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Original

Cholestasis induced by total parenteral nutrition; effects of the addition of Taurine (Tauramin®) on hepatic function parameters; possible synergistic action of structured lipids (SMOFlipid®)

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Abstract

Objective: Assess the hepatoprotective effect of Taurine (Tau) in cases of hepatic cholestasis induced by Total Parenteral Nutrition (TPN).

Methods: **We describe a retrospective series of 54 patients who received TPN, in which cholestasis was detected at an (Intermediate) point that separates the duration of TPN into 2 Phases. From this moment —Phase 2— on, and according to clinical criteria, some patients (Group A, n = 27) received amino acids with Tau (22.41 ± 3.57 mg/kg/day)(Tauramin®), while the rest (Group B, n = 27) received the standard solution without Tau. The mean TPN durations were 39.2 ± 17.1 and 36.4 ± 18.1 days respectively, with the Intermediate points on days 19.56 ± 10.51 and 17.89 ± 11.14. They all received diets that were homogeneous in terms of kcal and macronutrients. In Phase 2, 21 patients from Group A received structured lipids (SMOFlipid®); while 20 from Group B received soy MCT/LCT [Medium Chain Triglycerides/Long Chain Triglycerides] (physical or structured mixture). In a retrospective study, differences could not be avoided. The analytical parameters from three periods (Initial, Intermediate, and Final) were obtained from Nutridata® and Servolab®. We compared interperiod values using the Wilcoxon test SPSS® ($p < 0.05$).**

Results: **After introducing Taurine AST, ALT, and GGT were significantly reduced; Bilirubin was also reduced, but not significantly. The values obtained for GGT in Group A were (Mean(σ)/median): Initial 48.6 (23.1)/46; Intermediate 473.7 (276.2)/438, and Final 328.9 (190.4)/305. We stress that the mean GGT value is reduced by 30.56% after adding Taurine, while in its absence all parameters are elevated, and mean GGT increases 45.36%.**

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COLESTASIS INDUCIDA POR NUTRICIÓN PARENTERAL TOTAL; EFECTO DE LA ADICIÓN DE TAURINA (TAURAMIN®) SOBRE LOS PARÁMETROS DE FUNCIÓN HEPÁTICA; POSIBLE ACCIÓN SINÉRGICA DE LÍPIDOS ESTRUCTURADOS (SMOFLIPID®)

Resumen

Objetivo: **Evaluar el papel hepatoprotector de Taurina (Tau) en situación de colestasis hepática inducida por Nutrición Parenteral Total (NPT).**

Métodos: **Se describe una serie retrospectiva de 54 pacientes, que recibieron NPT, detectándose colestasis en un momento (Intermedio) que separa en 2 Fases la duración de la NPT. A partir de este momento —Fase 2— y según criterios clínicos, unos —grupo A, n = 27— recibieron aminoácidos con Tau -22,41 ± 3,57 mg/kg/día (Tauramin®), mientras otros —grupo B, n = 27— recibieron solución estándar sin Tau. La duración media de NPT fue de 39,2 ± 17,1 y 36,4 ± 18,1 días respectivamente; con el punto Intermedio en día 19,56 ± 10,51 y 17,89 ± 11,14. Todos recibieron dietas homogéneas en kcal y macronutrientes. En la Fase 2, 21 pacientes del grupo A recibieron lípidos estructurados (SMOFlipid®); mientras que 20 del grupo B recibieron MCT/LCT soja (mezcla física o estructurada). Las diferencias no se han podido obviar en un estudio retrospectivo. Se rescataron de Nutridata® y Servolab® los parámetros analíticos en tres momentos (Inicio, Intermedio y Final). Utilizando SPSS® se compararon según Test de Wilcoxon para valores intermomentos ($p < 0,05$).**

Resultados: **Hubo disminución significativa de AST, ALT y GGT tras la introducción de Taurina; Bilirrubina desciende sin significación. Los valores obtenidos para GGT en el Grupo A fueron (Media(σ)/mediana): Inicio 48,6 (23,1)/46; Intermedio 473,7 (276,2)/438 y Final 328,9 (190,4)/305. Destacamos que el valor medio de GGT disminuye un 30,56% tras adición de Taurina; mientras en su ausencia se elevan de todos los parámetros, aumentando un 45,36% la media de GGT.**

Conclusión: **Estos resultados abundan en el papel hepatoprotector de la Taurina, y apoyan su utilización en situación de colestasis inducida por NPT. Asumimos la posibilidad de que la diferencia de perfil entre SMOF y**

Conclusion: **These results show Taurine's hepatoprotective effect and support its use in cases of TPN-induced cholestasis. We acknowledge the possibility that the differences between SMOF and the MCT/LCT mixtures also may have influenced the results in a combined effect with taurine.**

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Key words: *Parenteral nutrition. Cholestasis. Taurine. Liver. Fat emulsions intravenous.*

Conclusión: Estos resultados muestran el efecto hepatoprotector de la taurina y apoyan su uso en casos de colestasis inducida por NPT. Reconocemos la posibilidad de que las diferencias entre SMOF y las mezclas MCT/LCT haya influido como efecto combinado utilizado junto a taurina.

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Palabras clave: *Nutrición parenteral. Colestasis. Taurina. Hígado. Emulsiones lipídicas intravenosas.*

Introduction

As early as 1971 Peden[1] described hepatic damage in a child that had received total parenteral nutrition (TPN) for 71 days. These pathological changes are brought about by TPN itself, the liver's attempt to compensate them, and their interaction over time.[2]

During TPN nutrients reach the liver through the hepatic artery instead of the portal vein; this causes a redirection of the hepatic blood flow which can lead to relative over-saturation or deficits in its metabolic functions. The changes in the nutritive mixture's composition, almost always different from the physiological one due to hyperosmolarity, affect the cholangioles.[3] Changes in the cholangioles' ionic resorption, especially of Ca and Na, are induced, and this increases water reabsorption and alters the bile's final composition. The reduction in the tauro/glyco conjugates and conjugated/not conjugated ratios is especially important, as is the intrahepatic increase of lithocholic acid, the most hepatotoxic of them. Different publications confirm these findings.[4]

Long-lasting TPN may give rise to progressive and potentially irreversible pathological phenomena (adaptive changes), in which the hepatic ultrastructure is affected, especially in the cell membrane and organelles, with an increase in lipid peroxidation and fibrogenesis.[5] We may speak of pathologies associated with parenteral nutrition (Parenteral Nutrition-Associated Liver Disease, PNALD).

In children, PNALD's more common manifestation is cholestasis[6] while in adults steatohepatitis is more frequent. This difference becomes less evident in prolonged TPN.[7] Alterations in hepatic function tests have been described in 20 to 90% of patients receiving TPN.[8] Cholestasis is the blocking of bile flow, both in the hepatocytes and the cholangioles and the rest of the intra- and extra-hepatic biliary tract.

PNALD pathogenesis is not known for certain, and probably has a multifactorial origin.[9] Some of the risk factors for developing the condition are the following: 1) Consequences of TPN: lack of enteral stimulation, bacterial overgrowth, activation of the inflammatory process; 2) factors related to TPN: excessive caloric supply, specific nutrients present in the mixture —amino acids, lipids—, deficiencies in certain nutrients —carnitine and others—; and 3) factors related to the underlying process: prematurity and low weight, sepsis, short bowel syndrome (SBS), medication.[10]

In certain situations, such as SBS, with cholangitis or sepsis, with multiple surgical procedures (for example, Crohn's Disease), hepatic changes are faster and progressive, progressing to irreversible damage, with fibrosis and cirrhosis.[11] Short Bowel Syndrome (SBS) and PNALD onset are correlated. The livers of 60% of infants and 40% of adults with long-term TPN due to bowel failure are affected.[12] Bacterial overgrowth may contribute to the liver being affected.[13]

Among the components of TPN, lipids are the ones that cause changes in liver structure and function with the highest frequency.[14] In addition, the composition of administered fats, as long or medium chain triglycerides (respectively, LCTs and MCTs), can also cause changes in liver composition, function, and ultrastructure.[15] Existing data suggest that an MCT/LCT mixture is less likely to cause liver complications than LCTs alone.[16] In addition, the onset of cholestasis has been associated with administration of more than 1 g/kg/day of lipids (adult patients).[12] Thus, TPN alters the composition of the liver's fat and its histomorphology.[17]

Phytosterols, soy derivatives present in many commercial lipid formulations, have been considered potentially toxic and may accumulate and alter bile flow. The amount of phytosterols present in 100% soy emulsions is three times greater than that in soy/coconut/olive/fish emulsions (143.6 mg/l *vs.* 47.6 mg/l).[18]

The protein content and amino acid mixture composition in TPN have also been suggested as possible liver dysfunction inducing factors. In fact, cholestasis develops earlier in patients receiving TPN with higher protein content.[19] Some associations, such as taurine or carnitine deficits and lipid supply in the form of LCTs, as well as glutamine and glutathione deficits have been shown experimentally.[20] All of these are essentially associated with nutrient solution formulations. Currently, it is recommended that a mixture of carbohydrates (70-85% of non-protein kcal) and fats (15-30%) be used. The excess in calories caused by glucose and the excess of lipids may be toxic to the liver and cause steatosis and cholestasis.[21]

The term cholestasis is associated with an increase in the serum concentrations of compounds that are normally excreted with bile, such as bile acids, bilirubin, cholesterol, and, among other enzymes, alka-

line phosphatase (ALP) and gamma glutamyl transpeptidase (GGT). In addition, and as a consequence of retaining potentially toxic compounds inside the hepatocytes, these cell may become necrotic, which in turn elevates the serum concentrations of alanine transaminase (ALT or SGPT) and aspartate transaminase (AST or SGOT), and trigger the processes of liver fibrosis that may lead to cirrhosis.[22]

GGT is characterized by its extreme sensitivity, and in cases of cholestasis it becomes elevated before ALP. However, given its lack of specificity, GGT determination has no clinical value unless its values are compared with those of other, more organospecific, enzymes such as ALP and ALT.[16] Both dissociated and intrahepatic cholestasis result in elevated ALP, with its value increasing twofold or threefold.[16]

In its initial phase, TPN-Induced Cholestasis (TPN-IC) manifests itself as a dissociated cholestasis, characterized by increases in AST, ALT, GGT, and ALP (two or three times its normal value), and normal serum bilirubin. When we speak of intrahepatic cholestasis proper, we see an increase of total bilirubin, above 1.5 mg/dl and up to 10 mg/dl, at the expense of direct bilirubin.[16] Elevated bilirubin values are seen after the first two weeks of TPN, although they may also appear several months later.[23]

Pharmacological hepatotoxicity is still a relatively unknown phenomenon. Its mechanism is probably double: direct hepatotoxicity and adverse immune reactions. The list of possible drugs is long, and among those more frequently associated with cholestatic liver damage we could mention chlorpromazine, phenothiazines, sulphamides, NSAIDs, ACEs, tricyclic antidepressants, carbamazepine, erythromycin, sulfonylureas, anabolic steroids, and oral contraceptives.[24]

Twenty years ago, Cooper et al. reported a marked taurine deficiency in children with TPN-IC.[25] Later studies showed that adding taurine increased taurine-conjugated bile acids in rats,[26] increased the flow and secretion of bile acids and protected from hepatotoxic bile acids in pigs.[25]

Taurine has been shown to promote bile flow,[27] increase the maximum bile acid secretion rate,[28] and prevent cholestasis induced by sulfated lithocholic acid, both in its free and glycine-conjugated forms.[27] Because taurine is involved in the formation of bile acid conjugates, its deficiency seems to play a role in the pathogenesis of TPN-induced cholestasis.[29] It is known that, in adults, the plasma concentration of taurine is reduced in cases of prolonged parenteral nutrition, starvation, surgery, and a variety of clinical conditions [such as] chronic liver pathology, chronic heart failure or kidney failure.[30] Taurine is essential in newborns and conditionally essential in some adults requiring long-term TPN.[30] Because most episodes of TPN-IC take place after 2 weeks of TPN,[31] longer study times are needed to demonstrate taurine's effect.

In healthy adults, the proportion of taurine and glucose conjugated bile acids is 3:1; this varies from one individual to another, and is influenced by the *pool* of hepatic taurine.[32] In addition, and differently form nonconjugated or glucose-conjugated bile acids, taurine-conjugated bile acids have a choleretic effect and prevent cholestasis.[33] Supplementing with taurine improves the hepatic activity of cholesterol 7-α-hydroxylase, the enzyme that limits the rate at which bile acids are synthesized.[34] Taurine stimulates bile flow, increases bile acid production, and protects against cholestasis.[35]

Adding taurine to newborns' TPN is well documented, but few studies have been performed regarding taurine use in adults receiving TPN. In his review, *Belli* suggests that taurine plays a key role in several biological actions, especially in the liver, and recommends that it be added to the amino acid solutions used in parenteral nutrition.[36] At present, the taurine content in TPN solution is highly variable. It is generally accepted that adults receiving long-term parenteral nutrition have a nutritional requirement for taurine.[37]

All this justifies performing a study on the effects of adding taurine on the hepatobiliary function of adult patients without a primary biliopancreatic pathology that are receiving long term TPN.

Objective

The objective of this study is to determine the effect on the hepatic function parameters of patients with long term TPN-IC of adding taurine to the amino acid solutions used in nutritional support .

Material and methods

This is a 3-year retrospective, observational, and analytical study of cohorts performed at the Virgen de la Victoria University Hospital (VVUH) that took place between January 2008 and December 2010. All patients without biliopancreatic pathologies that received TPN according to protocol, i.e., standard diets or diets for their specific clinical condition, during their hospitalization, and that developed cholestasis during nutritional support were selected. Patients were excluded if their hepatic parameters that denote cholestasis increased in the first five days of support or if TPN lasted less than five days after cholestasis onset.

Following clinical criteria, some of these patients received TPN supplemented with taurine (Tauramin® 1.2 or 1.5 g/l of Tau) while the rest did not receive the supplement. Thus the following two groups are defined as follows:

- *Group A:* After the apparition of parameters suggesting cholestasis, they received TPN supplemented with taurine.
- *Group B:* After the apparition of parameters suggesting cholestasis, they continued to receive unsupplemented TPN.

Table I
TPN macronutrient composition mean (σ)

	Initial	*Intermediate*	*Final*
Group A			
N g/kg/day	0.20 (0.05)	0.24 (0.05)	0.23 (0.06)
Lipid g/kg/day	0.97 (0.28)	0.81 (0.28)	0.79 (0.30)
Glucose g/kg/day	3.69 (1.06)	3.75 (0.87)	3.53 (0.93)
Kcal/kg/day	29.63 (7.89)	29.54 (6.86)	27.85 (7.20)
Group B			
N g/kg/day	0.19 (0.05)	0.20 (0.05)	0.18 (0.6)
Lipid g/kg/day	0.86 (0.20)	0.86 (0.29)	0.82 (0.32)
Glucose g/kg/day	3.34 (0.88)	3.48 (0.97)	3.27 (0.81)
Kcal/kg/day	26.83 (6.00)	27.79 (6.99)	25.87 (7.75)

With the aid of Pharmacy (Nutridata® and X-farma®) and laboratory (Servolab®) databases, and the patients' medical records we obtained the following parameters:

- Anthropometric (weight, height, Body Mass Index [BMI]).
- Demographic (age, sex).
- Clinical (parenteral nutrition indication, sepsis or septic shock, SBS).
- Analytical (serum levels of ALP, GGT, AST, ALT, total bilirubin).
- Nutritional (reason why TPN was discontinued, its duration, time to cholestasis onset, grams of nitrogen, glucose, lipids, total kcal, and mg of taurine per kilogram and day, type of lipid administered).
- Pharmacological (drugs that induce acute liver damage administered during nutritional support).
- Metabolic.

The presence of sepsis or septic shock of either bacterial or fungal origin during TPN support, before or during TPN-IC, was established through the Clinical Documentation computerized database, as stated in the ICD-9-CM code for the Hospital's MBDS.

Analytical, nutritional, and metabolic parameters were gathered at three points in time:

- *Initial:* the time at which nutritional support with TPN begins.
- *Intermediate:* the time at which the analytical data suggest cholestasis onset. In the group receiving taurine this point is the time at which it was decided to administer a solution enriched with taurine. The clinician in charge of the patient made the decision to administer taurine or not, with or without previous advice from the nutritional support team. Patients receiving taurine do so from this moment until the end.
- *Final:* the end of TPN support.

These points in time determine two phases in the study: Phase 1 (from initial to intermediate) and Phase 2 (from intermediate to final).

The serum levels of patients receiving TPN according to hospital protocol are measured before it begins and then weekly, as are the remaining analytical parameters of the nutritional profile. The reference ranges used are: GGT (9-69 IU/l), ALP (40-130 IU/l), AST (10-37 IU/l), ALT (12-78 IU/l), total bilirubin (0.2-1.10 mg/dl). AST, ALT, GGT, ALP and total bilirubin were determined using analytical spectrophotometry and the Dimension Vista® Auto Analyzer, Siemens Healthcare Diagnostic Inc., Newark (USA).

In Phase 1, both groups received a diet with a standard amino acid (Aa) source (Synthamin®, Aminoplasmal®, or Aminosteril KE®), and the sources of lipids were soy LCTs or soy MCTs/LCTs as a physical or structured mixture. In Phase 2, Group A received Aas enriched with taurine (Tauramin®, 1.2 or 1.5 g/l of Tau), and —preferably— soy-olive-fish MCT/LCT structured lipids (SMOF®). Group B continued to receive the standard source of Aas and -preferably- soy MCT/LCT lipids as a physical or structured mixture (Lipofundin® or Structolipid®). Table I summarizes the macronutrient and total kilocalories provided. The types of lipids administered to both groups in each phase of the study are shown in table II. During Phase 2 patients in Group A received an average of 22.41 ± 3.57 mg of taurine/kg/day.

In both groups the source of carbohydrates was glucose at different concentrations.

The drugs that induce acute liver damage administered to each patient were recorded in both phases, as were pharmacological treatment duration and the kind of associated acute liver damage (hepatocellular, cholestatic, or mixed).[38] According to the CIOMS scale,[39] for an initial treatment to be considered suggestive of liver damage it must be maintained between 5 and 90 days.

A data collection sheet was designed, and patients were identified and individualized. After data collection was complete, the data collection sheet was imported into the SPSS® statistical software for its posterior analysis. Hepatic parameters were compared with the Wilcoxon test for nonparametric quantitative

Table II
Types of administered lipids

Group / *Phase*	*Group A*				*Group B*			
	Phase 1		*Phase 2*		*Phase 1*		*Phase 2*	
Types of lipids	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Soy LCT	12	44.4	1	3.7	18	66.7	3	11.1
MCT/LCT*	13	48.1	5	18.5	9	33.3	20	74.1
SMOF	2	7.4	21	77.8	–	–	4	14.8

*Physical (Lipofundin®) or structured (Structolipid®) mixtures.

variables, and the significance level chosen was $p < 0.05$.

Results

Fifty-four patients were included. Twenty-seven of them received taurine-supplemented TPN from the Intermediate moment (Group A), while the remaining 27 continued to receive nutritional support without taurine supplementation (Group B).

The weight, height, and demographic data of patients from both groups were homogeneous. The data from Group A are: 66.7% males, 33.3% females, mean age: 59.41 (± 13.9) years old, weight: 67.02 (± 14.18) kg, height in meters: 1.68 (± 0.08). The data for Group B are: 59.3% males, 40.7% females, mean age: 59.37 (± 15.7) years old, weight: 70.21 (± 13.24) kg, height in meters: 1.65 (± 0.09).

Total TPN duration (Group A: 39.2 ± 17.1 days; Group B: 36.4 ± 18.1 days). Phase 1 duration (Group A: 19.56 ± 10.51 days; Group B: 17.89 ± 11.14 days), and Phase 2 (Group A: 16.07 ± 11.75 days; Group B: 18.96 ± 12.42 days). TPN at the VVUH lasted an average of 15.8 ± 15.3 days (n = 460 patients) in 2008, 15.4 ± 13.1 days (n = 450 patients) in 2009, and 14.2 ± 11.8 days (n = 411 patients) in 2010. TPN duration was determined by the conditions that made hospitalization necessary.

The most common reasons to begin TPN in Group A were: digestive tract obstruction with moderate to severe malnutrition and deferred intervention (26%), followed by post surgical peritonitis (13%), total gastrectomy (9%), hypoalbuminemia (9%), and other causes (43%). Only one patient had SBS.

In Group B they were: digestive tract obstruction with moderate to severe malnutrition and deferred intervention (22%), followed by inflammatory diseases (15%), total gastrectomy (11%), peritonitis (7%), and other causes (45%). Only one patient had SBS.

We found patients with sepsis or septic shock previous or simultaneous with TPN-IC onset in both groups. It was diagnosed in 9 patients from Group A and 8 patients from Group B.

During nutritional support patients in both groups received drugs that cause acute liver damage. Eleven of 12 patients in Group A received cholestatic drugs, as did all 13 patients in Group B. The mean number of acute liver damage-inducing drugs received per patient was 2 in Group A and 1.54 in Group B; and the mean number of cholestasis-inducing drugs per patient was 1.67 in Group A and 1.15 in Group B.

The hepatic profile analytical parameters were collected in the three moments that define the study, and the results are shown in table III.

Figure 1 is a box plot depicting how GGT changed in both groups. The mean ALT and AST values for each group at the three different study moments are shown in figure 2.

The number of patients with bilirubin > 1.5 mg/dl at the Intermediate and Final moments were 9 and 3 respectively in Group A and 8 and 6 respectively in Group B.

Discussion

It might seem surprising that patients in Group A have higher values of the cholestasis-suggesting studied parameters than patients in Group B in the intermediate point of the study, i.e., when the decision to introduce Taurine or not is made. However, this is reasonable given that, as explained above, during the study the clinician in charge was at liberty to modify the patients' diets. Although the nutritional support team could advise the clinician, the decision was never made automatically when certain predetermined analytical thresholds were reached. Thus, it is logical that the more significant increases are the ones that catch our eye.

In Phase 1, there is a significant elevation of all studied parameters in both groups. In Phase 2, patients in treated with Taurine experience a significant reduction in GGT, AST, and ALT, and their final values are lower than those not treated with Taurine, even though at the Intermediate point the values for this group were lower than those for the group treated with Taurine. The same is true for total bilirubin, although in this case the decrease in the Taurine group is not significant.

ALP behaves differently during the course of TPN. After the big increase in both groups during Phase I, it

Table III
Hepatic parametes by group mean (σ) median

Parameter	*Initial*	*Intermediate*	*Final*
Group A			
GGT (IU/L)	48.6 (23.1)/46	473.7 (276.2)*/438	328.9 (190.4)**/305
AST (U/L)	23.4 (12.5)/20	100.5 (120)*/67	36.2 (24.1)**/29
ALT (U/L)	34.7 (13.8)/31	119.7 (79.1)*/89	68 (55.5)**/52
Total bilirubin (mg/dl)	0.45 (0.24)/0.37	1.19 (1.16)*/0.65	0.79 (0.58)NS/0.6
ALP (U/l)	85.2 (26.9)/83	281.9 (196.2)*/183	309.9 (360.3)NS/203
Group B			
GGT (IU/L)	49.8 (29.5)/47	270.5 (124.1)*/237	393.2 (271.9)**/282
AST (U/L)	24.6 (18.6)/21	42.9 (27.3)*/35	77.1 (113) NS/41
ALT (U/L)	28.6 (15.2)/24	58.6 (60.7)*/41	94 (122.7) NS/56
Total bilirubin (mg/dl)	0.62 (0.36)/0.61	1.37 (1.42)*/0.82	1.31 (1.85) NS/0.67
ALP (U/l)	82.3 (29.1)/79	189.6 (98.4)*/140	293 (245.8)**/227

*p ≤ 0.05 when compared with initial; **p ≤ 0.05 when compared with intermediate; NS: Not significant.

continues to increase in Phase 2; although only in Group B does it reach significance, while in the taurine-treated group it tends to stabilize.

Moderate AST and ALT elevations take place in both groups, as is the case with GGT and ALP. This may reveal that cholestasis accompanies an incipient steatosis (a benign accumulation of hepatic fat). The significant reductions in AST and ALT that accompany the GGT reduction due to the effect of Taurine may be evidence of an improvement in liver fat mobilization. We do not have histological studies.

It is worth noting that at the Intermediate point total bilirubin reaches values above 1.5 mg/dl in only 9 of 27 patients (max. 5.3 mg/dl), and this number is reduced to 3 (max. 2.5 mg/dl) after taurine treatment. This means that in most cases the intrahepatic Cholestasis was Dissociated Cholestasis.[23] The number of patients in whom total bilirubin was above 1.5 mg/dl was greater in the non-taurine treated group than in the treated one, but even in the final moment it did not reach values above 10 mg/dl in any patient. Given TPN duration in Groups A and B (39.2 ± 17.1 and y 36.4 ± 18.1 days respectively) it doesn't seem strange, given that there are no patients with very long TPN, although it is enough (more than 2.5 times the mean overall duration) to have the aforementioned effects.

Among the results obtained we can highlight that the taurine-treated group's mean GGT value in the Final moment fell 30.56% when compared with the mean value before using a taurine-enriched Aa source in the TPN. On the other hand, in Phase 2 the group without taurine experiences a 50.9% increase.

Septic conditions and SBS, which can favor the onset of cholestasis, were equally distributed between the groups Also, by rejecting primary biliary, pancreatic, or hepatic pathologies, and patients in whom drugs caused any of the initial parameters to be higher than normal, we ensured that both groups did not differ in terms of factors other than TPN.

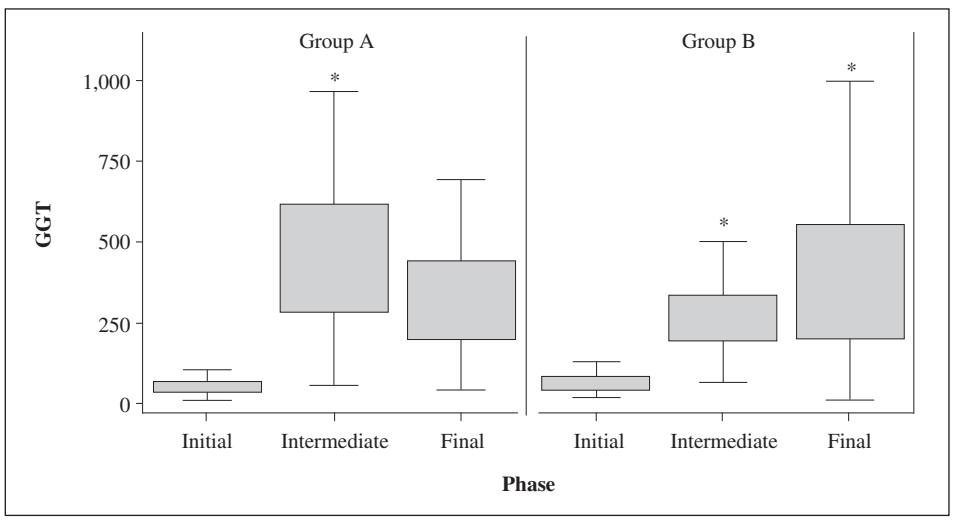

Fig. 1.—GGT Progress (IU/L).

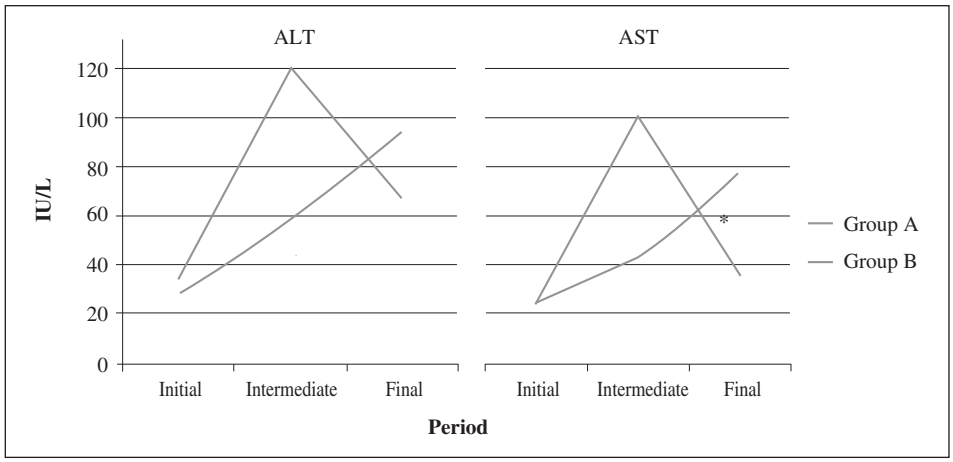

Fig. 2.—Mean ALT and AST values (IU/L) in the different study periods.

The variety in the lipid sources used in both Phases, depicted in table II, can be explained by the clinician in charge choosing between the different diets available in the TPN protocol, case by case recommendations made by the Nutritional Support Team, and even by the possibility of customizing the diets by choosing a certain type of fat. In addition, some standard diets begin with 100% soy LCT fats and after > 15 days of treatment switch, following protocol, to MCT/LCT to reduce cholestatic effects.[40] It may also be due to switching to prepared bags with mixed or structured MCT/LCT or to catered diets with those characteristics. Depending on the clinical condition, they could contain MCT/LCT from the start. During the time the study was being performed we did not have lipid emulsions based on olive oil (OOBE).

We will now raise some considerations about the possible influence of this variability in utilized fats on the results. In Phase 1, 44.4% of patients in the group that in Phase 2 was treated with Taurine received soy LCT, while in the other group this value was 66.7%. However, this difference was not correlated with a smaller increase in the analytical parameters in the group receiving less soy in Phase 1; in effect, the opposite was true. Regarding Phase 2, which measures the effect of Taurine, we see that the most important difference is that 74.1% of patients in Group B received MCT/LCT (mixture or structured), while those in Group A (treated with taurine) 77.8% received SMOF. We may ask ourselves if the lower Phytosterol[41] content of the olive LCT fraction that substituted the soy LCT, or the use of SMOF, could explain the observed effect. This question cannot be answered by this retrospective study, but we prefer to think that such a reduction in soy content (from 50 or 65%, depending on if the MCT/LCT is mixed or structured to 30% in SMOF) is not responsible for the results. This is supported by the observation that the modification in the lipids performed in Phase 2 was not enough to stop the enzymatic increases in Group B patients, and also by the total lipid doses administered, and, finally, patients whose lipid source in Phase 2 that they recieved different source from the mayority of the group, had the same trend in the overall results of each group. There may be a theoretical basis for the use of OOBE or SMOF from the start of TPNs that there is reason to believe will be long-lasting, or if there are other cholestasis risk factors present: it may reduce the incidence and severity of the negative effects due to fats. In any case, studies to determine up to what point OOBE and SMOF are better than the MCT/LCT sources in preventing and/or treating cholestasis or successive and more severe complications associated with TPN have to be designed. Clinical trials to determine what lipid composition is best at preventing or reverting TPN's hepatic toxicity are lacking.[40,41] The study by Puiggross et al.[42] did not show the superiority of any emulsion over the others, but this may be due to its the small number of patients and short duration.

For the reasons explained above, we believe that the administered Taurine dose (22.41 ± 3.57 mg/kg/day) is the main cause of the improvement in the hepatic profile parameters considered. This is so even if we admit the possibility of a synergistic or coadjutant effect between taurine and the change in lipid profile used: in the presence of taurine it was predominantly SMOF (78%) while in its absence it was the MCT/LCT (physical or structured) mixture (74.1%). We are planning a new study in which we will measure the effect of taurine when SMOF is the only source of fat. Our current local protocol for TPN-IC includes taurine and SMOF.

The possibility that standard use of an A.a solution enriched with taurine may reduce the incidence of cholestasis, as well as its cost/benefit ratio and the optimal taurine dose, could be studied.

Conclusions

The 22.41 ± 3.57 mg/kg/day dose of taurine in the TPN's source of amino acids significantly reduces the hepatic profile analytical parameters that define cholestasis. We acknowledge the possibility that the different profiles between SMOF and the MCT/LCT

mixtures may also have had an influence together with taurine.

These results show taurine's hepatoprotective effect and support its use in cases of cholestasis that arise during TPN.

It is worth considering a reduction in the incidence of cholestasis by including taurine from the start in the TPN of patients at risk, as well as in those that are anticipated to be long-lasting or, in any case, to reach 15 days of treatment without any enteral or oral elements.

References

1. Peden VH, Witzleben CL, and Skelton MA. Total parenteral nutrition. *J Pediatr* 1971; 78 (1): 180-1.
2. Moran Penco JM, Salas Martinez J, Macia Botejara E, [What happens in the liver during artificial feeding?]. *Nutr Hosp* 2001; 16 (5): 145-51.
3. Hofmann AF. Defective biliary secretion during total parenteral nutrition: probable mechanisms and possible solutions. *J Pediatr Gastroenterol Nutr* 1995; 20 (4): 376-90.
4. Botello Martínez F, Morán Penco JM, Salas Martínez J, Espín Jaime T, Maciá Botejara E, Caballero Loscos MJ et al. ¿Previene la suplementación con taurina la Cholestasis inducida por nutrición artificial (intravenosa y enteral)? *Cir Esp* 1997; 62: 364-369.
5. Moss RL, Amii LA. New approaches to understanding the etiology and treatment of total parenteral nutrition-associated cholestasis. *Semin Pediatr Surg* 1999; 8 (3): 140-7.
6. Ukleja A, Romano MM. Complications of parenteral nutrition. *Gastroenterol Clin North Am* 2007; 36 (1): 23-46.
7. Quigley EM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology* 1993; 104 (1): 286-301.
8. Salvino R, Ghanta R, Seidner DL, Mascha E, Xu Y, Steiger E. Liver failure is uncommon in adults receiving long-term parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2006; 30 (3): 202-8.
9. Kelly DA. Intestinal failure-associated liver disease: what do we know today? *Gastroenterology* 2006; 130 (2 Suppl. 1): S70-7.
10. Shaffer JL. Hepatic complications of parenteral nutrition. *Clin Nutr* 1995; 14 (Suppl. 1): 59-64.
11. Bashir RM, Lipman TO. Hepatobiliary toxicity of total parenteral nutrition in adults. *Gastroenterol Clin North Am* 1995; 20 (4): 1003-25.
12. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000; 132 (7): 525-32.
13. Rudman D, Williams PJ. Nutrient deficiencies during total parenteral nutrition. *Nutr Rev* 1985; 43 (1): 1-13.
14. Moran JM, Macia E, Salas J, Mahedero G, Climent V. Liver lipid composition and intravenous, intraperitoneal, and enteral administration of intralipid. *Nutrition* 1994; 101 (1): 26-31.
15. Espín-Jaime MT, Moran JM, Maciá E, Salas J, Botello F. Composición lipidica hepática tras TPN con LCT *vs* MCT/LCT como fuente de aporte. *Nutr Hosp* 1996; 11: 36-39.
16. DeLegge MH, Ireton-Jones C, Core Currículum en Apoyo Nutricional. Una aproximación basada en casos clínicos-paciente adulto. D. Farma, Editor. 2008: Madrid.
17. Morán JM, Leal A, Espín MT, Maciá E, Amaya JL, Correa MI et al. Cambios en la composición de la grasa y en la histomorfología hepáticas tras TPN, con y sin intestino ultra-corto. *Nutr Hosp* 2011; 26 (1): 107-115.
18. Ellegard L, Sunesson A, Bosaeus I. High serum phytosterol levels in short bowel patients on parenteral nutrition support. *Clin Nutr* 2005; 24 (3): 415-20.
19. Vileisis RA, Inwood RJ, Hunt CE, Prospective controlled study of parenteral nutrition-associated cholestatic jaundice: effect of protein intake. *J Pediatr* 1980; 96 (5): 893-7.
20. Morán JM, Salas J, Maciá E. What happens in the liver during artificial nutrition, in 22nd Espen Congress. 2000: Madrid, pp. 117-120.
21. Messing B, Colombel JF, Herebach D, Chazouillères O, Galian A. Chronic cholestasis and macronutrient excess in patients treated with prolonged parenteral nutrition. *Nutrition* 1992; 8 (1): 30-6.
22. Whitington PF. Chronic cholestasis of infancy. *Pediatr Clin North Am* 1996; 43 (1): 1-26.
23. Casals G, Augé JM. Pruebas de funcionalismo hepático: cholestasis. *El farmacéutico de hospitales* 2003; 158: 46-49.
24. Wilmore DW, Dudrick SJ, Growth and development of an infant receiving all nutrients exclusively by vein. *JAMA* 1968; 203 (10): 860-4.
25. Cooper A, Betts JM, Pereira GR, Ziegler MM. Taurine deficiency in the severe hepatic dysfunction complicating total parenteral nutrition. *J Pediatr Surg* 1984; 19 (4): 462-6.
26. Sweeny DJ, Barnes S, Diasio RB. Bile acid conjugation pattern in the isolated perfused rat liver during infusion of an amino acid formulation. *JPEN J Parenter Enteral Nutr* 1991; 153 (3): 303-6.
27. Dorvil NP, Yousef IM, Tuchweber B, Roy CC. Taurine prevents cholestasis induced by lithocholic acid sulfate in guinea pigs. *Am J Clin Nutr* 1983; 37 (2): 221-32.
28. Belli DC, Fournier LA, Lepage G, Yousef IM, Roy CC. The influence of taurine on the bile acid maximum secretory rate in the guinea pig. *Pediatr Res* 1988; 24 (1): 34-7.
29. Howard D, Thompson DF. Taurine: an essential amino acid to prevent cholestasis in neonates? *Ann Pharmacother* 1992; 26 (11): 1390-2.
30. Lourenco R, Camilo ME. Taurine: a conditionally essential amino acid in humans? An overview in health and disease. *Nutr Hosp* 2002; 17 (6): 262-70.
31. Kubota A, Yonekura T, Hoki M, Oyanagi H, Kawahara H, Yagi M et al. Total parenteral nutrition-associated intrahepatic cholestasis in infants: 25 years' experience. *J Pediatr Surg* 2000; 35 (7): 1049-51.
32. Paauw JD, Davis AT. Taurine concentrations in serum of critically injured patients and age- and sex-matched healthy control subjects. *Am J Clin Nutr* 1990; 52 (4): 657-60.
33. Wasserhess P, Becker M, Staab D. Effect of taurine on synthesis of neutral and acidic sterols and fat absorption in preterm and full-term infants. *Am J Clin Nutr* 1993; 58 (3): 349-53.
34. Van der Meer R, Vonk RJ, Kuipers F. Cholestasis and the interactions of sulfated glyco- and taurolithocholate with calcium. *Am J Physiol* 1988; 254 (5 Pt 1): G644-9.
35. Caglieris S, Giannini E, Dardano G, Mondello L, Valente U, Testa R. Tauroursodeoxycholic acid administration as adjuvant therapy in cirrhotic patients on transplantation waiting lists. *Hepatogastroenterology* 2000; 47 (34): ¡1045-7.
36. Belli DC. Taurine and TPN solutions? *Nutrition* 1994; 10 (1): 82-4.
37. Geggel HS, Ament ME, Heckinbelly JR, Martin DA, Koppel, JD. Nutritional requirement for taurine in patients receiving long-term parenteral nutrition. *N Engl J Med* 1985; 312 (3): 142-6.
38. Chang CY, Schiano TD. Review article: drug hepatotoxicity. *Aliment Pharmacol Ther* 2007; 25 (10): 1135-51.
39. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46 (11): 1323-30.
40. Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. *Nutr Clin Pract* 2006; 21 (3): 279-90.
41. Forchielli ML, Bersani G, Tala S, Grossi G, Puggioli C, Masi M. The spectrum of plant and animal sterols in different oil-derived intravenous emulsions. *Lipids* 45 (1): 63-71.
42. Puiggrós C, Sánchez J, Chacón P, Sabin P, Rossello J, Bou R et al. Evolution of lipid profile, liver function, and pattern of plasma fatty acids according to the type of lipid emulsion administered in parenteral nutrition in the early postoperative period after digestive surgery. *JPEN J Parenter Enteral Nutr* 2009; 33 (5): 501-12.