

## Clinical Communications

### Anaphylaxis to parenteral nutrition in a pediatric oncology patient treated with induction of drug tolerance protocol

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#### Clinical Implications

- This case describes the successful management of a rarely reported hypersensitivity reaction of anaphylaxis to the nonlipid component of total parenteral nutrition by applying an induction of drug tolerance treatment.

Anaphylaxis to total parenteral nutrition (TPN) in pediatrics is rarely reported.<sup>1,2</sup> TPN includes dextrose, amino acids, electrolytes (sodium, potassium, phosphate, magnesium, calcium, chloride/acetate), trace elements, multi-12/K1 Ped multivitamins, heparin, and lipids (intralipid/SMOF [soybean oil, medium-chain triglycerides, olive oil, fish oil]/omegaven). Oncology patients depend on TPN for nutritional support. Understanding TPN reactions and identifying methods of overcoming hypersensitivity are crucial. We report a case of anaphylaxis to TPN without the lipid emulsion. Induction of drug tolerance successfully permitted continued TPN use and cancer treatment.

An 11-month-old nonatopic male was diagnosed with localized posterior fossa medulloblastoma and treated with surgery and intensive chemotherapy, which caused significant mucositis. TPN with Primene protein 10% amino acid injection by Baxter International Inc (Mississauga, Canada), and MICRO+6 trace elements and multi-12/K1 multivitamins by Sandoz Canada Inc of Baxter (compounded by hospital pharmacy) plus infusion of SMOFlipids 20% (including soybean oil, medium-chain triglycerides, olive oil, fish oil, purified egg phospholipids, and All-rac- $\alpha$ -tocopherol) by Fresenius Kabi (Toronto, Canada), was initiated. Within an hour of commencing TPN and lipids, he developed urticaria, emesis, wheeze, oxygen desaturation to 85% on room air, and decreased level of consciousness. TPN with lipids was discontinued. Symptoms resolved within 20 minutes on treatment with intramuscular (IM) epinephrine, intravenous (IV) famotidine, IV hydrocortisone, IV diphenhydramine, and oxygen.

This infant received piperacillin-tazobactam and ciprofloxacin 4 hours before initiation of TPN due to viral-induced fever and neutropenia, and these antibiotics were subsequently tolerated. No other suspected allergens were identified. Because lipids are often the suspected culprit for reaction, 48 hours later, TPN was reinitiated without the lipid infusion ordered. Within 15 minutes of the infusion start, tachycardia, respiratory distress, facial swelling, urticaria, and decreased level of consciousness occurred. TPN was discontinued and symptoms resolved within 20 minutes on treatment with IM epinephrine, IV famotidine, IV hydrocortisone, IV diphenhydramine, salbutamol, oxygen therapy, and fluid resuscitation.

Alternate enteral nutritional options were poorly tolerated in this medically fragile infant. Because the patient was expected to have an intense treatment course requiring prolonged nutrition support, a pediatric allergy consultation was obtained and an induction of drug tolerance protocol for TPN was developed. No tryptase levels were sent. Epicutaneous skin prick testing was performed to a 1:100 dilution (with the previously listed ingredients without lipids or multivitamins) of TPN and testing result was negative with a 2-mm histamine response (antihistamines recently administered). Intradermal testing was not performed because nonirritating concentrations are not known and there is a possibility of a systemic reaction. Seven days after last exposure to TPN, induction of tolerance was initiated with a dilution of 1:10,000 without lipids, but containing multivitamins. An acceleration schedule of TPN with increasing concentrations every 15 minutes over 3 hours was administered (Table 1) using premedications with IV famotidine and IV hydrocortisone antihistamine and corticosteroids given the severity of previous reactions. Target TPN rate of 10 mL/h was reached, but within 30 minutes symptoms of respiratory distress with increased work of breathing, urticaria, and decreased capillary refill developed. TPN was discontinued. Ninety-six hours after discontinuation, retreat using the same induction of drug tolerance protocol was initiated without multivitamins and lipids. The patient reached his target TPN rate of 10 mL/h without adverse reaction. He continued his goal rate of TPN but was deficient in calories. Lipids were reintroduced using the induction of drug tolerance method with no adverse reaction. Because he continued to be quite ill when requiring TPN, rechallenge with multivitamins in the TPN was not performed.

TPN was discontinued on discharge. During 2 subsequent scheduled chemotherapy admissions, TPN with lipid infusion but without multivitamins was reinitiated using the same desensitization protocol with premedications and tolerated.

A systematic review in 2018 identified 28 published cases of TPN hypersensitivity with an estimated rate of hypersensitivity of 1.5 per million patients exposed to TPN.<sup>1</sup> Most anaphylaxis cases (48.4%) occurred secondary to the intravenous fat emulsion, followed by multivitamins (33.3%) and amino acids (9%). The lipid component of TPN contributed to 64.2% of the severe reactions.<sup>1</sup> Lipid emulsions often contain soybean oil, olive oil, fish oil, and purified egg phospholipids,<sup>1</sup> whereas amino acid and multivitamin components contain ingredients such as mannitol, sodium citrates, citric acid, polyethylene glycol, polysorbate 80, and other inert substances, which are unusual but recognized food allergens with limited testing available or testing that is difficult to perform in unwell patients.<sup>1,3</sup>

Pediatric cases described in the literature removed the offending agent or discontinued TPN. Desensitization to TPN has not been described in the literature. Studies with drug tolerance testing show successful induction of tolerance to pharmacological agents.<sup>4,5</sup> Rapid desensitization escalates exposure of an antigen over a period of several hours with an aim to provide essential medications at a therapeutic dose while preventing IgE reactions.<sup>6</sup> This technique was first used for the administration of penicillin and subsequently expanded to other drugs.<sup>7</sup> A comparable model was successfully adapted in our case as the TPN exposure rate was escalated with the goal of

TABLE I. Induction of drug tolerance plan

| Step | Concentration      | Time | Cumulative time (min) | mL/h | Fold increase per step |
|------|--------------------|------|-----------------------|------|------------------------|
| 1    | 1:100              | 15   | 15                    | 0.1  | NA                     |
| 2    | 1:100              | 15   | 30                    | 0.2  | 2                      |
| 3    | 1:100              | 15   | 45                    | 0.4  | 2                      |
| 4    | 1:100              | 15   | 60                    | 0.8  | 2                      |
| 5    | 1:100              | 15   | 75                    | 1.6  | 2                      |
| 6    | 1:100              | 15   | 90                    | 3.2  | 2                      |
| 7    | 1:100              | 15   | 105                   | 6.4  | 2                      |
| 8    | 1:100              | 15   | 120                   | 12.8 | 2                      |
| 9    | Full concentration | 15   | 135                   | 0.2  | 1.5                    |
| 10   | Full concentration | 15   | 150                   | 0.4  | 2                      |
| 11   | Full concentration | 15   | 165                   | 0.8  | 2                      |
| 12   | Full concentration | 15   | 180                   | 1.6  | 2                      |
| 13   | Full concentration | 15   | 195                   | 3.2  | 2                      |
| 14   | Full concentration | 15   | 210                   | 5    | 2                      |
| 15   | Full concentration | 15   | 225                   | 10   | 2                      |

NA, Not applicable/available.

treatment to increase the production of IgG<sub>4</sub> antibodies and to minimize the chance of an IgE-mediated reaction. Potential allergens could include the multivitamins or additives such as polysorbate. This infant previously tolerated 3 intramuscular immunizations containing polysorbate 80. Because our patient was unwell and in urgent need of nutrition, further testing for these agents was not completed.

This case adds to the sparse literature describing severe TPN hypersensitivity to a nonlipid component. Desensitization for tolerance testing, similar to a model used for medication rapid desensitization, was successful. This model could be trialed for future patients with TPN hypersensitivity.

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