filling pattern.

Next day, widespread purpura was noted on both hands, lower extremities, and buttocks. Platelet count dropped to 10,000/cm, prothrombin time was prolonged at 29 s (control 12 s), and partial thromboplastin time was prolonged at 110 s. Fibrin degradation products were elevated at 80 to 160 mg/dl, and fibrinogen was low normal at 180 mg/dl (normal 170–410). Spinal fluid and urine counterimmunoelectrophoresis were both positive for *Hemophilus influenzae* antigen. Dopamine and dobutamine infusions were in progress for circulatory support. The child developed recurring seizures and pupil inequality. Anticonvulsants were started without success, then meperidine and pancuronium were administered periodically for uncontrolled motor activity. A head computed tomography scan was performed and showed abnormalities suggestive of superior sagittal sinus thrombosis and left frontal infarction. Blood glucose values fluctuated between 70 and 140 mg/dl. Blood cultures from the referring hospital and spinal fluid cultures were reported as positive for beta lactamase negative *Hemophilus influenzae*. The organism was later identified as type b. Cefotaxime was discontinued and ampicillin continued. The BUN and creatinine peaked at 30 and 1.6 mg/dl, respectively, before trending downward as adequate urine output resumed. The child was comatose. Electroencephalograms on that day and subsequently showed diffuse, severe electrocortical suppression. A cerebral blood flow study was normal.

On hospital Day 3 lumbar puncture was repeated and cloudy serosanguineous fluid was obtained. Glucose concentration was 36 mg/dl and protein 1,090 mg/dl. The dobutamine infusion was weaned off, but dopamine at the reduced dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was continued to maintain an adequate blood pressure. Further seizure activity occurred over the next several days, with ongoing attempts at control with phenobarbital and phenytoin. The disseminated intravascular coagulation pattern improved slowly. Total parenteral nutrition was instituted, and blood glucose values fluctuated between 80 and 180 mg/dl without the addition of insulin. All four extremities remained very cool, purple, and mottled, with the new development of skin sloughing over the right hand and dry gangrene of multiple finger and toe tips.

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By hospital Day 6 there was further stabilization of the child's condition with improved respiratory gas exchange and renal function. Blood pressure was more stable although still supported with dopamine, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The child was still experiencing seizures on a daily basis and mentally was minimally responsive only to painful stimuli. HBO treatments were requested in an attempt to salvage at least some of the ischemic limb tissue. After due consideration of the potential risks and benefits, the parents consented for treatments to begin, and hyperbaric oxygen at 2 ATA for 30 min 4 times daily was started. The child appeared to tolerate the first 5 treatments without visible seizures or other complications. Extensive areas of ischemic tissue involving all extremities showed visible improvement in the cyanosis during each treatment. Blood glucose levels were stable at 100 mg/dl.

Lumbar puncture was repeated on hospital Day 7. Spinal fluid glucose had dropped to 6 mg/dl, and protein further increased to 1,224 mg/dl. One hour before the 6th HBO treatment, blood glucose was 148 mg/dl. Three hours after this treatment the blood glucose had fallen to 43 mg/dl. No insulin or other agents known to induce hypoglycemia were administered over this interval, and a central venous total parenteral nutrition infusion containing 12.5% dextrose had been running continuously, except for the very brief changeover pauses associated with preparing the child for the hyperbaric chamber then converting back to regular i.v. infusion equipment after the HBO treatment. There was no discernible malfunction of the infusion pump used while the child was undergoing the HBO treatment. Fifteen milliliter of 25% dextrose was administered i.v., and repeat blood glucose 1 h later was 86 mg/dl. After an additional 90 min the blood glucose was 84 mg/dl.

One hour before the next (7th) HBO treatment, the child was pretreated with 18 ml of 25% dextrose i.v.; 2.25 h later the blood glucose was 76 mg/dl, and after an additional 1.75 h it was 82 mg/dl. Again the 12.5%-dextrose-containing infusion was running continuously except for the brief changeover interruptions. At this point HBO was discontinued. Blood glucose values next day (hospital Day 9) ranged from 78 to 100 mg/dl without further therapeutic changes and were in the 100 to 120 mg/dl range over the subsequent week. A graphic display of blood sugar levels in relation to HBO is provided in Fig. 1. Mean blood glucose before HBO was 123.8 mg/dl with a standard deviation of 38.9. Mean blood glucose during and up to 6 h after HBO was 91.0 mg/dl, with a SD of 27.8. Mean blood glucose beyond 6 h post-HBO was 100.3 with a SD of 12.7. Using a two-sample t test a statistically significant ($P = 0.028$) reduction occurred in blood glucose during HBO when compared to pre-HBO levels. There were no statistically significant differences between blood glucose values during and beyond 6 h post-HBO ($P = 0.40$), and no statistically significant difference in the glucose levels before HBO compared to more than 6 h post-HBO ($P = 0.11$). Cerebrospinal fluid glucose on hospital Day 9 increased to 14 mg/dl. Spinal fluid data are listed in Table 1.

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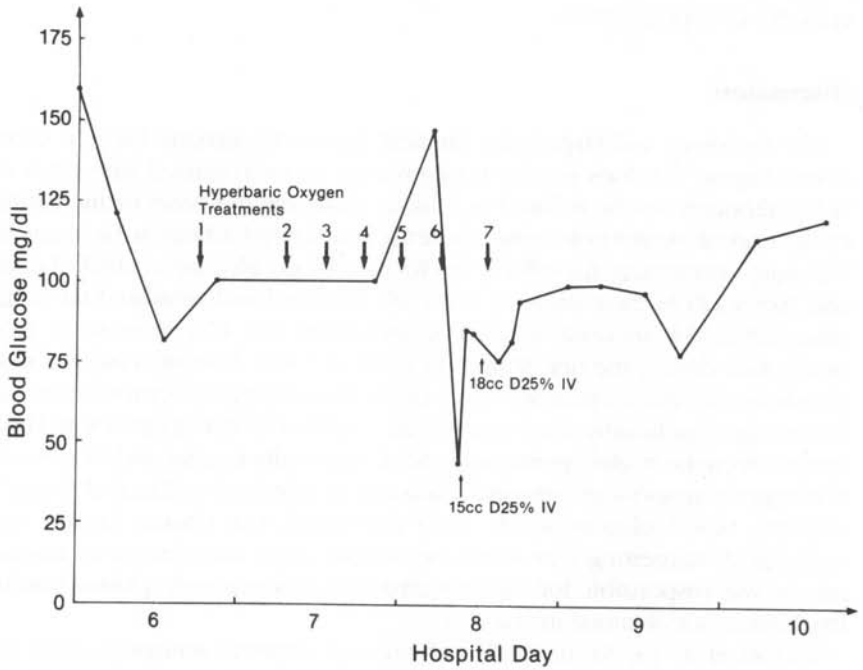

FIG. 1—Relationship of blood glucose values and HBO treatments.

Table 1: Cerebrospinal Fluid Data.[a]

Hospital Day	Glucose, mg/d1	Protein, mg/d1	Culture
1	none detected	970	*Hemophilus influenzae* type b
3	36	1090	no growth
7	6	1224	no growth
9	14		no growth

[a]Hyperbaric oxygen was started on hospital Day 6 and discontinued on hospital Day 8.

Five weeks after admission the child underwent right below-knee amputation, right radial carpal disarticulation, and left carpometacarpal disarticulation. Split thickness skin grafting has since been performed on the remaining skin defects. After 2 mo. in the hospital the child remained minimally responsive, but seizures were much less frequent and he was supporting his own

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respirations without an artificial airway. There have been no known further episodes of hypoglycemia.

Discussion

The Undersea and Hyperbaric Medical Society Hyperbaric Oxygen Committee Report (1) does not list hypoglycemia as a recognized side effect of HBO, although insulin is listed as a factor hastening the onset or increasing the severity of oxygen poisoning. There are conflicting findings in the scientific literature concerning the effects of HBO on blood glucose control. Bassett and Fisher (2) in their study of artificially perfused and ventilated rat lungs observed a 55% increase in glucose utilization and 47% increase in CO_2 production during the first 80 min in HBO at 5 ATA. This increase was due primarily to increased pentose cycle activity. Mitochodrial CO_2 production did not change significantly. Yusa et al. (3) in a study of rabbits treated with HBO noted a decrease in glucogenic amino acids, especially alanine, and an increase in ketogenic amino acids, especially leucine. In rabbits given lactated Ringer's solution, blood glucose levels were decreased, but plasma insulin was unchanged, suggesting that some mechanism other than increased insulin release was responsible for the hypoglycemia. Unfortunately, plasma insulin levels were not obtained in our case.

Torbati et al. (4, 5), in studies of regional cerebral metabolic rates for glucose in rats exposed to HBO, found that with increasing HBO pressures up to 5 ATA an associated increase occurred in metabolic rate for glucose in progressively more cerebral structures. In apparent conflict with these findings are multiple older studies on brain homogenates and slices referred to in Haugaard's review article (6) demonstrating marked inhibition of carbohydrate metabolism with HBO. Haugaard indicates that enzyme inactivation by oxygen is the possible reason for the observed inhibited carbohydrate metabolism. It may be that inadequate perfusion of the study tissues limited carbohydrate availability, thereby depressing carbohydrate metabolism. Yakovlev and Leonov (7) observed increased glucose levels in rats with acute blood loss treated with HBO. With this preparation also, lack of adequate perfusion may have reduced glucose availability to the point of being the limiting substrate. Stress-related endocrine changes may also have played a role in elevating blood glucose. Itsubo et al. (8) reported that male rabbits exposed to HBO have increased corticosterone levels, most marked with acute exposures. These authors did not report glucose levels, but increases would be expected if other factors affecting blood glucose did not change.

In our case we suggest that HBO may have caused increased glucose utilization through one or more of the following mechanisms. Most attractive is the concept of a preexisting depression of glucose utilization due to hypoxia in the large areas of ischemic tissue. HBO may have resulted in increased oxygen availability and glucose utilization. With repeated HBO treatments,

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hepatic glycogen may have become progressively depleted until profound hypoglycemia occurred after the 6th HBO treatment. Alternatively, HBO may have caused hypoglycemia by some other means hinted at in animal studies, such as suppression of gluconeogenesis and/or glycogenolysis. However, if this were the mechanism, it is difficult to explain why the effect was not evident after the first HBO treatment.

Despite administration of 18 ml of 25% dextrose 1 h before the 7th HBO treatment, the blood glucose dropped again, although the fall was attenuated. This observation, added to the absence of further episodes of hypoglycemia following cessation of HBO, further suggests that HBO may have been responsible for the hypoglycemia. Reduction in spinal fluid glucose concurrent with HBO administration with a post-HBO rise in spinal fluid glucose adds further weight to this argument. Treatment failure would be an alternative explanation for the drop in cerebrospinal fluid glucose; however, the causative organism was sensitive to both antibiotics used, and the child's subsequent clinical course was not compatible with treatment failure.

Although the possibility remains that some other, unknown factor caused the hypoglycemia in this case, we considered it prudent to make this case report available to clinicians who utilize HBO. First, we are concerned for patient safety and, to minimize any risk of hypoglycemic tissue injury, we would encourage the monitoring of blood glucose levels when critically ill children with large amounts of ischemic tissue are treated with HBO. Second, if our observations are reproduced, a number of important and practical questions arise, such as, who is at risk for HBO-induced hypoglycemia, what are the mechanisms, and how can the phenomenon be adequately anticipated and prevented?

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