

Journal of Parenteral and Enteral Nutrition

<http://pen.sagepub.com/>

Parenteral Nutrition–Induced Hypersensitivity in an Adolescent

Cathy L. Bartels, Christine Sanz, Robin Stec and Don W. Coulter
JPEN J Parenter Enteral Nutr published online 30 September 2011
DOI: 10.1177/0148607111399288

The online version of this article can be found at:
<http://pen.sagepub.com/content/early/2011/09/30/0148607111399288>

Published by:



<http://www.sagepublications.com>

On behalf of:



American Society for Parenteral
and Enteral Nutrition

[The American Society for Parenteral & Enteral Nutrition](#)

Additional services and information for *Journal of Parenteral and Enteral Nutrition* can be found at:

Email Alerts: <http://pen.sagepub.com/cgi/alerts>

Subscriptions: <http://pen.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [Version of Record](#) - Sep 30, 2011

[What is This?](#)

Parenteral Nutrition–Induced Hypersensitivity in an Adolescent

Cathy L. Bartels, PharmD¹; Christine Sanz, RPh¹;
Robin Stec, PharmD¹; and Don W. Coulter, MD^{1,2}

Financial disclosure: none declared.

A case report of a 15-year-old adolescent male who developed a hypersensitivity reaction to a parenteral nutrition (PN) solution containing multivitamins (MVI) is presented. Within 30 minutes after initiation of PN and lipids, the patient developed a total-body pruritic urticarial rash that resolved after discontinuation of the infusions and administration of diphenhydramine. Rechallenge with the same PN solution excluding heparin, as well as lipids, resulted in a similar urticarial reaction that also resolved within 30 minutes after discontinuation of the infusions and administration of diphenhydramine. Another rechallenge with a solution containing dextrose and amino acids at the

same concentrations contained in the original PN solution did not elicit an allergic reaction, whereas addition of MVI to the dextrose and amino acids resulted in a similar allergic reaction 20 minutes after the start of the infusion. It was determined that the MVI component of the PN was the most likely causative agent of this patient's urticarial reaction. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords: parenteral nutrition; allergy; hypersensitivity; pediatrics

Parenteral nutrition (PN) is a widely used form of medical therapy to meet the nutrition requirements of patients who have inadequate oral intake or who are unable to use their gastrointestinal tract. PN provides carbohydrate, amino acids, electrolytes, vitamins, and trace elements. A lipid emulsion is often administered with PN as a source of essential fatty acids and nonglucose calories. Lipid emulsions consist of egg phospholipids, plant-derived oils, glycerol, and sterile water for injection.^{1,2}

Very rare cases of hypersensitivity reactions to various constituents of PN and lipids have been reported. Adverse effects associated with PN administration have centered on metabolic, infectious, and mechanical complications.² Adverse effects associated with intravenous (IV) lipid emulsions are usually mild and transient and are typically related to the dosage and infusion rate.¹ Dyspnea, chest or back pain, tachycardia, headaches, nausea, vomiting, cyanosis, flushing, hyperhidrosis, fever, hyperlipidemia,

hypercoagulability, and drowsiness have been reported in less than 1% of patients.¹

This article reports a case of a hypersensitivity reaction to the multivitamin (MVI) product contained in the PN received by an adolescent and reviews the available literature on this adverse effect in pediatrics.

A 15-year-old male with a diagnosis of acute lymphocytic leukemia was hospitalized 7 days after completion of phase 3 of his chemotherapy because of the development of severe mucositis. He had no known allergies to medications or other products. His laboratory values at the time of admission were within normal limits except for a low red blood cell count of 4.09 million (normal 4.69–6.07 million), low hemoglobin of 12.3 g/dL (normal 14.6–17.5 g/dL), low hematocrit of 34.4% (normal 40.8%–51.9%), and low platelets of 101,000 (normal 177,000–406,000). His eosinophils and basophils were within normal limits throughout his hospital stay.

He was given a normal saline bolus, fluconazole 300 mg IV every 24 hours, esomeprazole 40 mg IV every 24 hours, analgesic mouthwash (Maalox [aluminum hydroxide, magnesium hydroxide, simethicone; Novartis Consumer Healthcare, Parsippany, NJ], 2% viscous Xylocaine, and diphenhydramine) 5 mL 4 times daily as needed for topical pain, and morphine sulfate 3 mg IV every 4 hours as needed for pain. After rehydration with normal saline, he was started on dextrose 5% with 0.45% normal saline and 20 mEq potassium chloride per liter (D5% 0.45% NS with 20 mEq/L KCl). His mouth ulcers were cultured for herpes

From ¹Children's Hospital & Medical Center, Omaha, Nebraska, and ²University of Nebraska Medical Center, Section of Hematology/Oncology, Omaha, Nebraska.

Received for publication October 20, 2010; accepted for publication December 27, 2010.

Address correspondence to: Cathy L. Bartels, 8200 Dodge St., Omaha, NE, 68114, 402-955-5488, cbartels@childrensomaha.org

Table 1. Parenteral Nutrition Formula Used on Day 2 of Hospital Stay

Ingredient	Amount
Aminosyn 10% sulfite-free (Hospira, Lake Forest, IL)	1 g/kg/d
Calcium gluconate 0.465 mEq/mL calcium (American Regent, Shirley, NY)	10 mEq/L
Dextrose 70% injection, USP (Hospira, Lake Forest, IL)	385.71 mL (final concentration 10%)
Heparin 1000 units/mL (APP Pharmaceuticals, Schaumburg, IL)	500 units/L
Infuvite adult multivitamin (Baxter, Deerfield, IL)	10 mL
Intralipid 20% IV fat emulsion (Fresenius Kabi, Uppsala, Sweden)	25 mL/h $\times$ 12 h
Magnesium sulfate 4.06 mEq/mL (American Regent, Shirley, NY)	5 mEq/L
Multitrace-4 trace elements, USP (American Regent)	5 mL
Potassium chloride 2 mEq/mL (Hospira, Lake Forest, IL)	10 mEq/L
Potassium phosphate 4.4 mEq/mL (American Regent, Shirley, NY)	20 mEq/L
Sodium chloride 4 mEq/mL (Hospira, Lake Forest, IL)	40 mEq/L
Sterile water for injection, USP (Hospira, Lake Forest, IL)	1506.90 mL

simplex virus, and he was empirically started on acyclovir 300 mg IV every 8 hours.

Because the patient was unable to maintain oral nutrition, PN and lipids were started on the second day of his hospitalization. The PN ingredients are listed in Table 1. Within 30 minutes of initiation of PN, the patient developed a total-body pruritic urticarial rash. The PN and lipids were discontinued, as was the acyclovir, because he had received a dose of acyclovir prior to admission and it was unknown whether he had developed a delayed allergic reaction to the acyclovir. Intravenous diphenhydramine was administered, and the patient's symptoms resolved within 30 minutes.

On the third day of hospitalization, the patient was rechallenged with the same PN and lipid formulations; however, heparin was withheld from his PN because of the possibility that it had caused the rash. A similar rash developed within 30 minutes of the start of the PN infusion, and the PN and lipids were again discontinued. The patient's symptoms resolved within 30 minutes of administration of IV diphenhydramine.

On the fourth day of the patient's hospital stay, 3 trial bags were prepared in an attempt to determine the causative agent of his rash. The first and second bags consisted of dextrose and amino acids at the same concentrations as those contained in the original PN solution, one using a Hospira Single-Use IV Container for Admixing Compatible Medications (Lake Forest, IL), and the second using the original Baxa Multilayer Bag for Parenteral Nutrition (Deerfield, IL) to rule out a potential reaction to constituents of the Baxa bag or to the amino acid solution. Both bags were administered as separate 30-minute infusions with no adverse effects noted. Neither bag contained MVI or trace elements. The third bag contained dextrose, amino acids, and MVI at the same concentrations contained in the original PN solution but also excluded the trace elements. Within 20 minutes, the patient developed a similar rash, and the solution was

discontinued. The hives resolved within 30 minutes of administration of diphenhydramine. No further challenges were performed.

It was determined that the MVI component of the PN was the most likely the causative agent of this patient's urticarial reaction, with the polysorbate 80 constituent as the most likely culprit. Table 2 lists the ingredients of the Infuvite Adult Multiple Vitamins for Infusion used in the PN. On day 5 of hospitalization, the patient was restarted on D5% 0.45% NS with 20 mEq/L KCl, and his oral intake improved sufficiently to warrant discharge. Although the possibility of skin prick testing was discussed, it was decided that this would be inconclusive because there are several causes of false-negative skin prick tests, including medications that can modulate an allergic reaction, using too dilute a concentration of the allergen, inability of the allergen to penetrate into the epidermis, decreased reactivity of the skin, diseases that can attenuate the skin response such as eczema, and application of the skin prick test too soon after a systemic anaphylactic reaction.^{3,4} Additionally, several case reports have reported inconclusive allergy test results with various PN components.⁵⁻⁸

Discussion

Several cases of PN-related hypersensitivity reactions in pediatrics have been published, many of which have suggested the MVI constituent of the PN as the causative agent for allergic reactions. The manufacturer of MVI warns that allergic reactions have been known to occur following IV administration of thiamine and phytonadione (vitamin K), both of which are included in the preparation.⁹ Previous case reports have suggested that the specific allergenic components of the MVI may be the polysorbate emulsifiers,¹⁰ thiamine,⁹ vitamin B complex,⁸ vitamin K,^{5,9} and magnesium sulfate.⁶ Other case reports

Table 2. Infuvite Adult Multiple Vitamins for Infusion³

Ingredients	Concentration per 5 mL
Vial 1	
Ascorbic acid (vitamin C)	200 mg
Vitamin A ^a (as palmitate)	3300 international units
Vitamin D ₃ ^a (cholecalciferol)	200 international units
Thiamine (vitamin B ₁) (as the hydrochloride)	6 mg
Riboflavin (vitamin B ₂) (as riboflavin 5-phosphate sodium)	3.6 mg
Pyridoxine hydrochloride (vitamin B ₆)	6 mg
Niacinamide	40 mg
Dexpanthenol (as d-pantothenyl alcohol)	15 mg
Vitamin E ^a (as dl- α -tocopherol acetate)	10 international units
Vitamin K ₁ ^a	150 mcg
Polysorbate 80	1.4%
Sodium hydroxide	For pH adjustment
Hydrochloric acid	For pH adjustment
Water for injection	Unspecified
Vial 2	
Folic acid	600 mcg
Biotin	60 mcg
Vitamin B ₁₂ (cyanocobalamin)	5 mcg
Propylene glycol	30%
Citric acid	For pH adjustment
Sodium citrate	For pH adjustment
Water for injection	Unspecified

^aPolysorbate 80 is used to water solubilize the oil-soluble vitamins A, D, E, and K.

suggest that the bisulfite component of amino acid solutions^{5,6,11} may be responsible for hypersensitivity reactions. Individuals with a history of soybean or other legume allergies may be particularly susceptible to these allergic reactions. The lag time between the initial administration of PN or lipid emulsions and the manifestation of symptoms may occur because of the necessity of a period of allergen exposure for sensitization to occur.¹

An 8-year-old girl with adhesion ileus complicated by jejunal perforation developed an allergic reaction to PN containing MVI. She had no personal or family history of allergies. PN consisting of amino acids, dextrose, electrolytes, minerals, trace elements, and MVI was started on the 10th day of hospitalization, together with an infusion of fat emulsion. After receiving PN for 21 days, the patient developed a pruritic red rash on her face and chest, which was resolved after diphenhydramine administration. The patient was readmitted to the hospital 15 days after discharge because of malnutrition combined with electrolyte imbalance. PN and lipids were started using the same ingredients and concentrations as the

previous PN. The patient became irritable and developed a pruritic rash over her face and trunk with swelling of her eyelid soon after the PN was started. The symptoms resolved within 20 minutes of discontinuation of the PN and administration of diphenhydramine. PN was then administered without lipids, and the patient developed similar symptoms. Trace elements and MVI were then removed from the PN, and this was infused without adverse effects. Trace elements were reintroduced to the PN and infused with no allergic reaction. The MVI 2 (folic acid, cyanocobalamin, biotin, sodium citrate, citric acid, propylene glycol) was added to the PN and infused with no allergic reaction. MVI 1 (ascorbic acid, vitamin A, vitamin D, thiamine, riboflavin, pyridoxine, niacinamide, d-pantothenol, vitamin E, chlorobutanol, benzyl alcohol, mulgofen EL-719) was then added to the PN and infused. Within 10 minutes of starting the infusion, the patient developed swelling of the eyelid and lips, pruritic rash of the trunk, tachycardia, and tachypnea. Thirty minutes after discontinuation of the PN and administration of diphenhydramine, the symptoms resolved. A dermal allergy test of a vitamin B complex solution was performed 1 year after the anaphylactic reaction and demonstrated sensitivity to this solution. The authors concluded the patient's allergic reaction was attributed to the vitamin B complex contained in the MVI.⁸

A 4-year-old boy with presumed small bowel obstruction developed an anaphylactic reaction to PN containing MVI. He had been diagnosed with Wilms' tumor at 10 months of age and underwent radiation and chemotherapy followed by resection of both kidneys. PN containing amino acids, MVI, dextrose, electrolytes, mineral, and trace elements together with lipids was started on hospital day 5. On hospital day 11, the patient developed a fever, and IV vancomycin was started for a suspected central line infection. On day 12, the patient complained of pruritic palms and soles, which resolved following diphenhydramine administration. The patient developed an urticarial rash on his lower abdomen and neck on day 15. The vancomycin was discontinued on day 17, and the central line was changed. His oral intake at that time was approximately half of his estimated daily requirements, and his PN was cycled off for 8 hours. The rash persisted during both the cycle-off and cycle-on periods. The lipids and MVI were excluded from the PN for 1 infusion period, but the symptoms did not change. The lipids and MVI were restarted the next day. On day 21, central access was lost, and the rash persisted for 5 days without PN. A Broviac catheter was placed, and the PN was resumed with the same cycle-on and cycle-off schedule. Within 40 minutes of the PN infusion, the patient developed edema of the lips, tachycardia, tachypnea, and stridor. The PN was discontinued, IV diphenhydramine and subcutaneous epinephrine were administered, and the symptoms resolved within 24 hours. Skin prick tests of

Table 3. Summary of Case Reports of Parenteral Nutrition–Induced Hypersensitivity

Citation	Patient's Age	Hypersensitivity Reaction	Most Likely Causative Agent
Bartels et al (present study)	16 y	Total-body pruritic urticarial rash	MVI component of PN
Wu and Chen ⁸	8 y	Pruritic erythematous rash on face and chest	Vitamin B complex contained in MVI component of PN
Market et al ⁵	4 y	Urticarial, pruritic rash on palms, soles, lower abdomen, and neck; edema of lips; tachycardia; tachypnea; and stridor	Sulfites contained in amino acids or vitamin K ₁ in MVI component of PN
Bullock et al ¹²	34 mo	Pruritus and hives along diaper line and thighs	MVI component of PN
Levy and Dupuis ¹⁰	16 y	Pruritic rash on arms, check, back, and head	Polysorbates in MVI component of PN
Pomeranz et al ⁶	4 y	Tachycardia, severe stridor, unmeasurable blood pressure, dyspnea, cyanosis, and generalized edema of skin	Travasol, magnesium sulfate, or MVI component of PN

MVI, multivitamin; PN, parenteral nutrition.

the PN solution, lipids, and undiluted Aminosyn 10% (Abbott Laboratories, Abbott Park, IL) were negative, whereas undiluted MVI (MVI-Pediatric, Armour Pharmaceutical, Kankakee, IL) was slightly positive. Intradermal injection of Aminosyn 0.1% resulted in a moderate response. The authors stated that the results of the skin testing were inconclusive and believed that the risks associated with rechallenge of the vitamin-free PN solution outweighed the benefits. The authors concluded the anaphylactic reaction was an immunoglobulin E–mediated type I allergic response, but they could not identify the causative agent with certainty. They did state, however, that the reaction may have been due to the sulfites contained in the amino acid solution or to the vitamin K₁ component of the MVI.⁵

Bullock et al¹² reported a suspected allergic reaction to a PN solution containing a pediatric MVI preparation in a 34-month-old female hospitalized with a left upper quadrant mass and a diagnosis of stage IV neuroblastoma. The child developed anorexia, weight loss, and mucositis after completion of her chemotherapy. PN was initiated containing amino acids, dextrose, IV lipids, electrolytes, minerals, trace elements, and MVI and was cycled over 12 hours at night. The child developed pruritus and hives along the diaper line and thighs 5 hours after initiation of PN, which resolved with diphenhydramine administration. The following day, PN was administered without lipids, and the child developed a similar rash within 90 minutes, which again resolved after diphenhydramine. The next PN solution was prepared without addition of the MVI, with lipids piggybacked into the central venous catheter, and no adverse effects were noted. The authors suspected that a component of the parenteral MVI preparation or of the diluent was responsible for this patient's allergic reaction.

Another case report described a suspected allergic reaction to a PN solution containing MVI in a 16-year-old male with Burkitt's lymphoma and a history of hypersen-

sitivity to sulfonamides. PN was started on his third day of admission as an amino acid and glucose solution containing MVI (MVI Pediatric; Rorer Canada). The total daily amount of PN solution was divided into 2 IV bags, one of which did not contain the MVI. Shortly after starting the PN with MVI, the patient developed a raised white pruritic rash on his arms, chest, back, and head, which resolved after discontinuation of the PN. The bag containing PN without vitamins was administered after 24 hours and was not associated with any adverse effects. The patient was rechallenged with the PN and MVI solution and developed a similar rash, which again disappeared after the infusion was discontinued. PN without MVI was continued for another 4 days with no adverse effects. The authors concluded that the polysorbate 80 and polysorbate 20 contained in the MVI were the most likely cause of this patient's urticaria.¹⁰

Pomeranz et al⁶ reported a case of a 4-year-old boy hospitalized for colostomy closure who developed an anaphylactoid reaction to peripheral parenteral nutrition (PPN) containing dextrose, Travasol (Baxter, Deerfield, IL), MVI-12 (Hospira, Lake Forest, IL), magnesium sulfate, zinc, and calcium. Within 15 minutes of PPN initiation, the patient developed tachycardia, severe stridor, unmeasurable blood pressure, dyspnea, cyanosis, and generalized edema of the skin. Within 2 hours of discontinuation of the PPN and administration of IV hydrocortisone, the symptoms improved. Ten weeks after the anaphylactoid reaction, dermal skin testing was performed and demonstrated sensitivity to the Travasol solution as well as the MVI-12 and magnesium sulfate. The authors concluded the anaphylactoid reaction was most likely due to the Travasol, magnesium sulfate, or a component of the MVI-12.

The MVI component in the PN in our case report contained polysorbate 80 and polysorbate 20, both of which were also contained in the MVI used in the case report by Levy and Dupuis.¹⁰ Polysorbates are hydrophilic,

nonionic surfactants that are used as oil-in-water emulsifiers for pharmaceutical products. Polysorbate 80 is a known allergen, most likely as a result of complement activation.¹³ Polysorbate 80 has been shown to inhibit lymphocyte transformation in vitro, and it is suspected of causing thrombocytopenia, azotemia, renal failure, hepatomegaly, splenomegaly, cholestatic jaundice, ascites, and pulmonary deterioration in premature neonates.⁷

If an allergic reaction to PN or lipid emulsion is suspected, the infusion should be immediately withheld, and, if necessary, the patient should be treated with antihistamines until the reaction resolves. The allergen must be identified and removed from the PN solution if PN therapy must be restarted. If MVI is the suspected causative agent, consider using single-entity vitamins without polysorbate if available. Desensitization procedures may be considered if PN therapy is to be prolonged. Although allergic reactions are a rare complication of PN or lipid emulsion therapy, clinicians should be aware of the potential for a hypersensitivity reaction to occur and understand how to best manage this complication.

References

1. Hiyama DT, Griggs B, Mittman RJ, Lacy JA, Benson DW, Bower RH. Hypersensitivity following lipid emulsion infusion in an adult patient. *JPEN J Parenter Enteral Nutr.* 1989;13:318-320.
2. Mirtallo JM. Parenteral formulas. In: Rombeau JL, Rolandelli RH, eds. *Clinical Nutrition Parenteral Nutrition*. 3rd ed. New York, NY: Saunders; 2001:118-139.
3. Canani RB, Ruotolo S, Discepolo V, Troncone R. The diagnosis of food allergy in children. *Curr Opin Pediatr.* 2008;20:548-589.
4. Barbaud A, Reichert-Penetrat S, Tréchet P, et al. The use of skin testing in the investigation of cutaneous adverse drug reactions. *Br J Dermatol.* 1998;139:49-58.
5. Market AD, Lew DB, Schropp KP, Hak EB. Parenteral nutrition-associated anaphylaxis in a 4-year-old child. *J Pediatr Gastroenterol Nutr.* 1998;26:229-231.
6. Pomeranz S, Gimmon Z, Ben Zvi A, Katz S. Parenteral nutrition-induced anaphylaxis. *JPEN J Parenter Enteral Nutr.* 1987;11:314-315.
7. Kamath KR, Berry A, Cummings G. Acute hypersensitivity reaction to Intralipid. *N Engl J Med.* 1981;304:360.
8. Wu SF, Chen W. Hypersensitivity to vitamin preparation in parenteral nutrition: report of one case. *Acta Paediatr Taiwan.* 2002;43:285-287.
9. Infuvite [package insert]. Deerfield, IL: Baxter Healthcare Corporation; September 2007.
10. Levy M, Dupuis LL. Parenteral nutrition hypersensitivity. *JPEN J Parenter Enteral Nutr.* 1990;14:213-215.
11. Huston RK, Baxter LM, Larrabee PG. Neonatal parenteral nutrition hypersensitivity: a case report implicating bisulfite sensitivity in a newborn infant. *JPEN J Parenter Enteral Nutr.* 2009;33:691-693.
12. Bullock L, Etchason E, Fitzgerald JF, McGuire WA. Case report of an allergic reaction to parenteral nutrition in a pediatric patient. *JPEN J Parenter Enteral Nutr.* 1990;14:98-100.
13. Coors EA, Seybold H, Merk HF, Mahler V. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Ann Allergy Asthma Immunol.* 2005;95:593-599.