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**ORIGINALS**

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**Phytosterol determination in lipid emulsions for parenteral nutrition****Determinación de fitoesteroides en emulsiones lipídicas para nutrición parenteral**

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**Abstract**

**Objective:** The presence of phytosterols in vegetal lipid emulsions has been associated with alterations of liver function tests. Determination of phytosterols content, currently undeclared, would allow the development of strategies to prevent or treat these alterations.

**Method:** 3-4 non-consecutive batches of 6 lipid emulsions from different providers (Clinoleic<sup>TM</sup>, Intralipid<sup>TM</sup>, Lipofundina<sup>TM</sup>, Lipoplus<sup>TM</sup>, Omegaven<sup>TM</sup> and Smoflipid<sup>TM</sup>) were analyzed. Differences in total phytosterol assay between providers and batches were statistically studied by a one-way ANOVA and Kruskal-Wallis non-parametric approximation and post hoc Scheffé test ( $p < 0.05$ ).

**Results:** The absence of phytosterols was confirmed in Omegaven<sup>TM</sup>, emulsion based on fish oil. The highest assay of phytosterols ( $422.4 \pm 130.5 \mu\text{g/mL}$ ) has been related with the highest percentage of soya bean oil in Intralipid. In the remaining emulsions, concentrations were from 120 to 210  $\mu\text{g/mL}$  related to the percentage of soya bean oil. Statistically significant differences of phytosterol content in lipid emulsions were observed among different providers ( $F = 23.59$ ;  $p = 0.000$ ) as well as among non-consecutive batches. Clinoleic<sup>TM</sup> ( $F = 23.59$ ;  $p = 0.000$ ), Intralipid<sup>TM</sup> ( $F = 978.25$ ;  $p = 0.000$ ), Lipofundina<sup>TM</sup> TCL/TCM ( $F = 5.43$ ;  $p = 0.045$ ), Lipoplus<sup>TM</sup> ( $F = 123.53$ ;  $p = 0.000$ ) and Smoflipid<sup>TM</sup> ( $16.78$ ;  $p = 0.000$ ). Except for Lipofundina<sup>TM</sup> TCL/TCM, the differences between batches were marked.

**Conclusions:** Lipid emulsions, registered on Spanish pharmaceutical market, contain variable quantities of phytosterols dependent on commercial brand and batch.

**Resumen**

**Objetivo:** La presencia de fitoesteroides en emulsiones lipídicas de origen vegetal se ha relacionado con la aparición de alteraciones de los parámetros de la función hepática. El objetivo es determinar la presencia de fitoesteroides en las emulsiones registradas en el mercado farmacéutico.

**Método:** Se analizaron tres-cuatro lotes no consecutivos de seis marcas distintas de emulsiones lipídicas (Clinoleic<sup>®</sup>, Intralipid<sup>®</sup>, Lipofundina<sup>®</sup>, Lipoplus<sup>®</sup>, Omegaven<sup>®</sup> y Smoflipid<sup>®</sup>) y las diferencias en contenido de fitoesteroides totales entre marcas y entre lotes se estudiaron estadísticamente (ANOVA de un factor, aproximación no paramétrica de Kruskal-Wallis y análisis *post hoc* Scheffé;  $p < 0,05$ ).

**Resultados:** Se encontró ausencia de fitoesteroides en el preparado Omegaven<sup>®</sup> con aceite de pescado. El contenido más alto de fitoesteroides ( $422,4 \pm 130,5 \mu\text{g/mL}$ ) coincidió con el porcentaje más alto de aceite de soja (Intralipid<sup>®</sup>). En el resto de las emulsiones se detectaron concentraciones de fitoesteroides entre 120 y 210  $\mu\text{g/mL}$ , relacionadas con el contenido de aceite de soja. Se observaron diferencias estadísticamente significativas entre todas las marcas de emulsiones lipídicas ( $F = 42,97$ ;  $p = 0,000$ ) y entre lotes no consecutivos. Clinoleic<sup>®</sup> ( $F = 23,59$ ;  $p = 0,000$ ); Intralipid<sup>®</sup> ( $F = 978,25$ ;  $p = 0,000$ ); Lipofundina<sup>®</sup> TCL/TCM ( $F = 5,43$ ;  $p = 0,045$ ); Lipoplus<sup>®</sup> ( $F = 123,53$ ;  $p = 0,000$ ); y Smoflipid<sup>®</sup> ( $16,78$ ;  $p = 0,000$ ). Excepto en el caso de la Lipofundina<sup>®</sup> TCL/TCM las diferencias entre lotes fueron marcadas.

**Conclusiones:** Las emulsiones lipídicas registradas en el mercado farmacéutico español contienen cantidades variables de fitoesteroides en función de la marca comercial y el lote. La determinación del contenido de fitoesteroides, actualmente no declarados, permitiría desarrollar estrategias para prevenir o tratar la aparición de estas alteraciones.

**KEYWORDS**

Phytosterols; Lipid emulsions; Parenteral nutrition; Soybean oil; Liver function tests.

**PALABRAS CLAVE**

Fitoesteroides; Emulsiones lipídicas; Nutrición parenteral; Aceite de soja; Parámetros de función hepática.



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## Introduction

Lipid emulsions (LEs) are routinely used in parenteral nutrition (PN). Prior to the inclusion of LEs in these formulas, PN required high amounts of glucose, which was associated with a range of problems<sup>1</sup>. The high energy efficiency of lipids led to a reduction in the use of glucose.

In Spain, the use of LEs in PN became routine practice in the 1980s. Initially, all LEs were based on soybeans, but since then a range of formulations has been developed. Currently, 5 LEs are registered for the Spanish pharmaceutical market. They are based on soybeans, olives, medium-chain triglycerides (MCTs), and fish oil in different concentrations and combinations.

Although LEs were initially used as an energy substrate, the anti-inflammatory effect of fish oil<sup>2,3</sup> and the lower lipid peroxidation effect of olive oil<sup>4</sup> has led to these lipids being proposed as pharmaconutrients.

Parenteral nutrition-associated liver disease is one of the most relevant complications of PN. Parenteral nutrition-associated liver disease has a multifactorial component<sup>5,6,7</sup>, and the quantity and type of lipid<sup>8,9</sup> have clearly been established as among the factors associated with the disease. Therefore, it is relatively common in clinical practice to reduce doses or to even temporarily stop the administration of lipids altogether<sup>10,11</sup>. For several years, it was hypothesised that these complications were associated with the use of plant-based LEs. Since the time of the study by Clayton in the paediatric population<sup>12</sup>, this possibility has been attributed to the presence of phytosterols, which hypothesis was subsequently confirmed in adult patients by our study group<sup>13</sup>. The phytosterol content of LEs is currently undeclared, and thus does not appear in the Summary of Product Characteristics or on the label. Currently, all emulsions available on the Spanish pharmaceutical market contain variable amounts of plant-based lipids and therefore contain phytosterols. This means that LE use entails their erratic administration.

Phytosterols occur in plants and are considered to be equivalent to cholesterol due to their having a similar sterol structure and similar functions in cell membrane regulation. There has been a recent increase in their clinical importance due to their demonstrated beneficial effects on cholesterol reduction when orally administered<sup>14,15,16</sup>. Due to their potential hepatotoxicity, the determination of phytosterol content in LEs would improve the management and prevention of hepatic complications in PN.

Gas chromatography (GC) and high-performance liquid chromatography (HPLC) analytical methods, particularly for the analysis of food and plant extracts, are available for the qualitative and quantitative determination of phytosterols. Gas chromatography can simultaneously determine phytosterols, whereas the available HPLC methods can only identify a few phytosterols and only under particular conditions<sup>17</sup>.

We developed a simple HPLC analytical method for the routine determination of phytosterol content in parenteral LEs. The objective of this study was to determine differences in the phytosterol content of LEs available on the Spanish pharmaceutical market according to their formulation, brand, and batch.

## Methods

We prospectively analysed intravenous LEs with different compositions available on the Spanish pharmaceutical market (Table 1) to determine daily exposure to phytosterols in patients with PN.

To better simulate clinical practice in Spain, we established different scenarios according to the brand of LE and batch. Thus, we studied 3-4 batches of each of the 5 plant-based LEs available on the Spanish pharmaceutical market. Batches corresponded to non-consecutive shipments.

We included Omegaven<sup>TM</sup>, which is an LE exclusively based on fish oil. This LE was imported because it is not registered in the Spanish pharmaceutical market.

We developed an HPLC analytical method for the routine quantification of phytosterols by establishing a sample preparation protocol. This method can simply and effectively separate phytosterols from the matrix. The aim was to obtain phytosterol samples with a high extraction percentage and good repeatability in a short period of time. Liquid chromatography was performed using a Dionex Ultimate 3000<sup>18</sup> chromatography system.

Differences in total phytosterol assay between the 5 brands and between batches were analysed using one-way ANOVA, post hoc multiple-comparison Scheffé test ( $P < .05$ ), and nonparametric Kruskal-Wallis test.

Data were analysed using IBM SPSS 22.0 software. A  $P$  value of  $< .05$  was used as a cutoff for statistical significance, using a two-tailed test.

## Results

The proposed analytical method allowed us to simplify sample preparation and conduct a single analysis, which led to the successful separation of 8 phytosterols, cholesterol, and squalene. The validation process showed that the method is suitable for routine analysis.

The analysis of LE brands (Table 2) showed that the fish-oil-based LE Omegaven<sup>TM</sup> did not contain phytosterols. This finding was in line with previously published results<sup>3,5</sup>, and therefore Omegaven<sup>TM</sup> was excluded from the statistical analysis. Intralipid is based completely on soybean oil. Its analysis showed that it contained the highest concentration of phytosterols ( $422.4 \pm 130.5 \mu\text{g/mL}$ ) and confirmed that soybean oil was the source of its high phytosterol content. The analysis showed that the other LE brands had variable phytosterol content ranging from  $120 \mu\text{g/mL}$  to  $210 \mu\text{g/mL}$ , depending on the percentage of soybean oil. Statistically significant differences were found between these brands ( $F = 42.97$ ;  $p = 0.00$ ). A weak correlation was found between phytosterol concentrations and greater plant-based lipid content, especially when the LE was based on soybeans.

The second part of the study analysed phytosterol content in various non-consecutive batches of LEs (Table 3). Statistically significant differences were also found between different batches: Clinoleic ( $F = 23.59$ ;  $p = 0.000$ ), Intralipid ( $F = 978.25$ ;  $p = 0.000$ ), Lipofundin LCT/MCT ( $F = 5.43$ ;  $p < 0.045$ ), Lipoplus ( $F = 123.53$ ;  $p = 0.000$ ), and Smoflipid ( $F = 16.78$ ;  $p = 0.000$ ). Except in the case of Lipofundin LCT/MCT, the differences between batches were substantial.

## Discussion

We developed an HPLC analytical method to simplify and reduce the cost of determining phytosterol content in LEs<sup>18</sup>. The validation process demonstrated its selectivity, linearity, precision, accuracy, and robustness, all of which support its routine use<sup>18</sup>. The sample treatment protocol for the commercially available LEs is an adapted version of published protocols<sup>19</sup>, and it took into account the properties of the samples and the requirements of the analytical method. We used this method to determine the phytoste-

**Table 1.** Intravenous Lipid Emulsions and Their Composition as Declared by the Manufacturer

Commercial name (pharmaceutical laboratory)	Composition
Clinoleic <sup>TM</sup> (Baxter)	80% olive oil and 20% soybean oil
Intralipid <sup>TM</sup> (Fresenius Kabi)	100% soybean oil
Lipofundin <sup>TM</sup> (LCT/MCT) (Braun)	50% soybean oil and 50% MCT
Lipoplus <sup>TM</sup> (Braun)	50% MCT, 40% soybean oil, and 10% fish oil
Omegaven <sup>TM</sup> (Fresenius Kabi)	100% fish oil
Smoflipid <sup>TM</sup> (Fresenius Kabi)	30% soybean oil, 30% medium chain fatty acids, 20% olive oil, and 15% fish oil

MCT: medium chain triglycerides; LCT: long chain triglycerides.

**Table 2.** Differences in Total Phytosterol Content by Brand

ID	Lipid emulsion	Mean total phytosterol concentration (µg/mL)	Statistically significant differences by ID (P<0.05)*
1	Clinoleic™ 20% (n=12)	208,8±39,4	2 y 5
2	Intralipid™ 20% (n=9)	422,4±130,5	1,3,4 y 5
3	Lipofundin™ LCT/MCT (n=9)	187,9±9,1	2
4	Lipoplus™ 20% (n=9)	140,1±20,9	2
5	Smoflipid™ 20% (n=15)	124,2±15,3	1 y 2

F = 42.976; significance value = 0.000. Statistically significant difference using one-way ANOVA variance analysis and non-parametric Kruskal-Wallis test (Omegaven™ was excluded from the statistical analysis). \*Post hoc Scheffé test: 1, Clinoleic™; 2, Intralipid™; 3, Lipofundin™ LCT/MCT; 4, Lipoplus™; 5, Smoflipid™.

rol content of all the LEs registered in the Spanish pharmaceutical market, and thus we were able to determine their impact on clinical practice in Spain.

A recent observational study on the use of LEs in 22 hospitals in Catalonia clearly showed the diversity of LEs used and differences in use criteria. These criteria were mainly based on economic management policies and, in some cases, on the level of stress of the candidate participants<sup>20</sup>. Apart from the established criteria for LE selection, our study introduces the new criterion of phytosterol content in order to prevent or correct the abnormalities in liver function parameters commonly seen in patients with PN.

Few studies have analysed different series of LEs to assess their phytosterol content and their impact on liver function. Meisel *et al.*<sup>21</sup> compared 5 LEs in a murine model and showed that liver function abnormalities depended on the formulation of the administered LE. In this murine model, fish oil prevented hepatic steatosis. Forchielli in 2010<sup>22</sup> found statistically significant differences in phytosterol content between different commercial preparations. In the clinical setting, Savini *et al.*<sup>23</sup> found an association between phytosterol intake and plasma phytosterol concentrations in uncomplicated preterm infants receiving routine PN. The latter two studies on different types

of LEs showed that phytosterol content ranged from 50 µg/mL to 400 µg/mL. This range was also confirmed in our series.

In 2014, the American Society of Parenteral and Enteral Nutrition (ASPEN) published an updated position paper<sup>24</sup> that analysed several studies<sup>25,26,27</sup> on phytosterol concentrations in LEs in order to gain better knowledge of phytosterol content in LEs for clinical purposes. ASPEN consulted with the manufacturers to validate the accuracy of the information in the document.

The determination of phytosterols in LEs would enable the amount administered to be quantified, thus facilitating better control of one of the relevant factors that may lead to parenteral nutrition-associated liver disease. An alternative could be the administration of LEs with a low phytosterol content or of non-plant-based emulsions, such as fish oil. The promising results obtained by replacing plant-based LEs with fish oil-based LEs<sup>28,29</sup> suggest that the elimination of phytosterols could be associated with improvements in liver function parameters, although randomized studies are needed to determine if the absence of phytosterols is also compensated by other properties or components of fish oil-based LEs.

The present study is the first to determine the presence of phytosterols in all the lipid emulsions registered on the Spanish pharmaceutical market

**Table 3.** Differences in Total Phytosterol Content by Batch

Lipid emulsion* Snedecor's F/ sig. (P value)	ID	Batch	Mean total phytosterol concentration (µg/mL)	Statistically significant differences between batches by ID (P<0.05)**
<b>Clinoleic™ 20%</b>  F = 23.59; P = 0.000	1 (n=3)	14H29N30	231.9±15.7	3
	2 (n=6)	15F15N31	227.2±21.0	3
	3 (n=3)	16F22N30	149.0±3.9	1 and 2
<b>Intralipid™ 20%</b>  F = 97.26; P = 0.000	1 (n=3)	10HB3671	451.3±23.2	2 and 3
	2 (n=3)	10IK7012	554.1±36.5	1 and 3
	3 (n=3)	10KC3584	261.6±12.8	1 and 2
<b>Lipofundin™ LCT/MCT</b>  F = 5.43; P = 0.045	1 (n=3)	143638082	178.8±3.7	3
	2 (n=3)	144718082	189.7±9.3	-
	3 (n=3)	154818081	195.4±3.0	1
<b>Lipoplus™</b>  F = 123.53; P = 0.000	1 (n=3)	144538082	145.9±6.1	2 and 3
	2 (n=3)	153938083	160.5±1.5	1 and 3
	3 (n=3)	160128082	113.8±1.6	1 and 2
<b>Smoflipid™ 20%</b>  F = 16.79; P = 0.000	1 (n=3)	16IF1650	137.6±2.9	3 and 4
	2 (n=3)	16HI0273	138.9±7.6	3 and 4
	3 (n=6)	16I61719	121.1±9.3	1, 2, and 4
	4 (n=3)	16K65043	102.3±1.9	1, 2, and 3

\* Statistically significant differences with one-way ANOVA and non-parametric Kruskal-Wallis test.

\*\* Post hoc Scheffé test: 1, Clinoleic™; 2, Intralipid™; 3, Lipofundin™ LCT/MCT; 4, Lipoplus™; 5, Smoflipid™.

and, unlike the aforementioned studies, it confirms the great variability in phytosterol content by brand and batch with its consequent clinical implications. The results highlight the relevance of including the total phytosterol concentration of each preparation released onto the market in the Summary of Product Characteristics to facilitate better and safer use in clinical practice.

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## Conflicts of interests

No conflict of interest.

## Contribution to the scientific literature

Recent studies have shown that long-term PN leads to liver function abnormalities, which have been attributed to the phytosterol content of LEs. This study determined the total phytosterol content of the LEs registered on the Spanish pharmaceutical market. The results confirm that there is significant variability between different brands of LEs and between different batches. The results provide a basis on which to design strategies to prevent their hepatotoxic effects.