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JPEN J Parenter Enteral Nutr 2005 29: 451

DOI: 10.1177/0148607105029006451

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Brief Communication

Urticaria Associated With Parenteral Nutrition

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ABSTRACT. We report a 53-year-old female patient with short bowel syndrome who developed urticaria after administration of cyclic parenteral nutrition (PN). The urticaria occurred 2 hours into the 12-hour nocturnal infusion and resolved completely 1 hour after discontinuation of the PN infusion. The urticaria occurred despite removing lipids from the 3-in-1 PN solution. The urticaria did not occur when the multivitamin preparation was removed from the PN. Upon rechallenge with a PN solution containing a multivitamin,

the urticaria reoccurred. Prick skin testing using the multivitamin in increasing aliquots was negative. Serum tryptase and 12-hour urinary histamine level during PN infusion containing the multivitamin was unchanged compared with baseline measurements. The patient had no allergic reaction using a similar dose of an oral multivitamin. This case illustrates that allergic reactions from PN infusion may occur and that the multivitamin preparation can be the cause. (*Journal of Parenteral and Enteral Nutrition* 29:451–453, 2005)

Previous published case reports have suggested allergic-type reactions with parenteral nutrition (PN) infusions. However, the actual constituent of the PN formula responsible for the allergic reaction has never been clearly determined. The published case studies would suggest that either the lipid emulsion or the multivitamin preparation is responsible for the observed responses.^{1–10} In this clinical study, we have attempted to better understand the etiology of the allergic reaction associated with a PN solution.

Case Study

After approval from the Mayo Clinic Investigational Review Board, the following case study was completed. A 53-year-old female patient was admitted to the hospital in June 2003 secondary to a small-bowel obstruction. The patient had an extensive medical history spanning nearly 20 years that included multiple abdominal surgeries for pelvic pain, fibroids, and more recently, vaginal cancer. The patient was the child of a mother who had been treated with diethylstilbestrol (DES). Her vaginal cancer was treated with surgery, including lymph node dissection followed by pelvic radiation. Her past medical history was also significant for seasonal rhinitis, and she had positive allergy skin testing for molds, dust, pollens, and ragweed. The patient had no record of asthma or any previous anaphylactic reactions to egg, seafood, or peanut-containing products. She had taken a daily, oral multivitamin (Centrum Performance, Wyeth Consumer Healthcare, Madison, NJ) and oral vitamin C, vitamin E, and nia-

cin for 5 years without adverse event. She was allergic to sulfa, manifested by a systemic rash, and noted a skin reaction to the fabric softener Snuggly.

Four months before the current hospitalization, the patient began to have signs and symptoms of a small-bowel obstruction marked by postprandial abdominal distention and nausea. She also had a 25-pound weight loss between March and the current hospital admission. During this June hospitalization, the patient was taken to the operating room for an unresolved, partial small-bowel obstruction. Given the extensive radiation-induced adhesions, all but 100 cm of her small bowel was resected. Although the entire colon was preserved, anastomosis to the small intestine was not possible, given the widespread radiation injury. The patient was left with an end jejunostomy with the intent for reanastomosis in 3–4 months. During this period, because of high ostomy output and short-bowel syndrome, the patient required PN.

Before obtaining central vascular access, the patient received a 3-in-1 peripheral parenteral nutrition (PPN) solution containing minimal concentrations of dextrose, amino acids, and lipids. The PPN was infused over a continuous 24-hour period at a rate of 90 mL/h. Infuvite adult multivitamins (Baxter Healthcare Corporation, Deerfield, IL) and concentrated trace elements (American Regent, Shirley, NY) preparations were added to the PPN. Sixteen days into the PPN infusion, she first noticed mild itching and small hives on her arms. Three days later, because of failure of appetite to return, a peripherally inserted central catheter was placed and a 2.0-L, 3-in-1 PN solution that included the same multivitamin preparation was initiated. Anticipating the patient would require home PN until the surgical reanastomosis was preformed, the PN was cycled over 12 hours at night. Each night during the nocturnal infusion, the patient developed

Received for publication February 18, 2005.

Accepted for publication June 9, 2005.

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FIGURE 1. Urticaria of the forearm, below the peripheral inserted central catheter.

itching followed by hives on her lower trunk and extremities, including her hands. This would occur approximately 1.5–2 hours into the infusion. As directed by protocol, the cyclic PN was ramped to its goal infusion rate by initiating the solution at 90 mL/h for 1 hour, then advancing to its maximal flow of 182 mL/h for 10 hours. The PN was then tapered to a rate of 90 mL/h during the final hour of infusion. Within 1 hour of discontinuing the PN, the patient would have complete resolution of her hives and itching. She had no hives or itching during the day without the PN infusion.

It was initially believed that her reaction may have been the result of adding famotidine to the PN. The famotidine was discontinued, but symptoms persisted during the PN infusion. Other suspect medications such as antibiotics and pain medications were discontinued, but symptoms continued during infusion of the PN. Only partial relief of her symptoms was achieved with diphenhydramine. In an attempt to rule out the lipid emulsion as the cause of her allergic reaction, the PN was infused without lipid, followed by a continuous infusion of only 20% lipids during the day. The patient had no symptoms during both PN infusion trials. The multivitamin preparation was then eliminated from the PN formula, and the patient has no reproducible

symptoms. The multivitamins were then added back to the PN, and the same symptoms of itching and hives occurred 2 hours into the infusion and once again dissipated an hour after discontinuing the solution. The patient was then observed during an IV infusion of the multivitamin preparation diluted in 2 L of a 0.9% saline solution. This was infused using the identical cyclic regimen for PN infusion described above. The same urticarial response was observed. A photograph of the rash appears as Figure 1.

A 12-hour urine collection was obtained for histamine, and serum blood samples were taken for tryptase analysis when the patient received the PN containing multivitamins. Serum tryptase was 2.81 ng/mL (0–11.4) during the PN infusion with multivitamins, and the 12-hour urinary histamine was 20.5 µg/g of creatinine (0–34.9). These values were unchanged from baseline measurements collected during PN infusion without the multivitamin. The patient's blood pressure and pulse oximetry was monitored during the reaction but did not drop from baseline measurements. Also, blood drawn during the reaction did not show an increase in the number of eosinophils.

Prick skin testing was then preformed using aliquots of the multivitamin mixed in a 0.9% saline solution at 1:10 dilution, full strength (10 mL in 2.0 L normal saline), twice full strength, and 4 times full strength. The prick skin test was performed by starting with the weakest aliquot and then advancing stepwise to the most concentrated solution. The patient did not elicit a positive prick test response, although the histamine control was strongly positive at 3+. Testing was then repeated using aliquots from the PN solution containing multivitamin, and the skin prick test was also negative. The patient was then challenged with 2 chewable multivitamins (Flintstone Multivitamin, Bayer Corporation, Morristown, NJ) containing similar components to the IV multivitamin (Table I). She did not have an allergic reaction to the multivitamin tablets. She was then given the IV multivitamin to drink and tolerated the oral delivery without a reaction.

TABLE I
Constituents of the IV and oral Flintstone multivitamin

Constituent	Quantity	
	Intravenous	Oral
A	3300 IU	5000 IU
C	200 mg	60 mg
D	200 IU	400 IU
E	10 IU	30 IU
K	150 µg	0
Thiamine	6.0 mg	1.5 mg
Pyridoxine	6.0 mg	2.0 mg
Riboflavin	3.6 mg	1.7 mg
Pantothenic acid	5.0 mg	10 mg
Niacin	40 mg	20 mg
B ₁₂	5.0 µg	6.0 µg
Folic acid	600 µg	400 µg
Biotin	60 µg	40 µg
Polysorbate-80	1.4%	0

DISCUSSION

This clinical study illustrates that through careful clinical observation and elimination of potential allergens, the multivitamin preparation used in PN can result in an allergic reaction manifested as a pruritic urticarial rash. Another observation made from this study was that the allergic reaction appears to be related to the duration and rate of infusion. The patient did not have symptoms until 16 days into her PPN infusion. Also, her symptoms were not observed until 2 hours into the cyclic infusion, when the rate of the PN reached 182 mL/h. This is most likely explained by the fact that a certain amount of allergen is usually required to trigger an allergic reaction. It is also interesting to observe that complete disappearance of the hives and improvement of the pruritus occurred within 60 minutes of discontinuing the PN infusion. Although the prick skin test was negative, it does not negate our clinical observation of the patient's allergic reaction during challenge and elimination of potential antigens in the PN solution. This may be explained by the limitations of the methods used in skin testing because we know from other true allergic reactions that skin testing may also be negative. The clinical history of this patient would also suggest that she is predisposed to allergy. She was noted to be allergic to sulfa and a variety of dusts and mites. She also had a strong history of seasonal allergies.

Another interesting observation was the lack of rise in urinary histamine and serum tryptase during the time of her allergic symptoms and PN infusion. This would suggest that the allergic reaction observed in this case was not associated with a significant release of histamine from mast cells. It is certainly possible to have similar allergic reactions to other allergens without laboratory evidence of increased urinary histamine or serum tryptase.

The fact that she did not have a reaction to the oral multivitamin that contained similar constituents would not be unexpected. It is known that IV reactions to allergens tend to be more severe than when digested orally. This is most likely the result of first-pass elimination of a medication or drug during oral consumption. Given that her stomach was completely intact and that she had 100 cm of small intestine remaining, it is expected that she would have had adequate absorption of the chewable vitamin to elicit an allergic response. We would also expect a similar or negative response with oral intake of the liquid IV multivitamin. Given her short-bowel syndrome and inability to place the vitamin preparation in her PN, it will be important that we monitor her for clinical signs and symptoms of

specific vitamin deficiency and check serum levels biannually.

Although direct skin testing was not performed using the inactive product of the IV multivitamin polysorbate-80, it is possible that polysorbate-80 was responsible for the observed allergic reaction. Polysorbates are hydrophilic, nonionic surfactants that serve as emulsifying agents for the preparation of oil-in-water emulsions in pharmaceutical products. Polysorbates are also copolymerized with a number of ethylene oxide molecules that themselves can be responsible for allergic reactions. Polysorbate-80 is also a larger molecule than vitamins, and larger-sized molecules are more likely to stimulate this type of cutaneous allergic reaction.

Although a rare occurrence, knowledge of allergic reactions during PN infusions is obviously important to both the clinician and the patient. Often, just as in this case, other medications are thought to be the culprit before considering the PN. Pain medications may be inappropriately discontinued and antibiotics inappropriately changed to another class. Furthermore, itching and hives create anxiety for the patient. Although anaphylaxis was not observed in this patient, it may certainly be a concern in some individuals. Also, as illustrated in this case, an oral chewable multivitamin appears to be an alternative choice of administration in patients allergic to IV multivitamin preparations.

REFERENCES

1. Levy M, Dupuis LL. Parenteral nutrition hypersensitivity. *JPEN J Parenter Enteral Nutr.* 1990;14:213–215.
2. 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.
3. Buchman AL, Ament ME. Comparative hypersensitivity in intravenous lipid emulsions. *JPEN J Parenter Enteral Nutr.* 1991;15:345–346.
4. 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.
5. Nagata MJ. Hypersensitivity reactions associated with parenteral nutrition: case report and review of the literature. *Ann Pharmacol.* 1993;27:174–177.
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, Cummins G. Acute hypersensitivity reaction to Intralipid. *N Engl J Med.* 1981;303:360.
8. Hansen LM, Hardie WR, Hidalgo J. Fat emulsion for intravenous administration: clinical experience with Intralipid 10%. *Ann Surg.* 1976;184:80–86.
9. Udall JN, Richardson DS. Allergic reactions to parenteral nutrition solutions. *Nutr Support Serv.* 1986;6:20–22.
10. Camarasa JM. Acute contact urticaria. *Contact Dermatitis.* 1982;8:347–348.