PHARMACONUTRIENTS IN PARENTERAL NUTRITION

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1 INTRODUCTION

Scientific research on parenteral nutrition (PN) has evolved in recent years towards the development of more complex mixture with specific components that provide value beyond nutrition. Not only do they have the objective of increasing tolerability and reducing the complications or adverse effects of PN when administered for a prolonged period; they also are aimed at adjusting to the wide variety of pathological situations in which individualized nutritional support plays a therapeutic role that complements the rest of the clinical approach to the patient.

The purpose of this review is to point out the benefits of the use of certain pharmaconutrients with specific functional activity that have sufficient scientific evidence for their use in PN to be considered beneficial in particular clinical situations.

2 PRIMARY PHARMACONUTRIENTS

Omega-3

CHARACTERISTICS

Fatty acids (FA) are a fundamental part of PN due to their high energy content, their structural role in the cell and because they are a source of essential nutrients such as linoleic acid (LA) and α-linolenic acid (ALA). Structurally, according to the size of the FA chains that bind to triacylglycerol to construct triglycerides, we refer to short-chain triglycerides (up to 4 carbon atoms), medium-chain or MCT (between 6 and 12 carbon atoms) and long-chain or LCT (> 14 carbon atoms). According to the degree of unsaturation of LCTs and the position and number of double bonds, different FAs are classified while at the same time their organic functionality and metabolism are determined.1

We will analyze the clinical benefits in depth based on the evidence on omega-3, taurine, and glutamine lipids, specifying the most relevant clinical situations in which their administration is recommended or may be beneficial in order to give our view on their most efficient use.

Because of their role in nutritional therapy, a brief summary of the importance of a daily supply of micronutrients is also included: Vitamins and oligoelements according to current recommendations and the technical considerations of preparing nutritional mixtures for parenteral use.

1
Omega-3 FAs (ω3) have their first double bond between carbon 3 and 4 and among these, ALA (18:3 n-3) is the most important due to its essential character. ALA, through a metabolic process of desaturation and elongation, gives rise to other ω3 components with important biological functions such as EPA (eicosapentaenoic acid, 10:5 n-3) and DHA (docosahexaenoic acid, 22:6 n-3), both of which are precursors called "Eicosanoids n-3", some of which become prostaglandins (PGI3, PCI3, TX3) and leukotrienes (LTs) due to the action of the cyclooxygenase and lipoxygenase enzymes, respectively. These compounds counteract the activity of eicosanoids from series 6, meaning they act as anti-platelet aggregation and anti-inflammatory substances (Figure 1). In addition to this functionality, the importance of these FAs in the regulation of gene expression mediated by their interaction with various nuclear receptors, primarily type PPAR and through stimulation of genetic transcription of certain genes associated with p-oxidation of FAs, the use of lipid energy, synthesis of steroid derivative and stimulation of bile acid synthesis have been described. Based on this activity on gene expression, ω3 FAs are considered therapeutic agents capable of improving situations such as dyslipidemia, metabolic syndrome, insulin sensitivity in type 2 diabetes and liver steatosis.

The immunomodulation benefits of ω3 FAs depend on a sufficient and balanced supply related to polyunsaturated ω6 FAs. The composition and effects of different lipid emulsions used for administration were compared, and it was determined that the most favorable ratio of ω6/ω3 is within a range of between 2:1 and 4:1.

In this way, the clinical results that have been obtained with the different lipid emulsions have evolved to improve their composition. The emulsions that were initially available commercially, with an elevated ω6 content often caused hypertriglyceridemia, hypercholesterolemia and phospholipidemia and resulted in long-term liver dysfunction.

Various lipid emulsions for nutritional support are currently available on the market for parenteral administration of necessary lipids. They are formulated with complex FA mixtures and contain different quantities of ω3 and ω6 in their composition. The ideal solution should easily metabolized and have anti-inflammatory properties and not increase oxidative stress or be immunosuppressive (Table I).

ω3 FAs are considered therapeutic agents capable of improving situations such as dyslipidemia, metabolic syndrome, insulin sensitivity in type 2 diabetes and liver steatosis.

Figure 1

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Endothelial cells</th>
<th>Leukocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>EPA</td>
<td>EPA</td>
<td>EPA</td>
</tr>
<tr>
<td>Cyclooxygenase pathway</td>
<td>Cyclooxygenase pathway</td>
<td>Cyclooxygenase pathway</td>
</tr>
<tr>
<td>Thromboxane A2 platelets agents vasoconstrictor</td>
<td>Thromboxane A3 biologically inactive</td>
<td>Leukotriene B4 pro inflammatory chemotaxic cellular adhesion</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin I2</td>
<td>Prostaglandin I3</td>
</tr>
<tr>
<td></td>
<td>vasoconstrictor</td>
<td>vasoconstrictor</td>
</tr>
<tr>
<td></td>
<td>anti-platelets</td>
<td>anti-platelets</td>
</tr>
</tbody>
</table>

Leukotriene B5 anti-inflammatory non-chemotaxic inhibits adhesion
**Benefits**

Independent of their energetic function, ω3 FAs have been shown to have effects on immunomodulation and organ protection. This has been demonstrated in many experimental studies that demonstrate how the supply of ω3 attenuates inflammatory reactions, improves defenses against aggressions, increases splanchnic flow and the intestinal barrier function in septic patients and prevents tumor growth.8

1. **Immunomodulatory effect**

The incorporation of ω3 in the phospholipids of cell membranes, replacing ω6, promotes fluidity and modifies the function of enzyme receptors, reducing signal transduction and thereby nuclear transcription and gene expression of TNF-α and IL-1 pro-inflammatory mediators.

Though the benefits of long-term dietary ω3 are known, studies have been carried out which demonstrate that short-term infusion (several hours) of parenteral ω3 significantly reduces the ω6/ω3 ratio in plasma and in cell membranes, which limits production of pro-inflammatory cytokines in monocytes when faced with endotoxins.9

The incorporation of ω3 in cell membranes occurs rapidly, both in circulating blood cells and tissues. This incorporation involves a structural change in the membranes and modifies the cascade response of phospholipids that act as secondary messengers in intracellular signal transduction. They also produce changes in the innate immune response since some receptors (TLR2 and 4) involved in the inflammatory response to bacteria and endotoxins are activated by ω6 FAs and are inhibited by ω3 FAs. Activation of TLR2 and 4 receptors stimulates expression of the κB nuclear factor involved in cyclooxygenase synthesis. Conversely, EPA and DHA act on PPAR-type intracellular receptors whose function is to limit this pro-inflammatory response by blocking gene expression.10

2. **Protection against liver damage**

Prolonged PN can provoke hepatobiliary dysfunction due to the action of pro-inflammatory phytosteroles and ω6 FAs contained in conventional soy-based lipid emulsions that can damage liver tissue through the production of free radicals and lipid hydroperoxides.

Hepatocellular tolerance following administration of different lipid emulsions has been studied. A comparison of administration of an olive and soy formula with another that also contained fish oil and MCT in postoperative patients for 5 days revealed poorer tolerance with the former. Liver enzyme markers and triglycerides were significantly altered in the first group versus the second.11

A solution based exclusively on fish oil has been successfully used to revert the liver damage produced by long-term lipid emulsions.12

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**Table I - Percentage of different types of lipids in commercially available lipid emulsions (in %)**

<table>
<thead>
<tr>
<th></th>
<th>Intralipid®</th>
<th>Lipofundina®</th>
<th>Clinoleic®</th>
<th>Lipoplus®</th>
<th>SMOFlipid®</th>
<th>Omegaven®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean oil</td>
<td>100</td>
<td>50</td>
<td>20</td>
<td>40</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Olive oil</td>
<td>-</td>
<td>-</td>
<td>80</td>
<td>-</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>MCT</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>50</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Fish oil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>15</td>
<td>100</td>
</tr>
</tbody>
</table>
Taurine

CHARACTERISTICS

Taurine is a β-amino acid whose chemical structure contains a sulfonic group instead of a carboxylic group (Figure 2). Metabolically, it is synthesized in the body from cysteine and it is primarily intracellular with a concentration of between 5-50 mM. It is synthesized fundamentally in the liver and the brain through a process that requires B6, with a daily synthesis capacity of between 50-125 mg/day. Although it can be synthesized in other tissues from other substrates such as N-acetylcysteine, glutathion or methionine, endogenous biosynthesis capacity is limited. Therefore, an exogenous supply from the diet is required, with a recommended daily dose of taurine of 200 mg/day in adults.

Taurine excretion, in addition to forming bile conjugates (tauro-conjugates) occurs in the urine through glomerular filtration in such a way that the kidney maintains homeostatic balance through tubular reabsorption mechanisms.

During the first weeks of life it is essential for premature babies and neonates due to the absence of the cysteine-sulphinic decarboxylase enzyme and their inability to carry out renal reabsorption,

and it is present in breast milk at concentrations of between 30-40 mmol/100 ml.

Despite being a non-protein amino acid, it is involved in several functions, primarily in the formation of conjugated bile acids, in the central nervous system, in muscle, the heart and the retina. It participates in stabilization of membrane potential, modulation of calcium transport, osmoregulation, neuromodulation, maintaining antioxidant capacity and inhibition of phosphorylation of certain proteins, in addition to being fundamental for leukocyte function (Table II).

BENEFITIS

Hepatic function

Bile acids are conjugated primarily with taurine and glycine (in a 3:1 proportion) in order to maintain solubility, facilitate excretion and avoid liver toxicity during the enterohepatic circulation. Conjugation in neonates is exclusively with taurine during the first three weeks of life. In addition, tauroconjugates have choleretic activity which avoids cholestasis.

Cholestasis associated with prolonged or inadequate PN is a common complication and has been associated with diets that are deficient in taurine and its precursors. A possible nutritional deficit in vitamin B6 or liver alteration that can limit endogenous synthesis of taurine from its precursors can transform this amino acid into essential.

Although the supplementary supply of intravenous taurine in PN allows plasma levels to normalize, it has not been shown to restore altered liver function in adults liver. The liver protective role has recently been studies in patients with cholestasis caused by prolonged PN and its possible synergistic action with ω3, obtaining favorable analytical results, though the synergy has not been able to be demonstrated.

Table II - Biological functions of taurine

<table>
<thead>
<tr>
<th>Biological functions of taurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated Bile acids formation</td>
</tr>
<tr>
<td>Cholesterol excretion</td>
</tr>
<tr>
<td>Osmoregulation and cell volume regulation</td>
</tr>
<tr>
<td>Ion transport (Na+, Cl- and Na + -Ca2 + exchange)</td>
</tr>
<tr>
<td>Membrane stabilization</td>
</tr>
<tr>
<td>Inhibition of protein phosphorylation</td>
</tr>
<tr>
<td>Development and maintenance of retinal function</td>
</tr>
<tr>
<td>Defensive action of neutrophils (Synthesis of N-chlorotaurine)</td>
</tr>
<tr>
<td>Antioxidant. Removing reactive carbonyl compounds</td>
</tr>
<tr>
<td>Glucose homeostasis</td>
</tr>
<tr>
<td>Neuronal development of the fetus and newborn</td>
</tr>
</tbody>
</table>

Figure 2 - Molecular structure of taurine

![Figure 2 - Molecular structure of taurine](image)
**Development and visual function**

Taurine is the most abundant amino acid in the retina and it is essential for normal vision in children fed by PN without taurine for a prolonged period of time, there were retinal anomalies with modifications in the electroretinogram associated with low plasma taurine levels. Supplemental administration of taurine reverted these anomalies.

**Immune system and sepsis**

Taurine is very abundant in platelets and neutrophils. It participates in N-chlorotaurine synthesis which is used by neutrophils in the defense against microorganisms. Its antioxidant activity protects against hypoxia, inhibits apoptosis and avoids formation of free radicals. In patients in a catabolic state (sepsis, trauma or critically-ill patients) a deficit in plasma taurine levels has been observed, which is associated with worsening of metabolic and cardiorespiratory function. In addition, malnourished oncology patients have a taurine deficit that may revert with a supplemental supply in PN.

**Diabetes**

Due to its antioxidant role and its role in eliminating cholesterol in the bile, a deficit in taurine has been shown to accelerate the onset of some complications of diabetes in the retina, nerves and kidneys, as well as the onset of atherosclerosis and microangiopathy. Its anti-inflammatory and osmoregulation effects, as well as its effects on glucose homeostasis, provide beneficial effects by reducing insulin resistance, increasing insulin secretion, improving the lipid profile and limiting the complications of diabetes.

**Cardiac function**

Binding of taurine to the sarcolemma of cardiac muscle cells promotes calcium transport and has an anti-arrhythmic, chronotropic and positive inotropic effect.

In patients with heart failure, it has beneficial effects due to its action in the kidney, which promotes diuresis by modulating secretion of natriuretic factor and vasopressin. In addition, it can minimize some of the adverse effects of angiotensin-II, such as hypertrophy and cardiac remodeling, due to its modulation of calcium transport.

**Neonatal and neurologic development**

Neonates have greater taurine requirements due to their needs for neurological and visual development. Taurine concentration is highest in nerve tissue, particularly in the developing brain, and it helps regulate neuron volume as a response to osmotic changes. Due to its antioxidant and membrane stabilization properties, it may be important in the prevention of tissue injuries such as periventricular hemorrhage, premature retinopathy, chronic pulmonary disease or necrotizing enterocolitis in premature neonates.

**Glutamine**

**CHARACTERISTICS**

Glutamine is the most abundant amino acid in blood, with baseline concentrations of up to 650 mmol/l. In addition, it is the most abundant intracellular amino acid and constitutes 61% of amino acids in skeletal muscle. It acts as its primary tissue donor and transports, together with alanine, more than half of the circulating nitrogen in amino acids.

Glutamine is an amino acid that was classically considered as non-essential since under physiological conditions it is synthesized in sufficient quantities to cover the body's needs. However, it is currently considered conditionally essential given that during conditions of metabolic stress, demand for glutamine increases and the body cannot synthesize it in sufficient quantities to satisfy demand.

The actions of glutamine in the body are very diverse and we can classify them into three groups (Table III):

a) Metabolic functions.

b) Cell proliferation, differentiation and survival.

c) Modulation of the inflammatory response.
Glutamine is a metabolic substrate with various possibilities since it is incorporated in protein synthesis but also is reversibly transformed into glutamate by glutaminase, being an amino group donort or vice versa, capturing it, playing an essential role in tissue ammonia elimination given that it captures it in peripheral tissues and releases it in the liver and renal cortex. In the kidney, the amino ions produces contribute to acid-base balance.

Other metabolic functions of glutamine, after deamination, include synthesis of the nucleotides asparagine and glucosamine by the amino group, amino acid synthesis (by transamination), proteins, GABA or folate by the resulting glutamate group, which can enter the Krebs cycle via transamination in which it is transformed into ketoglutarate and can be used in energy metabolism or for the synthesis of other diverse compounds.

In addition to being a metabolic substrate, it stimulates lipid synthesis of lipids, synthesis of glycogen, liver and renal gluconeogenesis and synthesis of muscle protein.

Glutamine also modulates the expression of genes that code for enzymes involved in amino acid metabolism in the liver and intesti ne (phosphoenolpyruvate kinase, glutamine synthetase and argininosuccinate synthetase) and the metabolism of FAs and adenine nucleotides in the heart (palmitoyl-carnitine transferase and adenylsuccinate synthetase isoenzyme 1). Finally, production of glutamate from glutamine reverts the stimulating effect of IL-1 beta on expression of the gene for argininosuccinate synthetase 1, which is why glutamine can regulate its own expression through different pathways based on the cell type and pathophysiological conditions.

b) Glutamine contributes to cellular trophic effects through the synthesis of proteins and nucleotides, decreasing proteolysis, modulating certain growth factors such as EGF and growth hormone and inhibiting apoptosis. Some of these effects are mediated by synthesis and activation of specific transcription factors in various cell types. It stimulates expression of factor c-jun and increases ornithine decarboxylase levels, which leads to polyami ne synthesis. It activates two types of kinases in enterocytes, ERK and JNK. These are involved in cellular differentiation and proliferation, respectively. It inhibits some genes involved in protein degradation and apoptosis while in tumor cells such as human breast cancer, and it has a pro-apoptotic effect.

c) The immunomodulation effects of glutamine are mediated by modulation of some transcription factors, especially NF-kappaB, reducing production of inflammation mediators through its ability to induce expression of heat shock proteins.

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Table III - Biological functions of glutamine

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Cell proliferation, differentiation and survival</th>
<th>Modulation of the inflammatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of tissue ammonium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contribution to acid-base balance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthesis of other substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulating of lipid, glycogen and muscle protein synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation of gluconeogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation of genes expression involved in metabolism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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a) **Glutamine is a metabolic substrate with various possibilities** since it is incorporated in protein synthesis but also is reversibly transformed into glutamate by glutaminase, being an amino group donor or vice versa, capturing it, playing an essential role in tissue ammonia elimination given that it captures it in peripheral tissues and releases it in the liver and renal cortex. In the kidney, the amino ions produces contribute to acid-base balance.

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BENEFITS

Parenteral administration of glutamine dipeptide in patients who have an increased demand, meaning in situations of metabolic stress, may halt the exiting of glutamine from muscle tissue, thereby avoiding depletion, given that skeletal muscle is the primary glutamine donor tissue, and it increases circulating levels of glutamine. Parenteral glutamine improves the response to metabolic stress by being able to contribute to arginine synthesis, and therefore nitrous oxide, which increases vasodilation. It also improves the nitrogen balance, preventing expansion of extracellular water, reducing fluid retention, and possibly having a beneficial effect on tissues that have an elevated level of proliferation, such as intestinal mucosa and lymphocytes. Administration of glutamine reduces atrophy of intestinal villi and the risk of intestinal necrosis and stimulates the immune system, facilitating the activity of natural killer cells. In patients with cancer, glutamine increases the selectivity of anti-tumor drugs by protecting healthy tissues from oxidative damage by increasing intracellular glutathion levels after being transformed into glutamate by deamination.

THE IMPORTANCE OF PHARMACONUTRIENTS IN DIFFERENT TYPES OF PATIENTS ON PARENTERAL NUTRITION

a) Surgical patients

Various comparative clinical trials have been carried out on surgical patients to evaluate the effect of lipid emulsions with or without omega-3. Although some non-significant results have been obtained, several studies demonstrated that lipid emulsions enriched with ω3 may reduce hospital stay, infectious complications and SIRS in postoperative patients, especially of the oncological type. Improvement in the immunological status and liver function has also been demonstrated in a comparative clinical trial on a mixture with MCT.

PN-associated liver affection is a significant problem in patients who require PN for a prolonged period, including surgical patients. Administration of low concentrations of taurine has been associated with changes in bile composition and liver histology. The hepatoprotective role of taurine has been demonstrated in patient in whom signs of cholestasis have appeared following PN, significantly reducing liver damage markers (ALT, AST and GGT).
Administration of glutamine in PN in patients undergoing abdominal surgery has been shown to improve nitrogen balance compared to similar patients who received PN not supplemented with glutamine. A meta-analysis published in 2006 by Zheng et al. demonstrated with statistical significance how patients who were administered glutamine in PN accumulated a mean of 8.35 grams more nitrogen (52 grams of protein) than the corresponding controls. In addition, glutamine supplementation in the PN of these patients improved the immune response. Studies have demonstrate that C-reactive protein levels were reduced and the postoperative inflammatory response was improved.

As a result, they also demonstrated in the aforementioned meta-analysis that there was a 76% decrease in the incidence of infection and this may be associated with another of the results in the same meta-analysis that showed hospital stay was reduced by 3.55 days, which is consistent with the 3.25-day reduction in another meta-analysis published in 2004 by Jiang et al.

b) Critically-ill patients

The evidence of the clinical benefits of supplying omega-3 to critically-ill patients is inconsistent. According to a systematic review carried out in 2011, including studies with ω3 both parenterally and enterally, significant benefit has only been obtained via the enteral route. A subsequent review revealed similar results, but the poor consistency of the studies stopped any conclusions on clinical benefit to be made except in the case of hospital stay.

However, a study that analyzed various analytical parameters on inflammation and liver damage revealed a significant reduction in markers such as IL-1, IL-6, IL-8, IFNγ and TNF-α and an insignificant decrease in liver markers and rate of infections.

The role of taurine in critically-ill patients and trauma patients has been studied for its importance in defense against infections, sepsis and the prevention of cholestasis. There is a decrease in plasma taurine levels in these types of patients that improves significantly with supplementation. It is justified to consider supplementation since the availability of taurine in plasma is functionally related to a greater defense capacity in effector cells. Susceptibility to the tissue damage and liver and lung dysfunction caused by inflammatory mediators is reduced.

Supplementation of the PN administered to critically-ill patients with glutamine has been shown to improve insulin resistance, thereby decreasing hypoglycemia when compared with non-supplementation, meaning patients require less insulin for metabolic control.

In addition, critically-ill patients supplemented with parenteral glutamine had a 24% lower incidence of infections in general and pneumonia in particular, which we see associated with mechanical ventilation in our hospitals.

Finally, but of great importance, a decrease in mortality of 33% or 29% has been demonstrated in a meta-analysis published by Wishmeyer in 2008 and the 2009 Canadian Guidelines.

c) Acute pancreatitis

Glutamine-supplemented PN administered to patients with acute pancreatitis improves nutritional parameters and the inflammatory response when compared to non-supplementation. As a result, it has also been shown to decrease the incidence of general and infectious complications and particular, as well as reduce mortality.

d) Pediatrics

The safety and utility of supplying omega-3 lipids to pediatrics and neonatology patients has been studies with good results. Comparative trials versus other conventional lipids revealed favorable effects in pediatric patients in reducing bilirubinemia, improving the plasma lipid profile (ω6:ω3 ratio) and EPA, DHA and α-tocoferol levels.

The safety and clinical benefits have also been studied against other lipids with results similar to the above. In this case, a significant decrease in GT levels was also seen, which is evidence
of an advantage in preventing cholestasis.\textsuperscript{39} Oxidative stress was also significantly reduced in neonates who were supplemented with \( \omega 3 \) as measured with serum antioxidant numbers such as vitamins A, E and the combined TAP variable (total antioxidant potential; a quantitative measure described by Griffits in 2002), though the differences in the clinical variables were not significant.\textsuperscript{40}

As stated previously, taurine in neonates is an essential amino acid, so the need and benefits of supplementing it have been widely documented for many years.

\section*{IMPORTANCE OF DAILY ADMINISTRATION OF VITAMINS AND TRACE ELEMENTS}

APrior to the development of the multilayer photoprotective PN bags currently being used universally, practice guidelines did not recommend adding vitamins and oligoelements concomitantly to PN and to administer them immediately after addition of micronutrients to avoid degradation.

Various studies were published in the 80s that described stability problems due to interactions between the microelements with vitamins and the action of light. According to studies, vitamin C suffers oxidation and copper catalyzes this reaction. Thiamine is degraded by a reduction process caused by sodium metabisulfite and exposure to light. Vitamin A is very sensitive to light, highly unstable in lipid-free PN and can absorb the plastic material. Losses of folic acid and riboflavin in the presence of light were also described, as were losses of vitamins A, D, E, C and folic acid in lipid-free PN in PVC bags. Therefore, the recommendations were to administer oligoelements and vitamins on alternate days and recommend that they be included in PN bags at the moment of administration or at least on the same day.

Currently, with our understanding of the causes of degradation, multilayer bags with EvA (Ethyl-Vinyl-Acetate copolymer) plus a UV filters have been developed in which ternary mixtures can be formulated in which vitamin degradation is minimal. The stability of vitamins and oligoelements was analyzed in this type of bag and it was determined that vitamins A, E, C, thiamine, riboflavin, nicotinamide, pirdoxine, biotin, cyanocobalamin, folic and pantothenic acid were stable for 4 days in refrigeration and that only 60\% of vitamin C remained on the first day and 40\% by the fourth day.\textsuperscript{41}

In the case of vitamin C, it is now known that its primary cause of degradation is the oxidation that results from the residual air in the bag and due to the permeability of the bag to oxygen. The new multilayer bags avoids the passage of oxygen through the bag and decreases this degradation in large part in addition to avoiding the interaction with copper, allowing the stability to be increased by between 2 and 7 days.\textsuperscript{42}

Independent of the technical limitations, clinical recommendations insist that a daily supply of micronutrients is necessary at least in critically-ill, malnourished or long-term PN patients.\textsuperscript{43} The inclusion in the market of triple-compartment bags allows PN to be used in certain situations in which the technical means necessary for adapted nutrition are not available, but it should be pointed out that these do not contain micronutrients and they must be added prior to administration.
Scientific societies and international organizations insist on these recommendations. The official organ of scientific expression of the Spanish Hospital Pharmacy Society, in its 2009 monograph on standardization of specialized nutritional support, states in the epigraph on patient safety (Practice Standard FE.16) that it is necessary to "add vitamins and oligoelements to PN daily."44

At the same time, the European Society of Enteral and Parenteral Nutrition, in its 2009 article "ESPEN Guidelines on Parenteral Nutrition: Surgery" offers a grade C recommendation on the following: "In those patients after surgery who are unable to be fed via the enteral route, and in whom total or near total PN is required, a full range of vitamins and trace elements should be supplemented on a daily basis."45

The Directory Committee of the American Society of Parenteral and Enteral Nutrition (ASPEN), in the number of Safe Practices in Parenteral Nutrition, insists that all patients with PN must receive the necessary dosage of vitamins and micronutrients in sufficient quantities that meet the specific FDA requirements for adults and children and parenteral preparations.46

Despite all of the currently available evidence on the stability of vitamins and oligoelements administered concomitantly in ternary PN formulas in multilayer bags, this practice is not universal. A survey was carried out in Spain in 2011 to evaluate adherence to the recommendations. It revealed that in almost a third of hospital, the practice of administering vitamins and oligoelements on alternate days was used despite the use of photoprotective multilayer bags.47

In conclusion, we should keep in mind that in malnourished hospitalized patients, it is very common to find micronutrient deficiencies, both in vitamins as well as oligoelements. In addition, these deficiencies may be aggravated during the pathological process because sufficient or adequate administration is not carried out, requirements or losses are increased, some biochemical processes are altered due to organic alterations or the immune status is diminished. Therefore, we must consider daily supply of micronutrients to be not simply a nutritional supplement but rather that it plays a fundamental therapeutic role.
RECOMMENDATIONS

Administration of the pharmaconutrients in PN is recommended in different cases according to published clinical trials and meta-analyses and, based on these, various clinical guidelines have been established whose conclusions we will explain.

European Society for Clinical Nutrition and Metabolism (ESPEN) (2009)

Level of recommendation in parentheses.

There are insufficient data to recommend supplying glutamine, omega-3 FAs or other pharmaconutrients in Crohn’s disease or ulcerative colitis (B).48

The addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Lipid emulsions enriched with fish oil probably reduces hospital stay in critically-ill patients (B).49

When PN is indicated in critically-ill patients, the amino acid solution should contain between 0.2 to 0.4 g/kg per day of L-glutamine (between 0.3 to 0.6 g/kg/day of alanylglutamine dipeptide) (A).49

Patients undergoing hematopoietic cell transplants may benefit from PN supplemented with glutamine (B).50

In patients with severe acute pancreatitis, when PN is indicated, supplementing the nutrition with glutamine should be considered (more than 0.3 g/kg/day of alanine-glutamine dipeptide) (B).51

The inclusion of omega-3 FAs in PN may benefit organ function and decrease stay in intensive-care and hospital units for patients who undergo major surgery or who are admitted to critical surgery unit (B).45

SERMICYUS-SENPE Consensus Clinical Guideline (2011)

Level of recommendation in parentheses.

The use of lipid emulsions that contain omega-3 FAs (fish oil) is recommended in patients with liver alterations during PN (B).52

The use of glutamine is recommended in patients with severe acute pancreatitis who are receiving PN (B).53

The use of glutamine supplements is recommended in patients on PN in order to contribute to glucose control (B).54

In critically-ill burn patients, administration of high-dose glutamine supplements is recommended (L-glutamine > 0.37 g/kg/day, glutamine dipeptide > 0.5 g/kg/day) (A).55

When PN is indicated in septic patients the use of glutamine supplements is recommended (B).56

In PN for septic patients, the use of lipid emulsions with a low omega-6 content is recommended (B); emulsions that contain omega-3 may be used in these patients (C).56

Supplementation of PN with alanylglutamine at a dosage of 0.5 g/kg/day is recommended in bone marrow transplant patients (A).57

Administration of omega-3 FAs may be considered in patients undergoing gastrointestinal surgery to improve outcomes (C).58

The PN of critically-ill surgical patients must be supplemented with glutamine (A).58

The use of glutamine is recommended in multiple-trauma patients (A).59

The use of pharmaconutrients (omega-3, arginine, antioxidants) is recommended for nutritional support of patients with severe trauma (C).59
**CONCLUSIONS**

Based on the demonstrated benefits of the pharmaconutrients reviewed and in accordance with clinical guidelines, for patients with PN:

- **Vitamins and oligoelements must be administered daily**

- **Supplementing nutrition with glutamine at a dosage of 0.2 to 0.4 g/kg/day (0.3 to 0.6 g/kg/day of alanylglutamine dipeptide) is recommended in the following cases:**
  - Critically-ill patient
  - Critically-burned patient
  - Multiple-trauma
  - Patient undergoing gastrointestinal surgery
  - Bone marrow transplant
  - Severe acute pancreatitis
  - Septic patient
  - Hyperglycemia due to stress or diabetes mellitus

- **The use of omega-3 FAs is recommended when PN is indicated in the following cases:**
  - Severe trauma
  - Liver pathology

- **Omega-3 FAs can be used when PN is administered in:**
  - Critically-ill patients
  - Critical non-surgical patients
  - Patient undergoing gastrointestinal/major surgery
  - Septic patients

**BIBLIOGRAPHY**

AMINOVEN 10%  

QUALITATIVE AND QUANTITATIVE COMPOSITION: 1000 ml solution of infusion contains: leucineine 5.00g, L-lysine 5.00g, L-methionine 1.50g, L-phenylalanine 1.50g, L-threonine 6.00g. The theoretical osmolarity: 985 mosmol/l. TITRATABLE ACIDITY: 25 - 45 mmol NaOH/l, pH-value: 5.4 - 6.0. LIST OF EXCipients: Water for injection. THERAPEUTIC INDICATIONS: Dipeptiven® is indicated as part of a clinical nutrition regimen in patients with intractable and/or hyperammonemic hypermetabolic state or in cases where liver function is severely impaired. Dipeptiven® should be used as part of total parenteral nutrition or combined with oral or enteral nutrition. It is a solution consisting for amino acids, vitamins, electrolytes, mineral substances and trace elements. It should be given together with compatible election solutions, fat emulsions, or an amino acid containing infusion. The most significant advantage of Dipeptiven® is the combination of an essential amino acid and an essential nutrient.

QUALITATIVE AND QUANTITATIVE COMPOSITION: 1000 ml solution of infusion contains: L-lysine 8.90 g, L-lysine acetate 15.66 g (L-lysine 11.1 g), L-threonine 3.80 g, L-glutamine 5.50 g. Total energy: 2520 kJ/l (= 600 kcal/l). pH: 5.5 - 6.3. TITRATABLE ACIDITY: 90 - 105 mmol NaOH/l. Theoretical osmolarity: 1500 mosmol/l. THERAPEUTIC INDICATIONS: Dipeptiven® should be used as part of total parenteral nutrition in combination with adequate amounts of energy and amino acids (carbohydrate solutions, fat emulsions, vitamins, electrolytes and trace elements). INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: None known when correctly administered. Those that occur during overdose may be treated with the usual methods. Clinical observations have shown that the parenteral administration of aminoglycosides and of cephalosporins may result in a decrease of their serum concentrations. This effect of aminoglycosides is thought to be related to their structural similarity with cephalosporins. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered. The administration of Dipeptiven® may result in a decrease of the serum concentration of digoxin. The possibility of a Diphosphocalcium-P and Diphosphoglycine-P absorption in the upper part of the intestine should be considered.
QUALITATIVE AND QUANTITATIVE COMPOSITION: Active ingredients: 1,000 ml of emulsion for infusion containing:
- Soya-bean oil, refined 60.0 g.
- Triglycerides, medium-chain 442.4 g.
- Olive oil, refined 55.5 g.
- Fish oil, rich in omega-3 fatty acids 30.0 g.
- List of excipients: Glycerol, egg lecithin, all-rac-α-tocopherol, water for injections, sodium hydroxide for pH adjustment, sodium citrate. Total energy: 8.4 MJ (≈ 2000 kcal). Compo-
nity: Approx. 380 minosrasing, pH approx. 8.

THERAPEUTIC INDICATIONS: Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.

PSYCHOLOGICAL AND METHODS OF ADMINISTRATION: The patient's ability to eliminate the fat infused, should govern the dosage and infusion rate. See section "Special warnings and precautions for use". ADULTS: The standard dose is 1.0 – 2.0 g fat/kg body weight (b.w.)/day, corresponding to 5 – 10 ml/kg b.w./day. The recommended infusion rate is 0.125 g fat/kg b.w./hour, corresponding to 0.63 SMOFlipid®/kg b.w./hour, and should not exceed 0.15 g fat/kg b.w./hour, corresponding to 0.75 SMOFlipid®/kg b.w./hour. PEDIATRIC PATIENTS: Neonates and infants: The initial dose should be 0.5 – 1.0 g fat/kg b.w./day followed by a successive increase by 0.5 – 1.0 g fat/kg b.w./day up to 3.0 g fat/kg b.w./day. It is recommended not to exceed a daily dose of 3.0 g fat/kg b.w./day, corresponding to 15 ml SMOFlipid®/kg b.w./day. The rate of infusion should not exceed 0.125 g fat/kg b.w./hour. Premature and low birthweight neonates: SMOFlipid should be infused continuously for about 24 hours. Children: It is recommended not to exceed a daily dose of 3.0 g fat/kg b.w./day, corresponding to 15 ml SMOFlipid®/kg b.w./day. The daily dose should be increased gradually during the first week of administration. The infusion rate should not exceed 0.15 g fat/kg b.w./hour. CONTRAINDICATIONS: Hypersensitivity to ish-, egg-, soya- or peanut protein or to any of the active substances or excipients. Severe hypothyroidism. Severe liver insuffi-
ciency. Severe blood coagulation disorders. Severe renal insufficiency without access to hemofiltration or dialysis. Acute shock. General contraindications to infusion therapy: acute pulmonary oedema, hypothy-
drosis, decompenrated cardiac insufficiency. Unstable conditions (e.g. severe post-traumatic stress, uncompromised diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis and severe sepsis and hypotonic dehydration). SPECIAL WARNINGS AND PRECAUTIONS FOR USE: The capacity to eliminate fat is individual and should therefore be monitored according to the routines of the clinics. This is in general done by checking the triglyceride levels. Special caution should be taken in patients with a marked risk for hypertriglyceridaemia (e.g. patients with high lipid dosage, severe sepsis and extremely low body weight infants). The concentration of triglycerides in serum should in general not exceed 3 mmol/l during infusion. Reduction of the dosage or cessation of the lipid emulsion should be considered if serum or plasma triglyceride concentrations during or after infusion exceed 3 mmol/l. An overdose may lead to fat overload syndrome; see section "Undesirable effects". This medicinal product contains soybean oil, fish oil and egg phospholipids, which may rarely cause allergic reactions. Cross allergic reactions have been observed between soya-bean and peanut. SMOFlipid should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism, and sepsis. Clinical data in patients with diabetes mellitus or renal failure are limited. Administration of medium-chain fatty acids alone can result in metabolic acidosis. This risk is to a great extent eliminated by the simultaneous infusion of the long chain fatty acids included in SMOFlipid. Concomitant administration of carbohydrates will further eliminate this risk. Hence, simultaneous infusion of carbohydrates or a carbohydrate-containing amino acid solution is recommended. Laboratory test gene-
really associated with monitoring of intravenous nutrition should be checked regularly. These include blood glucose levels, liver function tests, acid base metabolism, fluid balance, full blood count and electrolytes. Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion. SMOFlipid should be given with caution to neonates and premature neonates with hepatoblastoma and cases with pulmonary hypertension. In neonates, particularly pre-
mature neonates on long-term parenteral nutrition, blood platelet counts, liver function tests and serum triglycerides should be monitored. High levels of triglycerides in plasma may interfere with some laboratory blood tests, e.g. haemoglobin. The addition of other medicaments or substances to SMOFlipid should generally be avoided unless compatibility is known. Interactions with other medicinal products and other forms of interaction: Heparin given in clinical doses causes a transient increase in lipoprotein lipase release into the circulation. This may initially result in increased plasma lipolysis, followed by a transient decrease in triglyceride clearance. Soya-bean oil has a natural content of vitamin E. The content is however so low in SMOFlipid that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives. PREGNANCY AND LACTATION: There are no data available on exposure of SMOFlipid in pregnant or breast-feeding women. There are no studies available on reproductive toxicity in animals. Parenteral nutrition may become necessary during pregnancy and lactation. SMOFlipid should only be admin-
istered to pregnant and breast-feeding women after careful consideration. UNDESIRABLE EFFECTS: Undesirable effects observed during the administration of fat emulsions: Common ≥ 1/100 ≤ 1/10 (incidence ≥ 1/1000 to < 1/100); Rare ≥ 1/10000 ≤ 1/1000; Very rare < 1/10000 RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Rare: Dyspnoea, GASTROINTESTINAL DISORDERS: Uncommon: Lack of apetite, nausea, vomiting, MUSCULAR DISORDERS: Rare: Hypokinesia, hypertension, GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Common: Slight increase in body temperature; uncommon: Chills; rare: hypersensitivity reactions (e.g. anaphylactic or anaphylactoid reactions, skin rash, urticaria, flush, hae-
druse, heat or cold sensation, paleness, cyanosis, pain in the neck, back, bones, chest and limbs). NERVOUS SYSTEM AND BREAT DISORDERS: Very rare: Pruritus. Should these side-effects occur or should the triglyceride level during infusion rise above 3 mmol/l, the infusion of SMOFlipid should be stopped or, if necessary, continued at a reduced dosage. SMOFlipid should always be a part of a complete parenteral nutritional treatment including amino acids and glucose. Nausea, vomiting and hyperglycemia are symp-
toms related to conditions indicating parenteral nutrition and may sometimes be associated with parenteral nutrition. Monitoring of triglycerides and blood glucose levels are recommended to avoid elevated levels, which may be harmful. FAT OVERLOAD SYNDROME: Impaired capacity to eliminate triglycerides can lead to "fat overload syndrome" which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affec-
ted by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridemia, even at the recommended infusion rate, and in association with a sudden change in the patient’s clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterized by hyperpyrexia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anemia, leuko-penia, thrombocytopenia, coagulation disorder, hemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued. Should signs of a fat overload syndrome occur, the infusion of SMOFlipid should be discontinued. DATE OF LAST PARTIAL REVISION: September 2015. Registered product information may differ in your country. Before prescribing refer to nationally approved prescribing information.