Case Report

The Role of the Pharmacist in the Treatment of Infantile Botulism

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Abstract

Description

Infantile botulism is a potentially devastating disease caused by ingestion of Clostridium botulinum spores through food products or dust particles. The toxin produced by the spores can lead to descending paralysis requiring hospitalization for supportive care which sometimes includes mechanical ventilation. Human Botulism Immune Globulin-Intravenous (BIG-IV or BabyBIG) from the Infant Botulism Treatment and Prevention Program (IBTPP) has been shown to greatly improve outcomes. A previously healthy 5-month-old infant was admitted to her regional hospital for poor feeding and lethargy. When the weakness progressed and she had trouble with protecting her airway, she was intubated and transferred to our institution. The primary diagnosis was infantile botulism and the decision was made to treat with BabyBIG. The pharmacy department was able to assist with obtaining BabyBIG, ensuring proper preparation, and coordinating the team for swift administration. In the days following the BabyBIG administration, the patient slowly started to recover her respiratory function and muscle tone. On day five of admission the patient was extubated. After transfer to the general pediatric floor the patient was given a transpyloric feeding tube and worked with gastrointestinal and nutrition services to improve oral feeding. She was discharged on day seventeen with plans to continue working with therapy and nutrition. BIG-IV can have a major impact in the recovery of infantile botulism. Pharmacists are in an optimal position to assist with coordinating the multidisciplinary team regarding its procurement, preparation, and administration.

Keywords

infantile botulism; BabyBIG; botulism; neurotoxicity syndromes; intravenous immunoglobulins/therapeutic use; infant

Introduction

Infantile botulism occurs when an infant less than one year old ingests and becomes colonized with *Clostridium botulinum* spores in their gastrointestinal tract. It is the most common type of botulism infection with around 100 new cases reported each year in the United States. Although mortality has improved vastly in recent years from 90% to less than 15%, around half of patients with infantile botulism will require invasive mechanical ventilation, and recovery often takes several months to a year. Common pathways of ingesting *Clostridium botulinum* spores include raw honey, corn syrup, improperly sterilized canned foods and dust. Parents are often educated to avoid exposing their infants to honey and corn syrup in the first year of life since these two substances alone account for 20% of new infantile botulism cases. In addition to processed sugars, living in a rural area or being exposed to dust from construction sites has contributed to an increasing proportion of infantile botulism cases in recent years. Regional differences have been noted with more than 50% of new cases in the past 30 years being reported in infants living in California. This increase in incidents is attributed to a higher prevalence of *Clostridium botulinum* spores in California's soil compared to other states.[1]

Infants are more at risk for spore germination and botulism infection than other age groups due to their immature immune systems,

underdeveloped gastric bacterial flora and higher gastric pH compared to older children or adults. The *Clostridium botulinum* spore is a gram-positive, anaerobic, toxin-producing bacillus. This potent toxin inhibits the release of acetylcholine at neuromuscular junctions and leads to a descending flaccid paralysis that is commonly referred to as "floppy baby syndrome." Symptoms include poor feeding, lethargy, constipation, ptosis in the face and eyes, excessive drooling and shallow breathing.[1]

The differential diagnosis of infantile botulism often includes sepsis, electrolyte imbalances, metabolic disorders, Leigh disease, myasthenia gravis and Guillain-Barre syndrome.[1] While a proper disease workup is being completed, supportive care and antimicrobials should be initiated as indicated. Infants may experience descending paralysis that impacts their respiratory muscles prompting respiratory support.[1] It is imperative that as soon as infantile botulism is suspected, a diagnostic stool sample is sent and treatment is started, as quick intervention is critical in achieving optimal outcomes.

Human Botulism Immune Globulin-Intravenous (BIG-IV), otherwise known as "BabyBIG", is a human derived botulism antitoxin that has revolutionized the treatment of infantile botulism.[2] A randomized clinical trial completed in California by Arnon and colleagues compared infants with botulism who received either intravenous immunoglobulin (IVIG) (n=63) or BabyBIG (n=59).[2] In the BabyBIG group, mean length of hospital stay was 2.6 weeks compared to 5.7 weeks in the IVIG group ($p<0.001$). Hospital charges were used as a marker of illness severity and were $74,800 in the BabyBIG group and $163,400 in the IVIG group. In the subsequent nationwide, open-label study, investigators found that administration of BabyBIG saved $34.2 million through avoided hospital costs. With the noted improvements in hospital length of stay and overall medical costs, BabyBIG is now considered first line therapy for the treatment of infantile botulism. The pharmacy team should be notified as soon as the differential diagnosis includes infantile botulism since BabyBIG can only be obtained through the Infant Botulism Treatment and Prevention Program (IBTPP) located in California. This process can be complex and require input from several stakeholders.[3] Pharmacists are in an optimal role to assist the team with ordering, preparing and administering BabyBIG in a timely manner.

Case Presentation

A previously healthy five-month-old female presented to a regional emergency department with a three-day history of decreased oral intake, somnolence/lethargy, worsening head and neck control and constipation. She was eventually admitted for dehydration and lab abnormalities. Throughout the admission, the patient had frequent low blood sugars that were corrected with dextrose 10% bolus doses. Due to increased somnolence and inability to handle oral secretions, the patient was intubated and transferred to our pediatric intensive care unit (PICU), which serves as a tertiary referral center for Colorado and surrounding states. Upon arrival at our facility, the initial differential diagnosis included drug ingestion, hypoglycemia, seizures and meningitis. The initial workup included laboratory values, lumbar puncture, cerebrospinal fluid, blood and urine cultures and x-rays. The patient was empirically started on vancomycin (dosed to a goal trough of 15–20 mcg/mL) and ceftriaxone 100mg/kg/day while the workup was in progress. Infection was ruled out based on culture results and lab markers not indicating infection. Urine toxicology ruled out ingestion. A comprehensive list of admission lab and test results can be found in **Tables 1 and 2**.

On day two of admission, the presumed diagnosis was infantile botulism. The decision was then made to treat the patient with BabyBIG. Pediatric infectious disease and neurology services were consulted and in agreement with this decision. The patient was constipated and needed two enemas to produce a stool sample that could be sent for a botulism assay. To order BabyBIG, the attending physician and the PICU pharmacist completed the necessary paperwork and arranged for BabyBIG to be delivered to the hospital. Given the COVID-19 pandemic, there were less flights from Los Angeles to Denver. Therefore, the medication did not arrive at the facility until the next morning. A provider with the IBTPP was in communication with the health care team until the medication arrived at the facility. On day three of admission, BabyBIG 365 mg (50mg/kg) was administered with intravenous acetaminophen

Table 1. Admission Lab Results

Lab	Result [Range]
Complete Blood Count	
White Blood Cell Count	6.25 cells×10^9/L [7.7–13.7]
Red Blood Cell Count	4.40 cells×10^6/L [3.3–4.7]
Hemoglobin	11.3 g/dL [9.5–13.3]
Hematocrit	35.4% [27–38.5]
Platelet Count	412 cells×10^9/L [150–500]
Basic Metabolic Panel	
Sodium	140 mmol/L [136–145]
Potassium	4.1 mmol/L [3.4–4.5]
Chloride	111 mmol/L [98–107]
Carbon Dioxide	19 mmol/L [17–29]
Anion Gap	10 mmol/L
Random Glucose	103 mg/dL [60–100]
Blood Urea Nitrogen	14 mg/dL [1–14]
Serum Creatinine	0.25 mg/dL [0.1–0.4]
Total Protein	5.4 g/dL [5.7–8.2]
Albumin	4.2 g/dL [3.8–5.4]
Calcium	9.3 mg/dL [8.0–11.4]
Total Bilirubin	0.2 mg/dL [0.3–1.2]
Aspartate Transaminase	34 units/L [13–40]
Alanine Aminotransferase	26 units/L [10–49]
Alkaline Phosphatase	191 units/L [124–341]
Quantitative C Reactive Protein	< 0.4 mg/dL [<1.0]
Blood Gas	
pH	7.22 [7.36–7.40]
pCO2	46 mmHg [35–45]
pO2	60 mmHg [55–70]
Bicarbonate	19 mmol/L [20–22]
Oxygen Saturation	85% [90–96]
Base deficit	-9 mmol/L [-4.0–4.0]
Lactate	1.1 mmol/L [0.4–2.0]
Serology	
Herpes Simplex Virus Type 1	Not Detected
Herpes Simplex Virus Type 2	Not Detected

Table 2. Admission Culture and Imaging Results

Test	Result [Range]
Cerebrospinal Fluid	
Cerebrospinal Fluid Color	Clear/Colorless [Clear]
Red Blood Cell Count	4 cells/mcL [0–10]
Neutrophil Cell Percent	0% [0–5]
Nucleated Cell Count	0 cells/mcL [0–5]
Lymphocyte Cell Percent	55% [40–80]
Monocytes/Macrophages Cell Percent	45% [15–45]
Cultures	
Cerebrospinal Fluid	No growth
Blood	No growth
Urine	One colony at < 10,000 organisms/mL
Respiratory Viral Panel	No growth
MRSA* Nasal Swab	Negative
Imaging	
Chest X-ray	Mild bronchitis or viral lower respiratory tract infection
Abdomen KUB† X-ray	Stool limit at upper limit of normal

*MRSA: Methicillin-resistant staphylococcus aureus

†KUB: Kidneys, ureters, bladder

15mg/kg and intravenous diphenhydramine 1 mg/kg as premedications. The patient did not experience any infusion reactions.

After administering BabyBIG, the patient had notable improvement in muscle tone and strength over the next few days. She was extubated and transferred from the PICU to the general pediatric floor on day five of admission. With work from speech, respiratory, physical and occupational therapies, the patient's neurologic and respiratory functions continued to improve. Enteral feeding was reintroduced slowly, and the gastroenterology service was consulted to assist with the progression from transpyloric tube feeds to oral feeds. On day 14 of admission, the stool sample resulted as positive for botulinum toxin type A. On day 17 of admission, the patient was discharged with a nasogastric tube and follow-up appointments with an outpatient dietician as well as with speech, physical and occupational therapists. In total, the patient spent six days in the PICU, five days on a ventilator and 18 days in the hospital.

Discussion

The decision to administer BabyBIG can be paramount in an infant's recovery from infantile botulism. Quick coordination of the health care team is needed to order the medication, prepare for its arrival and ensure all necessary employees are educated on its preparation and administration. Pharmacists are vital to this process.

Ordering BabyBIG will involve the attending physician, covering pharmacist and pharmacy administration. The attending physician will begin the process by contacting the IBTPP's on-call physician and providing necessary information about the case. Once the on-call physician determines that the patient is eligible for BabyBIG, the attending physician and pharmacist can complete the invoice and purchase agreement found on the IBTPP website to order the medication.[3] This seven page document requires input from a pharmacy director/purchaser for completion as the medication costs $57,300, and payment must be secured before the medication can be shipped. Once all

documentation and payment is received by the IBTPP, the medication will be shipped from Los Angeles to the ordering facility with all transport arranged by the IBTPP. The on-call physician with the IBTPP will likely remain in contact with the facility pharmacist to confirm receipt of the necessary ordering materials and delivery of BabyBIG. They may also remain in contact with the attending physician for updates on the clinical status of the patient.

Given the high expense of this medication and complex procedure for obtaining it, any error in preparation or administration can be devastating. It is important that any health care worker who comes in contact with the medication in any capacity is educated on how to perform their role properly. The pharmacy team must be notified immediately upon the medication's arrival so that storage requirements can be met. The pharmacist and technicians who will be involved in reconstitution and preparation of the BabyBIG dose must be educated on preparation instructions so the medication can be prepared appropriately on the first attempt since no extra drug will be provided to the facility. BabyBIG must begin infusing within two hours of preparation and must be done infusing within four.[4] The typical infusion time for BabyBIG is one hour.[4] This strict timeline emphasizes the importance of effective communication between the nursing staff and the pharmacy prior to BabyBIG's arrival as well as when both parties are ready to move forward with its preparation and administration.

The nursing staff must be aware of the administration requirements prior to BabyBIG's arrival so any necessary adjustments can be made with staffing, resources, etc. An infusion pump is necessary for BabyBIG administration, which should occur through a dedicated IV line with no other medications or fluids running.[4] If this pump or IV access is not already available, it must be obtained prior to BabyBIG's arrival at the facility. Educating the nursing staff on the importance, expense and time sensitivity of this medication is important in reinforcing the urgency of these tasks.

BabyBIG is a form of immunoglobulin. Therefore administration, monitoring and infusion reactions are similar to that of IVIG. The infusion rate must start slower, at 25 mg/kg/hr, and, if no untoward reactions are seen after 15 minutes, the rate can be increased to 50 mg/kg/hr.[4] Common premedications such as analgesics and antihistamines can assist with tolerating the infusion. Appropriate monitoring for events such as infusion reactions, anaphylaxis, renal dysfunction, hemolytic anemia, thrombotic events, hyperproteinemia, hyponatremia, blood hyperviscosity, aseptic meningitis syndrome and transfusion-related acute lung injury (TRALI) should occur during and after BabyBIG infusion when appropriate.[4] After the infusion, the recipient will have six months of botulinum toxin neutralization and protection from the two most common types of botulinum toxin—types A and B.[2] As seen in this patient and in the trial listed above, full recovery is possible but can take time.

Conclusion

In this case, quick identification of infantile botulism, through typical presenting symptoms and noted exposure to common risk factors, allowed our patient to receive a dose of BabyBIG swiftly, which led to a prompt resolution of her infantile botulism, ultimately saving her life. While the patient's mother had ingested home-canned goods and breastfed the patient, it is not believed that *Clostridium botulinum* spores pass through breastmilk. Therefore, the final causative theory is the family's residence in a rural area or the father's work in construction. As medication experts, pharmacists are optimally positioned to assist members of the multidisciplinary team with all aspects of BabyBIG education and use so that its impact is maximized.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of Presbyterian/St. Luke's Medical Center/Rocky Mountain Hospital for Children, a hospital affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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