Nutrition in Clinical Practice
Volume 36 Number 2
April 2021 398–405

DOI: 10.1002/ncp.10443
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Lipid Emulsion Therapies and Type 1 Hypersensitivity Reactions: Risk Assessment and Management

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Abstract

Over the past decades, awareness and attention given to food allergies has extended further into the realm of pharmacotherapy. Despite the presence of similar ingredients, different intravenous lipid emulsion (ILE)–based medication products have a wide variety of warnings and contraindications for patients with food allergies. Only limited literature is available to guide clinicians in making appropriate medication therapy adjustments to reduce the risk of hypersensitivity reactions in atopic patient populations. Therefore, the authors sought to develop a comprehensive review of potential risk factors or approaches for management of patients with atopic history and need for ILE therapy. Through thorough review of available literature published worldwide, a description of potential contraindications, risk factors, and evaluation methods is presented. Although the current state of knowledge remains relatively poor, this review aims to provide clinicians a better understanding of which risk factors related to the development of hypersensitivity reactions are relevant to lipid emulsion products and how to best manage patients who may be at risk for severe reaction based on their history. Evaluating personal atopic history is essential to the development of an appropriate risk classification system and approaching an individual's therapeutic options. By applying this assessment to local populations, providers should be able to develop an institutional guideline for screening and minimizing risk of substantial hypersensitivity reactions. Finally, a brief review of methods for managing type 1 hypersensitivity reactions is provided in the event that a breakthrough reaction does occur. (*Nutr Clin Pract.* 2021;36:398–405)

Keywords

allergy; hypersensitivity; intravenous fat emulsions; lipid emulsions; parenteral nutrition

Introduction

Perceptions among both the lay public and healthcare professionals suggest that the overall prevalence of food allergies in the United States and around the world is increasing. Although epidemiologic studies struggle to provide consistent results because of the complicated assessment of allergies, recent literature has suggested that the prevalence of food allergy in the developed world is approaching or has surpassed 10%.[1] Assessments of self-reported allergies, immunoglobulin E (IgE) level testing, and rates of hospitalizations because of food-induced anaphylaxis seem to support this observation[1] and have put providers on higher alert when selecting and prescribing medications. A major question that has emerged from this trend is: which drug-food allergy interactions are legitimate (and therefore require change in therapy), and which are hypothetical or low risk? With the number of available lipid emulsion therapies increasing in recent years, the safety of use in patients with soy or egg allergies has been questioned. It is essential that providers have a solid understanding of the relative risks of lipid emulsions in patients with food allergies to make an informed assessment and decide when to alter therapy.

In the United States, there are currently 4 Food and Drug Administration (FDA)–approved intravenous lipid emulsions (ILEs) for the purpose of parenteral nutrition (PN) and 3 medications supplied in lipid emulsion vehicles. These include Intralipid (Fresenius Kabi, Uppsala), Smoflipid (Fresenius Kabi, Uppsala), Omegaven (Fresenius Kabi, Uppsala), and Clinolipid (Baxter, Deerfield) for PN, as well as propofol (Diprivan [Fresenius Kabi, Lake Zurich], generic), clevidipine (Cleviprex [The Medicines Company, Parsippany]), and aprepitant intravenous (IV) (Cinvanti [Heron

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Financial disclosure: None declared.

Conflicts of interest: None declared.

This article originally appeared online on November 25, 2019.

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Therapeutics, San Diego]). Each of these products meets the ASPEN definition of lipid injectable emulsion (aka ILE), "an intravenous oil-in-water emulsion of oil(s), egg phosphatides, and glycerin."[2] They each contain egg derivatives as well as soy, fish, and/or olive derivatives to maintain emulsification or provide appropriate caloric content from fatty acids.[3-9] The presence of these food product derivatives raises the possibility of allergic reaction in a patient with a history of food allergies to 1 or more components. Given that egg, soy, and fish are among the most common food allergens,[10] the likelihood of encountering a patient who requires lipid emulsion therapy and also has food allergies to 1 of its ingredients over the course of a career is high. Through interrogation of the literature surrounding food allergies and type 1 hypersensitivities to lipid emulsion products, this review aims to identify methods for providers to identify high-risk or low-risk interactions and decide whether an alteration of therapy is necessary, as well as to recognize gaps in knowledge requiring additional study.

Allergens in Lipid Emulsions

To determine the risk of allergic reaction to a lipid emulsion product, it is essential to understand the allergenic potential of its individual components. Egg phospholipids, egg lecithin, soybean oil, fish oil, and olive oil are potential allergens included in 1 or more of the aforementioned products, according to individual package inserts (see Table 1).[3-9] It is known that the majority of type 1 hypersensitivity reactions to food are the result of exposure to protein allergens, which tend to be present in low quantities in purified or extracted food products. This distinction is important when identifying allergenic potential, since bulk ingredients or excipients in drug products, which may be derived from an allergenic food but contain no proteins, are less likely to cause an allergic reaction in a sensitized patient. An in vitro study investigating samples of soy lecithin and soy oil suggested that although some proteins were present in very low quantities in all samples, the proteins were unlikely to be major allergens for soybean-allergic patients, if any IgE antigenicity occurred at all.[11] Although this study was specific to soy allergens, this evidence of reduced antigenicity should be consistent across all pharmaceutical-grade products (bulk ingredient or active pharmaceutical ingredient), which are required to meet United States Pharmacopeia–National Formulary ingredient standards for current good manufacturing practice as defined by ingredient-specific monographs and the FDA.

Additionally, individuals' response to allergens can vary significantly depending on how allergens are prepared or treated. This differentiation can lead to complexity in identifying the specific risk that individual products can pose for severe reactions, and likewise, which patients will react severely to a given product. For example, patients with egg allergies may range in reactions depending on whether the product is extensively heated or only lightly cooked.[12] Therefore, patients who have a history of severe reactions to egg in lightly cooked forms may nonetheless tolerate purified, heated, or otherwise treated products that are derived from egg, such as a lipid emulsion medication.

Another important consideration when anticipating potential reactions to lipid emulsion therapies is the concept of cross-sensitization. Across different food classes, varying degrees of cross-reactivity may occur, likely related to the

Table 1. Package Insert Labeling for Potential Allergens Contained In, and Hypersensitivity Contraindications To, Lipid Emulsion Products.[3-9]

Product	Package Insert–Specified Allergen (Mass/Volume %)	Package Insert–Specified Hypersensitivity Contraindication
Parenteral nutrition		
Intralipid (Fresenius Kabi, Uppsala)	Egg yolk phospholipids (1.2%), soybean oil (20%)	None listed
Smoflipid (Fresenius Kabi, Uppsala)	Egg phospholipids (1.2%), soybean oil (6%), olive oil (5%), fish oil (3%)	Fish, egg, soybean, or peanut protein
Omegaven (Fresenius Kabi, Uppsala)	Egg phospholipids (1.2%), fish oil (10%)	Fish or egg protein
Clinolipid (Baxter, Deerfield)	Egg phospholipids (1.2%), soybean oil (4%), olive oil (16%)	Egg and soybean proteins
Other products		
Propofol, Diprivan (Fresenius Kabi, Lake Zurich), generic	Egg lecithin (1.2%), soybean oil (10%)	Egg, egg products, soy, or soy products
Clevidipine, Cleviprex (The Medicines Company, Parsippany)	Egg yolk phospholipids (1.2%), soybean oil (20%)	Soy or eggs
Aprepitant IV, Cinvanti (Heron Therapeutics, San Diego)	Egg lecithin (14.4%), soybean oil (9.4%)	None listed

IV, intravenous.

prevalence of certain proteins within food groups. For example, the likelihood that patients with a food allergy to one fish will react to a distinct type of fish is relatively high, with frequency rates as high as 100% between some classes of fish. Many fish produce similar allergenic proteins (eg, parvalbumin [Gad c 1]), such that when a patient reports an allergy only to a single species of fish, that reaction is usually in the relative absence of IgE antibody to the common fish allergen noted above.[13] This particular cross-reactivity raises the likelihood of reaction to fish-containing ILEs in a patient with any fish allergy, regardless of which species of fish is used to produce the fish oil excipient. This is especially difficult, as manufacturers are unlikely to be able to identify exactly which types of fish are included in the production of fish oil excipients for a given lipid emulsion based on sourcing and manufacturing techniques.

On the other hand, legumes seem to have widely variable rates of cross-reactivity. When researchers looked at cross-reactivity of peanuts and soy or other legumes in US patients (primary legume allergy: peanuts), they found that the likelihood of reaction to other legumes capped at ≈5%.[14] However, a separate study looking at Spanish legume-allergic patients (primary legume allergy: lentils), the rates of cross-reaction to other legumes (including chickpeas, soy, and peanuts) was much higher at 82%.[15,16] This discrepancy likely reflects a difference in dietary habits and sensitization between cultures, in which American patients are more likely to have peanut or soy allergies because of higher exposure compared with chickpeas or other legumes. Despite this clear inconsistency in cross-reactivity between diet types, there is some evidence that the protein vicilin (Ara h 1) and homologues may be the molecular basis for the cross-reactivity that is sometimes seen.[17] Although the possibility of a cross-reactivity between legumes is possible, it remains unlikely that patients with clinical symptoms to only a single legume (especially if peanut or soy) would exhibit an allergic reaction to a different legume-based emulsion product (eg, isolated peanut allergy reacting to soy-based product) based on the available literature.[14-17] That being said, the package insert for Smoflipid does list known hypersensitivity to peanut protein as a contraindication,[4] despite the lack of clear evidence that a reaction is likely to occur. Intralipid contains a higher concentration of soybean oil but does not reflect this same contraindication in the package insert, emphasizing the inconsistency and clinical confusion surrounding this topic.

Finally, the source of medium-chain triglycerides (MCTs) has been noted as a potential source of concern or confusion for providers. Based on previous literature, the primary source of MCTs in ILE products (currently only Smoflipid incorporates MCTs in the United States) is coconut and potentially other tropical nut oils.[18] Although this information is reported in numerous articles, it is not included in the package insert[4] or clearly stated in the product composition information from the manufacturer. Nevertheless, providers and healthcare team members should be aware of this potential source of allergenicity in the unlikely event of a coconut-allergic patient. There have been reports of coconut cross-reactivity with legumes or tree nuts; however, this cross-reactivity is extremely rare and unlikely to occur.[19] In patients who have not been formally assessed for food allergies but have a documented allergy to coconut, a broader allergy workup may be prudent before starting Smoflipid.

Apart from food-based allergens, it is also possible that patients can react to the medication itself or to other product excipients, although the rates of these types of reactions have not been well characterized. This was clearly evident from the decrease in rates of propofol hypersensitivity reactions that occurred after the manufacturers changed the initial formulation from one containing a synthetic emulsion stabilizer to the current lipid emulsion formulation. Later in the development of current formulations, EDTA and/or sodium metabisulfite were added as antimicrobial agents, both of which have known potential for hypersensitivity reactions.[20] Although this example is specific to 1 agent, it raises another important consideration of allergenic potential of lipid emulsion products: hypersensitivity can occur to any component of a medication product, and identification of the compound specifically linked to the reaction can be extremely difficult to determine.

Lipid Emulsions for PN

At present, there are 4 lipid emulsion products that have FDA approval and are currently manufactured as a component of, or in combination with, PN. Based on the understanding of allergenic potential described above and known rates of hypersensitivity to ILEs,[21] history of food allergies or hypersensitivities are generally considered relative contraindications to the use of approved products (see Table 1). Weighing the risk-benefit ratio in patients with an atopic history is supported by the literature surrounding hypersensitivity reactions in patients receiving lipid emulsion–containing PN.

Because of the paucity of data at the intersection of hypersensitivity reactions and lipid emulsions, the majority of primary literature comes in the form of case reports and subsequent review articles. Although there is limited objective data to identify rates of hypersensitivity reactions to PN, this lack of evidence seems to support the notion that significant adverse events are rare, especially given the considerable use of PN in the broader population.

A 2018 article reviewed 28 articles and 33 individual cases of hypersensitivity reactions to PN among both pediatric and adult patients. The majority of these reactions had cutaneous involvement (82%), although rates of anaphylaxis (45%), hypotension (21%), and respiratory

difficulty (42%) after exposure to PN were elevated as well. The rates of severe reactions were exceptionally high in those who were reported to react, though this pattern is isolated from case reports, which are more likely to include severe reactions than may be seen in the normal patient population. Among the 33 individual cases, approximately half (48%) were confirmed or suspected to be associated with the fat component of PN, which included Intralipid, Smoflipid, and Lipofundin (not available in the United States) or an unidentified lipid emulsion. The next most common identified causes were multivitamin solution (33%) and amino acids (9%). Of particular note, 5 patients who developed hypersensitivity reactions attributed to the lipid emulsion component had reported prior atopic history to fish, legumes, egg, or peanut (anaphylaxis). At least 1 patient with no reported prior atopic history had positive radioallergosorbent skin testing for egg white, egg yolk, and soybean on further evaluation.[22]

A separate case report that was published in 2014 identified a 19-year-old patient who developed increased vasopressor requirements, rashes on the chest and forearm, diffuse bilateral rhonchi, and both laryngeal and epiglottal edema after the addition of ILE to PN therapy. Upon review, the patient had a history of soybean allergy and reported an episode of severe hypotension while undergoing short general anesthesia. The patient was treated appropriately, and follow-up revealed positive skin tests to Intralipid and propofol.[23]

This selection of case reports identifies an extremely small minority of the patients who receive PN and further supports the notion that patients without atopic history are highly unlikely to have mild-moderate or severe reactions to ILEs. Even among patients who have some degree of hypersensitivity to PN therapy, many are successfully retrialed or pretreated and have PN readministered without development of severe reactions. It is unlikely that these types of cases would be published or meaningfully reported, suggesting generally low severity of reactions if and when they do occur. Over the past 2 decades, the use of PN has increased,[24] wereas the literature surrounding rates of hypersensitivity reactions still consists primarily of isolated case reports and limited reviews. Regardless of global rates, it should be stated that patients with significant relevant atopic history should be identified and assessed before exposure to ILEs, as the potential for severe hypersensitivity reactions does exist, as evidenced by these case reports.

Additional Considerations for Prevention of Essential Fatty Acid Deficiency in Patients With Allergies

For patients requiring PN and who have severe allergies or are at very high risk of severe allergic reactions to lipid emulsion therapies, ILE may be withheld. In this patient population, there would be a substantial risk or likelihood of developing essential fatty acid deficiency (EFAD), which can occur when <10% of total energy delivery comes from polyunsaturated fat and <2%–4% of calories come from linoleic acid for an extended period.[25]

To prevent or treat EFAD, some options that depend on patient-specific factors and the clinical indication for PN remain. In those who would tolerate enteral challenge, it may be possible to provide small volumes of oral fats alone to try and minimize total intake while preventing EFAD. This may be beneficial in patients who have some enteral access but cannot achieve adequate nutrition through oral intake alone. Additionally, there is some data, though results are mixed, to consider the use of topical fats as a means for delivering some essential fatty acids. In studies that produced positive results, coconut oil, olive oil, safflower oil, or sunflower seed oil, applied topically, resolved some of the clinical and laboratory markers of EFAD. However, it should be noted that a number of reports and studies have also demonstrated unsuccessful attempts to use topical oils to resolve deficiencies. Although this method is not a sure method for resolution of EFAD, it may provide some benefit in select patients. Consideration should be made for a number of factors that can influence transdermal absorption, including skin thickness, hydration status, use of occlusive coverings, comorbid conditions, and whether patients are able to tolerate topical products without development of rash or other irritation. If ILE is not a therapeutic option, topical oils may be a reasonable alternative for prevention or treatment.[25] Finally, the option always remains to challenge (or rechallenge) or desensitize patients to the lipid emulsion therapy in a controlled environment with the guidance of allergy or immunology experts. This decision should include a thorough discussion of all available options before introducing the risk of anaphylaxis, especially in an outpatient setting.

Other Lipid Emulsions

A lipid emulsion can also serve as the carrier for medications with a wide range of indications. Currently approved products in the United States (by generic name) include propofol, clevidipine, and aprepitant IV, and package labeling information regarding potential allergens is described in Table 1.

Because of its long-standing approval, increase in use over the last decade, and multitude of settings of administration, there have been a number of publications addressing the risk of hypersensitivity reactions to propofol. Although there are multiple case reports available that address hypersensitivity reactions to propofol, some of them contain potential confounders. For example, 1 case study identified a 14-month-old patient who presented to their primary care provider and ultimately a local hospital because of increased difficulty breathing secondary to an

upper respiratory infection. The patient decompensated and required intubation with propofol and rocuronium, after which the patient appeared to be having an anaphylactic reaction. Given the patient's previous history of allergies to egg and peanut oil by skin testing, propofol was suspected to be the causative agent, though no confirmatory testing was reported.[26] However, it is also recognized that rocuronium has been associated with anaphylactic reactions,[27] making firm conclusions difficult to draw.

In a separate case report, a 74-year-old previously healthy woman underwent an esophagogastroduodenoscopy with propofol sedation, as she had done twice before without adverse effects. On this occasion, she developed stridor, wheezing, and a drop in oxygen saturation without improvement on nasal cannula oxygenation. Severe epiglottal edema was noted during the subsequent intubation. Patient-reported history included abdominal discomfort to soybean, and follow-up skin testing showed positive results for propofol and 20% Smoflipid, with all other allergens negative.[28] This particular case highlights the potential for lipid emulsions, as with any allergen, to cause sudden and severe reactions in patients with previous allergen sensitization and sensitivity. Although an important reminder, it should also be stated that this occurs infrequently enough to warrant a case report and cannot be expected to occur in every patient with a history of mild allergies to potential ingredients.

To further elucidate that point, propofol, unlike other lipid emulsion products, has been studied in retrospective reviews of hypersensitivity reactions. One article, published in 2016, highlighted 2 Danish studies (titled Study A and Study B) that looked at rates of hypersensitivity reactions in food-allergic patients with exposures to propofol. Study A identified 273 patients with suspected perioperative allergic reactions, 56% of whom received propofol, and performed skin testing, identifying only 4 (2.6%) with positive results on ≥1 allergy test. Only 1 of these patients had a positive serum tryptase level (standard for IgE-mediated reactions), and all 4 had negative specific IgE to egg and soy,[29] suggesting a reaction to the medication or other excipients, as opposed to cross-allergy between food allergens and the drug product. Study B identified 115 patients with positive IgE testing to egg, soy, or peanuts who had undergone 214 total procedures with general anesthesia. Among the 80% who received propofol, no allergic reactions were reported, despite the known sensitization to potential allergens or cross-allergens.[29]

In pediatric patients, a separate review of patients who received an esophagogastroduodenoscopy with general anesthesia noted that although rates of propofol use were lower in patients who had a history of egg or soy allergy, or of eosinophilic esophagitis, no significant difference was seen in total complication rates between those who received propofol and those who did not, regardless of atopic history.[30] The American Academy of Allergy, Asthma & Immunology recognizes and supports the conclusion based on the apparent safety across the literature and the relative lack of reports of hypersensitivity reactions compared with the frequency of use for sedation. An official statement by the organization states that "Patients with soy allergy or egg allergy can receive propofol without any special precautions."[31] This American Academy of Allergy, Asthma & Immunology statement is supported by anesthesia literature[32] and in clinical practice.

Given the recency of approval of clevidipine and aprepitant IV, as well as their relatively infrequent use compared with propofol, there were no case reports or primary literature identified that described hypersensitivity reactions to either agent. The conclusions drawn from the data surrounding propofol and ILE use can be considered when assessing the relative risks of other lipid emulsion–based IV therapies.

Clinical Assessment and Screening

Efficient assessment and screening of patients with potential for hypersensitivity reactions is vital to both risk mitigation and assurance of appropriate medication therapy. Since there are a number of non-modifiable patient factors that can influence reaction severity, it can be extremely difficult to assess potential risk based solely on previous exposures.[33] However, providing potential allergens directly to the bloodstream in the form of ILE, especially to patients who may have more sensitive immune systems because of atopic history or current illness, is unlikely to reduce the risk of severe reaction compared with oral exposure. Therefore, developing a screening tool for identifying which patients are more likely to experience a reaction may help guide risk-benefit assessments when questionable situations do arise. Based on overall literature analysis and clinical experience, there seem to be a few broad categories in which patients' risk of severe hypersensitivity reaction can be described (Table 2)[34]:

1. High risk: patients with known, moderate-severe atopic history to the product. In patients who have had a prior significant reaction (ie, hives, edema, anaphylaxis) to lipid emulsion–based products should be considered high risk for future severe reactions to the same or similar products.
   - For example, a patient who developed laryngeal edema from Intralipid should be considered high risk for reaction because of other ILEs.
2. Moderate-high risk: patients with known, severe atopic history to ingredients or potential ingredients within the product. Patients with anaphylaxis, hives, or other severe reactions to egg, soy, or other potential ingredients (especially cooked products) may be

Table 2. Risk Assessment of Varying Degrees of Atopic History for Patients Who May Need ILE Therapies.

Risk of Severe Reaction to ILE	Prior Atopic History	Example Scenario
High risk	Severe to product	Hives to ILE
Moderate-high risk	Moderate-severe to ingredients/potential ingredients	Anaphylaxis to cooked egg product
Moderate risk	Mild to product OR Severe to unadulterated ingredients but tolerates adulterated	Hives to raw egg (but tolerates cakes)
Low risk	Mild-moderate to potential ingredients	Mild pruritus to soybean
Minimal risk	None	No known allergies

ILE, intravenous lipid emulsion.

at a meaningful risk of allergy to products that have components associated with those allergies.
   - For example, a patient with anaphylaxis to cooked egg products should be considered moderate-high risk for reaction because of egg-containing lipid emulsion products.
3. Moderate risk: patients with known atopic history of mild reactions to the product OR patients with history of severe reactions to uncooked allergens but may have tolerated cooked allergens. If a reaction to lipid emulsion product has occurred before but was not severe or was easily treated and successfully retrialed, they should be considered moderate risk for reactions.
   - For example, a patient with hives to raw egg but who tolerates cakes may be considered moderate risk for reaction to egg-containing lipid emulsion products.
4. Low risk: patients with known atopic history of mild-moderate reactions to ingredients or potential ingredients within the product.
   - For example, a patient who develops mild pruritus eating soybeans should be considered low risk for a severe reaction from soy-containing lipid emulsion products.
5. Minimal risk: patients with no atopic history to potential ingredients.

An extensive allergy history, including the nature and timing of reactions, should drive the evaluation of risk. Through interpretation of medical records and conversation with the patient, it should be determined which allergies appear to be true type 1 hypersensitivity reactions and which may merely be intolerances, unrelated to immune sensitization. When a true type 1 reaction appears to exist, thorough understanding of past experiences and relevant exposures should be discussed and described whenever possible. If a patient or family/caregiver is unable to provide adequate information, it is reasonable to consider skin and/or serum testing to identify whether an allergy to the product exists. Interpretation of these tests should be based on standard of practice or institutional policies but should not preclude or replace a meaningful discussion of risks and benefits with the care team and the patient.

If a patient falls under moderate or greater risk categories, it is reasonable to consider or select alternative agents to achieve the same therapeutic objectives. Where this is not possible (eg, anaphylaxis to soy requiring long-term PN), appropriate explanation of the relative risks and benefits should be provided to the patient and clinical decisions based on that discussion. If the patient is in agreement with a trial of the agent, monitoring should be frequent, robust, and with adequate resources available to manage a severe allergic reaction should it occur. On the other hand, patients who fall under low-risk or minimal-risk categories are unlikely to experience meaningful or severe allergic reactions to lipid emulsion products. Administration in these patients should be accompanied by appropriate monitoring required for any drug product, and the materials necessary to treat a reaction should be readily accessible.

In the setting of hypersensitivity reactions, there is the potential to be both overaverse to risk as well as overly lax with patient exposures. It is clear that the possibility of hypersensitivity reactions to lipid emulsion products is a legitimate risk that should be considered in every patient, particularly in those with relevant atopic history. However, the risk is not so high that it should prevent appropriate therapy for patients who would benefit, especially if they are not at a high risk for severe or life-threatening allergic reactions. Every patient situation will be unique, but the development of institutional standards or guidelines may be beneficial in setting a framework for how to manage these cases when they occur.

Management of Hypersensitivity Reactions

With proper risk mitigation strategies such as those described above, the incidence of hypersensitivity reactions to lipid emulsion therapies should remain low. However, it is essential that appropriate treatment is available and administered should a reaction occur. Type 1 hypersensitivity reactions to lipid emulsion therapies occur by the same

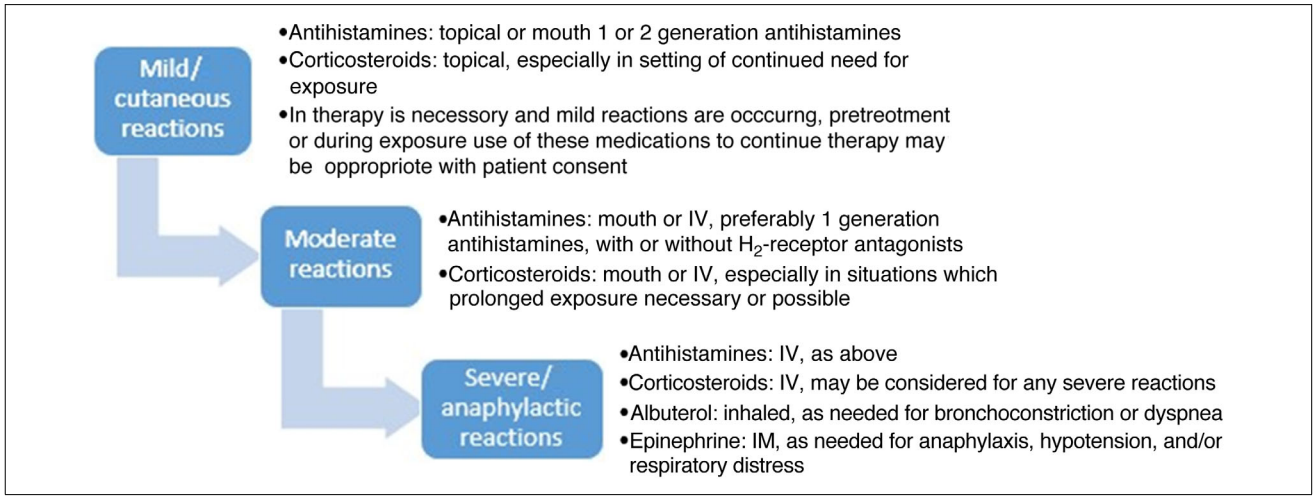

Figure 1. Pharmacologic treatments for type 1 hypersensitivity reactions. In patients who are receiving IV lipid emulsions, the first step in treatment of hypersensitivity reaction should always be to remove the offending agent to the greatest degree possible. IV, intravenous; IM, intramuscular.

mechanism as any other such reaction and should be treated in the same way. Since ILE therapies are administered over extended interval or continuous infusions, the first step to managing any episode of hypersensitivity is to stop the infusion. Without adequate "source control," other efforts will be ineffective in slowing the rate and severity of reaction. In deference to institutional allergy or anaphylaxis protocols, medications or medication classes which may be appropriate for the treatment of hypersensitivity reactions are presented in Figure 1.[35]

Before initiation of lipid emulsion therapy in a patient deemed to be at risk for a hypersensitivity reaction, the patient or caregiver should be educated on signs and symptoms to watch for and how to respond. In the inpatient setting, response can be quick and aggressive but only when symptoms are recognized and reported. In other settings, knowing when self-treatment may be appropriate and when to call emergency services may save a life if a severe reaction occurs. A thorough discussion of risk and benefits, along with how and when to respond to hypersensitivity reactions, should occur before final therapy decisions are complete. As with any allergy or medication intolerance, a thorough workup or assessment should occur after any reaction. This should be clearly documented and explained to the patient in plain language so that the patient or caregiver can describe the reaction and its potential impact on future medication therapies.[35]

Conclusion

The body of literature surrounding rates and risk factors for hypersensitivity reactions to lipid emulsion therapies in patients who have prior atopic history is limited at best. Outside of case reports and a few limited review articles, it is unclear exactly how cautious providers should remain in the setting of allergies to soy, egg, or other potential ingredients. This dearth of primary literature reflects the relatively infrequent incidence of severe hypersensitivity reactions but supports the idea that in many cases, a review of the patient's allergy history would have helped reduce or eliminate the risk of severe reaction. A broad, categorical risk stratification was developed through evaluation of the literature which, though not validated, may be useful in screening and assessing the patient's relative risk of hypersensitivity reaction. This tool should be used in conjunction with, rather than as a replacement for, a comprehensive allergy review, discussion with the patient/caregiver, and evaluation of alternative options. By assessing the patient's risk for reaction early and often, providers can reduce the risk of severe allergies and may be more likely to respond quickly and appropriately if the risk has been documented before initiation.

Lipid emulsion therapies may contain food allergen components and list contraindications for use in the package inserts after approval. The relative risk of hypersensitivity reaction in the overall population is very low, but the potential for severe reactions in certain patients with relevant atopic history does exist. The frequency of use of these medications should not lull providers into the notion that these medications carry no risk, and they should continue to evaluate the potential for allergic reaction in any and all patients to be initiated on lipid emulsion therapy.

Statement of Authorship

M. Pleva and S. Nordbeck equally contributed to the conception and design of the research; N. Franz contributed to the design of the research; N. Franz contributed to the acquisition

of and analysis of the data; N. Franz, M. Pleva, and S. Nordbeck contributed to the interpretation of the data; and N. Franz drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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