PharmaNutrition 1 (2013) 86–89

Contents lists available at SciVerse ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu

Therapeutic uses of high-dose omega-3 fatty acids to treat comatose patients with severe brain injury

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ARTICLE INFO

Article history:
Received 27 March 2013
Received in revised form 23 April 2013
Accepted 23 April 2013

Keywords:
Brain trauma
Neuro-inflammation
Omega-3 fatty acid
EPA
DHA

ABSTRACT

Severe brain trauma injury (TBI) is characterized by significant neuroinflammation. Long-chain omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to have anti-inflammatory properties. Since they can easily pass the blood–brain barrier, they have the potential to reduce the neuroinflammation that accompanies TBI. This review summarizes two case histories and protocols that have used high-dose omega-3 fatty acid concentrates in the treatment of brain injury in comatose patients. We also present some potential mechanisms to account for the beneficial effects of the omega-3 fatty acids and the clinical markers used to minimize the concern for increased bleeding at high levels of supplementation with omega-3 fatty acids.

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1. Introduction

More than 1.7 million cases of severe brain trauma injury (TBI) occur annually in the United States and constitute nearly one-third of all injury-related deaths [1]. Yet more than 30 clinical trials of pharmacological agents for the treatment of TBI have failed to demonstrate significant results in their primary end points [2]. It is also known that increased neuroinflammation is one of the primary secondary injury mechanisms of TBI [3]. It is likely much of the excessive neuroinflammation is due to activation of the microglia in the brain. These macrophage-like cells are the primary innate immune cells in the central nervous system and the primary source for the generation of inflammatory mediators.

Although there remains no beneficial pharmacological treatment for severe trauma brain injury (TBI) especially in patients who are comatose, there have been two published single case studies in which high-dose omega-3 fatty acid supplementation has been felt to contribute to the positive outcomes of two comatose patients with severe brain injury [4,5]. In this report we present detailed case studies that have demonstrated the ability to improve the outcomes of comatose individuals with severe brain trauma using the same protocol developed in 2005 for the treatment of children with attention deficient hyperactivity disorder [6], and first used in 2006 for the treatment of a comatose patient with TBI [4].

2. Experimental methods

The high-dose omega-3 fatty acid protocol used in all these studies was similar to that reported earlier [1]. In essence, it consisted of the delivery of 16.2 g of purified long-chain omega-3 fatty acids in the form of ethyl esters on a daily basis. The omega-3 concentrate consisted of a 2:1 ratio of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) so that the subjects were receiving 10.8 g of EPA and 5.4 g of DHA in two divided doses on a daily basis, supplied by The Inflammation Research Foundation. This dose of omega-3 concentrate was delivered in liquid form consisting of two equal daily doses of 15 ml of the omega-3 fatty acid concentrate. The omega-3 fatty acid concentrate was kept at −20 °C. Since it does not freeze, it can be easily poured. The volume of liquid omega-3 fatty acid concentrate was mixed with 45 ml of a polyphenol combination derived from various fruits and vegetables also containing seaweeds and a purified aloe vera for improved emulsification of the omega-3 concentrate and increased antioxidant protection for the omega-3 fatty acids. The polyphenol mixture was kept at 4 °C. This polyphenol mixture was mixed with the liquid fish oil prior to administration into the feeding tubes for each of the patients. Each 45 ml of the polyphenol mixture (also supplied by the Inflammation Research

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http://dx.doi.org/10.1016/j.phanu.2013.04.002

Foundation) contained 4500 units of Oxygen Radical Absorption Capacity (ORAC) based on its ability to quench hydroxyl free radicals as described by Prior and Cao [7]. This ORAC level provided by the polyphenol mixture is equivalent to consuming 100 ml of red wine.

The range of dosage of the combined EPA and DHA was approximately 200–300 mg per kg of body weight. This is consistent with other published studies on the use of similar dosages of omega-3 concentrates to treat attention deficit hyperactivity disorder in children [6,8]. The patients in both cases were constantly monitored to reduce the likelihood of bleeding by checking the ratio of arachidonic acid (AA) to EPA in the plasma to ensure the AA/EPA ratio did not drop below the levels normally found in the Japanese population [9]. If the AA/EPA ratio dropped below 1, then the dose of the omega-3 concentrate was reduced.

3. Results

The case history of the first patient has been extensively reported in a previous publication [4], but the following is a brief summary. The subject was exposed to a carbon monoxide and methane gas atmosphere for 41 h following an explosion at the Sago coal mine in West Virginia in January 2006. He was the only one of 13 miners to survive the explosion. When he was finally rescued, his breathing was labored, and he had significant neurological, cardiovascular, and renal dysfunction. These are classic symptoms of carbon monoxide poisoning. He also was suffering from respiratory failure. His Glasgow Coma score was 7 T. MRI scans indicated significant cytotoxic cell injury and demyelination. Initial enteral feeds used Nepro (Abbott Nutrition) because of the patient's renal failure but were switched to Pivot (Abbott Nutrition) by hospital day 2 to add enteral omega-3 fatty acids, glutamine, and arginine. He received 2000 calories/day and 124 g protein/day (based on his weight, i.e., 25 calories/kg/day and 1.6 g protein/kg/day.) Pivot provided 5 g omega-3 fatty acids (3.4 g eicosapentaenoic acid [EPA] and 1.7 g docosahexaenoic acid [DHA]). A liquid EPA/DHA concentrate supplied by the Inflammation Research Foundation at 2 tablespoons per day (16.2 g omega-3 fatty acids, 10.8 g EPA, and 5.4 g DHA) was added to his enteral feedings starting on hospital day 8 to enhance brain rebuilding. Enteral feeding of the omega-3 concentrate was at a level of approximately 0.210 g of EPA and DHA per kg of body weight. Because of the high dose of omega-3 fatty acids being administered, we used the AA/EPA ratio in the blood to ensure no excess bleeding might occur. After 22 days of high-dose omega-3 fatty acid supplementation by enteral administration, his AA/EPA ratio was 2.2, which was still above the AA/EPA ratio (approximately 1.6) found in the average Japanese [9]. He emerged from coma at the three-week mark and spent the next two months in a rehabilitation facility at which time the omega-3 fatty acid supplementation was continued for another two months. Nearly three months after the explosion, he was released to home care. Now nearly six years later he is functionally normally and has fathered two young children.

The second subject was an 8-year-old girl case history in August 2012 when she sustained severe anoxic brain injury in the setting of prolonged cardiac and respiratory arrest secondary to a near drowning accident. Her past medical history was significant for global physical and cognitive developmental delay, ''institutional autism'', and cognitive functional level estimated 12–18 months of age since she was non-verbal and non-ambulatory. The event occurred when the stroller she was riding in with appropriate restraints in place, rolled off the canal path and fell over the edge into the canal. At this location, the canal water was over 10 feet deep with a strong current and enclosed by a 10-ft cement embankment, which made rescue attempts very difficult. Her head and face was underwater for a prolonged period estimated at more than 5 min. When first responders pulled her out of the water, she was cyanotic, not breathing, not responsive and without a pulse. Cardiopulmonary resuscitation (CPR) was started immediately with bag and mask-assisted ventilations.

After an estimated 20 min of CPR, the patient arrived in the Emergency Department of the nearby academic medical center hospital where her initial rectal temperature was 31.4 °C (89 °F), and she immediately was intubated. Initial arterial blood gas showed pH 6.98, pCO_2 32, $pO2 > 500$, bicarbonate 7 and lactate 13.6. She received epinephrine (4 doses), bicarbonate (2 doses), and atropine with a perfusing rhythm restored after 18 min in the ED; now more than 30 min from the cardiorespiratory arrest. Upon arrival in the Pediatric Intensive Care Unit (PICU), physical examination revealed a temperature of 36.6 °C (97.9 °F), HR 144, RR 26, BP 127/86 Glasgow Coma Scale (GCS) of 3, bilateral fixed 5 mm pupils, and no corneal, gag, or cough reflexes. She showed gasping respirations and no response to deep pain. Rancho Los Amigos Cognitive Scale level was 1 with a complete absence of observable change with any stimuli.

During the first 24 h, the patient developed pulmonary edema requiring increased ventilator support, lactic acidosis, mild acute kidney injury, mild coagulopathy, and hypertension. Electroencephalogram (EEG) showed diffuse, polymorphic, delta wave slowing without epileptiform activity. Over the initial 72 h, her neurologic exam changed frequently with occasional withdrawal to pain, and occasional pupillary response to light. Enteral nutrition with Pediasure 30 kcal/oz was initiated on hospital day 4 via nasogastric tube, and tolerated well. By hospital day 7, she tolerated wean of the ventilator to minimal settings with spontaneous respirations. Her clinical course in the PICU was complicated by urinary tract infection, hypertension treated with clonidine, central venous catheter-related thrombus treated with enoxaparin, and intermittent episodes of tachycardia, flushing, and elevated blood pressure attributed to central autonomic dysfunction. Eight days after the accident, consultation of the Physical Medicine and Rehabilitation Service was obtained for help with the management of her spasticity, hypertonicity and autonomic instability. They recommended the start of baclofen and valium with some improvement. On hospital day 21, tracheostomy for airway protection and gastrostomy for enteral nutrition were performed. The following day the patient was transitioned successfully to tracheotomy collar with humidified room air. Repeat EEG (09/10/2012) showed absence of background organization with diffuse delta slowing with loss of state changes; no focal or epileptiform abnormalities.

The patient was transferred from the PICU to the general pediatric acute care unit on hospital day 34. At that time she was observed to have increased tone and spasticity (LE > UE) with frequent episodes of decerebrate posturing, multiple daily episodes of autonomic storming despite baclofen, clonidine and valium. Additional significant physical exam findings included: GCS 7 with occasional eyes open, roving eye movements, but no focus or tracking, no blink to threat, no purposeful movements and no cough or gag reflex. During the next 6 weeks the patient remained clinically stable and received daily passive range of motion exercises (PROM), custodial care and 2–3 times per week physical and occupational therapy (PT/OT). She continued with episodes of central autonomic dysfunction lasting for 1–2 h or more necessitating additional doses of clonidine and valium. These episodes were disruptive to her PT/OT sessions as well as distressing to family members and staff. Changes noted on her physical exam over this same 6-week period were improved tolerance to PROM of UE and upright position (required full head/neck/trunk assistance), significant heel cord tightness, some inconsistent generalized and localized responses to auditory and tactile stimuli (blinking, facial

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