NUTRITIONAL SUPPORT AND CARDIOPROTECTION WITH L-CARNITINE: PRESCRIPTION APPROPRIATENESS AND SAFETY CONCERNS IN MEXICAN NEONATES

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ABSTRACT

Medication errors are probably more common in neonates than is generally appreciated. In Mexican pediatric hospitals, L-carnitine is mainly used for nutritional support and to treat cardiomyopathy secondary to neonatal asphyxia**.** Using a longitudinal-retrospective approach we assessed the appropriateness of all L-carnitine prescriptions written during a 12-month period at a NICU of a second-level hospital located in Toluca, Mexico. Reports of adverse reactions possibly related to L-carnitine therapy were collected and characterized. Overall, administration of L-carnitine was considered justified and appropriate only in 18% of patients. 60.7% of L-carnitine prescriptions were rated as inappropriate because the prescribed doses fell outside the recommendations. The overall rate of ADRs calculated from the patient population was 18.03%. All of them were of gastrointestinal type: abdominal cramps (8 cases, 61.54%) and vomiting (5 cases, 38.46%). Our results supported the establishment of an L-carnitine rational use policy at the NICU of the hospital under study.

Key Words: *Drug use evaluation; levocarnitine; L-carnitine; neonate; adverse drug reaction*

The unique physiologic and pharmacologic factors in the neonate pose special vulnerabilities to achieve clinical efficacy and safety of drugs in this population. Despite advances in basic science research, our understanding of use and drug disposition pathways of medications in the premature and full-term neonate still remains an important challenge for the neonatal care team.[1]

The concern about lack of knowledge of adverse drug reactions (ADRs) in pediatric populations, and especially in neonatal age groups, is well-founded.[2] Newborn patients are often exposed to drugs whose efficacy and safety are unproven or have not been formally documented. Moreover, medication errors are probably more common in neonates than is generally appreciated. For adults, the reported incidence of errors in treatment with medications is 5% of all orders written, while in pediatrics, this number has been reported to be as high as 16 %.[3] Although the causes are multifactorial, error rates for children seem to be inversely related to the weight of the patient, with infants in the neonatal intensive

care unit (NICU) being most likely to experience medication errors and potential adverse drug events (ADEs).[3] Thus, the rational use of medication in pediatrics should be investigated to foster the improvement of the health care of children.

Levocarnitine or L-carnitine, an amino acid derivative, is described as a conditionally essential nutrient. Oral and intravenous L-carnitine is available as a nutritional supplement and as a prescribed orphan drug treatment for primary and secondary L-carnitine deficiencies. Although the majority of patients are capable of endogenous carnitine synthesis, especially neonates and infants have decreased biosynthetic capacity and are at risk of developing carnitine deficiency, particularly when receiving parenteral nutrition (PN).[4] Reduction of carnitine levels may affect fatty acid oxidation and thus be of potential pathophysiological relevance under conditions with higher energy demands, e.g., in sepsis, prematurity, dysmaturity and asphyxia.[5] Metabolic homeostasis of the heart can also be affected by carnitine deficiency. Cardiac anomalies including cardiomyopathy, cardiomegaly, and cardiac failure have been reported as clinical symptoms of carnitine deficiency.[4]

Some authors suggest that it is unclear whether there is any benefit of carnitine supplementation on weight gain and neonatal morbidity e.g., respiratory morbidity or apnea of prematurity.[5-7] Clearly, more research is needed to provide evidence of L-carnitine benefits and to be able to determine an appropriate dose and length of carnitine supplementation in pediatric nutrition.[4,6]

In Mexican pediatric hospitals and neonatology units L-carnitine is mainly used for nutritional support and to improve cardiac functioning in children with cardiomyopathy secondary to neonatal asphyxia. To date, FDA approved indications for L-carnitine include carnitine deficiencies, primary and secondary due to inborn error of metabolism, as well as treatment and prophylaxis of end stage renal disease requiring hemodialysis.[8] Use of levocarnitine is currently considered off-label for the treatment of pediatric cardiomyopathy.[8]

Since few drugs have been tested or labeled for use in newborns, and considering the fact that 47 to 59% of prescribed drugs that are used in a NICU are used off-label.[2] It is important to document drug utilization in all settings in order to prioritize drugs for future research aimed at evaluating their safety and efficacy for use among neonates.[9]

Thus, the purpose of our study was to evaluate L-carnitine utilization in Mexican neonates in order to determine prescription appropriateness and to identify safety issues that could lead to the creation of evidence-based prescription guidelines and policies.

MATERIAL AND METHODS

A longitudinal-retrospective drug utilization review of indication-prescription type[10] was carried out at a second-level hospital located in Toluca city, State of Mexico. Medical and pharmacy records were searched for all neonates treated with L-carnitine. We analyzed all neonatal L-carnitine prescriptions written in a 12-month period in the neonatology service of the Hospital para el Niño IMIEM. From a total of 464 medical consultations attended during the study period, 70 medical records were from patients who had been prescribed L-carnitine. 9 charts were excluded from the evaluation because of incompleteness of data. A total of 61 charts were analyzed in our study. Data on patient demographics, laboratory test results, indication for L-carnitine, dosage, dosage form, regimen and concomitant medications were collected. The study received prior approval from the hospital´s research ethics board. All data were devoid of personal identifiers in order to protect the confidentiality of patient information.

Appropriateness of prescription was assessed according to specialized drug information literature[8,11-17] and based on the following pharmacotherapeutic variables: indication, dosage regimen (dose, frequency and duration of therapy), dose adjustment for nutritional status, renal and hepatic failure, contraindications and drug interactions. Each pharmacotherapeutic criterion was treated as a binary categorical variable: appropriate and inappropriate. Prescriptions were rated as “appropriate” when no errors were found according to pharmacotherapeutic variables. “Inappropriate” prescriptions contained at least one error for any of the variables assessed.

Reports of adverse reactions possibly related to L-carnitine therapy were collected from the medical records in order to assess causality, severity, clinical significance and prevalence of L-carnitine-induced adverse reactions. Based on Naranjo algorithm[18], adverse reactions were classified as definite, probable, possible or doubtful. Depending upon the severity and clinical significance**,** ADRs were classified into mild**,** moderate and severe reactions.[19-21] Prevalence of L-carnitine-induced adverse reactions was calculated as the number of ADR patients divided by the total number of patients treated with this drug.

RESULTS AND DISCUSSION

Demographics

From 61 patients, 64% were preterm and 36% full-term newborns. This predominance of preterm babies treated with L-carnitine correlates with previous studies where gestational age has been found as an important risk factor for morbimortality in neonates.[22] There were 55.7% male and 44.3% female patients. The higher proportion of male newborns agrees with reports from other Latin American countries where male neonates are more frequently hospitalized in NICUs than females, possibly due to genetic predisposition.[23,24] All patients were undergoing polytherapy at the time of the study (up to 24 medications), which has widely been recognized as an important risk factor associated with morbimortality, medication errors and adverse drug reactions in neonates.

The pediatric hospital IMIEM attended 95,867 consultations during the period of study. Patients are usually of low socioeconomic status and come from the states of Mexico, Michoacán and Guerrero. During 2006, 464 neonates were admitted, from them, 17.2% died during hospitalization. Neonatal deaths (80 cases) were 37.7% of the total of deaths at the hospital that year. Average duration of neonatal hospital stay was 9.9 days and NICU bed occupancy rate was 87% (from a total of 18 beds). Antibiotics like ampicillin, amikacin, gentamicin and cefotaxime were the most widely prescribed drugs in the NICU together with ranitidine, midazolam, dexamethasone and dobutamine. L-carnitine was prescribed to 70 newborn patients.

Morbimortality statistics of the IMIEM pediatric hospital agree with national statistics for neonates[25], which confers good representativeness of the Mexican population to our population of study. Upper respiratory tract infections were the main cause of morbidity and mortality among children hospitalized in the IMIEM Hospital during 2006. Strikingly, malnutrition was listed as the 10th cause of morbidity (364 children deaths) of patients admitted at the IMIEM hospital that year. Morbidity of newborn patients admitted to the NICU was mainly caused by neonatal hyperbilirubinemia (92 cases, 19.8%), neonatal sepsis (72 cases, 15.5%), neonatal asphyxia (53 cases, 11.4%) and congenital cardiomyopathy (45 cases, 9.7%). Neonatal sepsis, neonatal asphyxia and congenital cardiomyopathy were also the main causes of mortality in the NICU during the 12-month period of our study. All these diseases justify L-carnitine prescription.

L-Carnitine Utilization Patterns

In the NICU of the IMIEM hospital, L-carnitine is used as a nutritional support for weight gain and as a cardioprotector for hypoxic (ischemic) cardiomyopathy due to neonatal asphyxia. Overall, administration of L-carnitine was considered justified and appropriate only in 18% of patients, given the clinical context, but the initial L-carnitine choice was considered appropriate for most patients (86.9%) (Table 1). When evaluating prescription appropriateness, the pharmacotherapeutic variable ‘indication’ was assessed by verifying the correspondence between the diagnosis and prescription. Results showed that 13.1% of L-carnitine patients did not have agreement between administration (pharmacy notes) and prescription (medical records) of L-carnitine.

TABLE 1 Assessment of L-carnitine prescription appropriateness according to specialized drug information literature and pharmacotherapeutic indicators.

	L-carnitine prescriptions	
Pharmacotherapeutic variables	**No. of Appropriate prescriptions (%)**	**No. of Inappropriate prescriptions (%)**
Indication	53 (86.9)	8 (13.1)
Dosage regimen[a] Dose Frequency	 24 (39.3) 46 (75.4)	 37 (60.7) 15 (24.6)
Dose adjustment[b]	61 (100)	0 (0)
Contraindications	61 (100)	0 (0)
Drug interactions	61 (100)	0 (0)
Appropriateness assessment	11 (18)	50 (82)

N= 61 L-carnitine prescriptions
[a] Duration of therapy was not assessed (see explanation within the text).
[b] Dose adjustment for nutritional status, renal and hepatic failure

For NICU patients treated with L-carnitine as a cardioprotector, elevated levels of creatinine phosphokinase myocardial binding isoenzyme (CPK-mb) are used as biochemical markers of myocardial-cell injury in order to decide whether L-carnitine should be prescribed or not. Nevertheless, CPK-mb levels were not measured for all patients diagnosed with hypoxic (ischemic) cardiomyopathy and treated with L-carnitine. This inconsistency hindered the possibility of generating valuable evidence of L-carnitine effectiveness on the reduction of CPK-mb levels and on the treatment of a clinical condition for which L-carnitine is used in an off-label manner in neonates. Future research should be focus on the correlation between L-canitine and CPK-mb plasma levels and myocardial recovery after neonatal asphyxia.

Due to the retrospective nature of this study, all identified medication errors belonged to the category of prescription errors. The most common types of prescribing errors were dosing errors (Table 1). Medical literature recommends the use of 50-100 mg/kg/24 hr of L-carnitine either oral or IV (bolus or infusion) for the treatment of its FDA approved indications in pediatric patients.[8,11-15,26-30] When using larger doses, gastrointestinal symptoms, specifically diarrhea, nausea, and cramping, may appear. Higher doses (up to 800 mg/kg/24 hr) may be required only in patients with excessive urinary loss. It is also recommended to administer oral doses with or following meals to maximize tolerance. Furthermore, although doses of 50–100 mg/kg/day L-carnitine are used for patients with carnitine deficiency syndromes, studies in neonates and infants have found increased serum carnitine concentrations with only 10–20 mg/kg/day and with little known or observed adverse effects.[4] In our study, 60.7% of L-carnitine prescriptions were rated as inappropriate because the prescribed doses fell outside the recommendations. Because of the special pharmacokinetic features in neonates and considering that most common L-carnitine-related adverse reactions are usually dose-dependent, dose recommendations should be strictly adhered to.

Taking an 8-hour dosing interval as reference[8,11-15], 75.4% of L-carnitine prescriptions in our study were adequate (Table 1). Dose adjustment for nutritional status, renal and hepatic failure was done for all patients treated with L-carnitine. The duration of therapy was not

assessed due to the lack of specific information about this pharmacotherapeutic variable on L-carnitine drug information sources. Moreover, duration of treatment in our patients was variable, with a minimum of 1 day and a maximum length of treatment of 37 days (average: 10 days). According to clinical studies, cardioprotection can be achieved after treatment with L-carnitine for 2 weeks until 1 year of treatment.[31,32] Taking the average hospital stay of our patients into consideration, to evaluate this pharmacotherapeutic variable would be useless to determine prescription appropriateness. No drug-drug interactions were found when assessing the prescriptions.

Multivariable logistic regression was used to identify factors that independently influenced the appropriateness of the L-carnitine prescriptions (Table 2). Dosage regimen (dose and frequency) and indication were the pharmacotherapeutic variables found to be significantly associated to prescription inappropriateness of L-carnitine in neonates. Influence of these variables on rational drug use was also described by us previously.[33]

TABLE 2 Logistic regression for L-carnitine prescriptions according to pharmacotherapeutic criteria used to assess L-carnitine utilization patterns (Enter-First method).

Variable	Statistical significance	Relative risk
Indication	**0.015**[a]	
Appropriate	0.028 [a]	1.73
Innapropriate	0.017 [a]	12.26
Dose	**0.008** [a]	
Appropriate	0.623	0.21
Innapropriate	0.031 [a]	28.15
Dosing interval	**0.037** [a]	
Appropriate	0.012 [a]	4.56
Innapropriate	0.028 [a]	18.45

Logistic regression; [a] statistical significance $p<0.05$.

TABLE 3 Characterization of adverse reactions possibly related to L-carnitine therapy.

Causality, severity, clinical significance and prevalence of L-carnitine-induced adverse reactions (n=13 ADRs; 12 patients)	
Causality [a]	Probable (15%) Possible (61%) Doubtful (24%)
Severity and clinical significance	Moderate (14.3%) Mild (85.7%)
Prevalence	18.03%

[a] Assessed using the internationally recognized Naranjo algorithm[18]

Adverse Reactions

From 61 patients, we detected 13 ADRs possibly associated with L-carnitine. All of them were of gastrointestinal type: abdominal cramps (8 cases, 61.54%) and vomiting (5 cases, 38.46%). Nausea, vomiting, abdominal cramps, diarrhea, body odor, high blood pressure and headache are the most common adverse reactions associated with L-carnitine use.[8,11-15] The overall rate of ADRs calculated from the patient population was 18.03%. No significant difference was seen in the overall rate of ADRs in males vs. females.

Causality assessment using Naranjo´s Scale[18] showed that for our neonatal population of study, association of gastrointestinal adverse reactions with L-carnitine was in the 'possible' category for the majority of the detected cases (61.5%) (Table 3). According to severity assessment, no serious reactions were detected (Table 3). No cases required of drug discontinuation and for the cases of vomiting, an antiemetic was administered. Our results confirm knowledge about well-known ADR risk factors that were also present in our patients: drug-related (dose and dosing interval, polytherapy) and patient-related factors (neonatal age, concomitant diseases, nutritional status).

Our study results underline the importance of developing evidence-based treatment guidelines, in this case specific for L-carnitine use in neonates. Especially when resources are limited, health institutions should develop strategies to determine which drugs are most important for study in neonates or any other population of interest.[2]

Wirtz and cols. did a systematic review of all original research studies published between 1990 and 2004 on the access and use of medicines in Mexico.[34] From their analysis, they found that 50% of all original studies on prescription practice identified problems with inappropriate and harmful prescription behavior, as well as lack of implementation and monitoring of evidence-based treatment guidelines. Only 10% (11 of 108) of the studies analyzed by Wirtz and cols. investigated drug prescriptions in hospitals.

Where does the 'evidence' come from in order to practice evidence-based medicine in Mexican hospitals? What if our patients do not benefit from standardized dosage regimens established by controlled clinical trials or for patients with a different genetic make-up? For special patient populations and in developing countries, evidence must be generated through targeted and local strategies.

This study diagnosed L-carnitine prescription issues in neonates of a Mexican NICU. Even when our study population was quite representative of Mexican neonates, next step should be carrying out a multi-centric study in Mexico to validate our results and to establish nation-wide prescribing guidelines. Neonatal malnutrition is an important health issue in Mexico, thus L-carnitine rational use should be a priority.

CONCLUSIONS

The present study revealed inappropriate prescribing patterns of L-carnitine in Mexican neonates. Errors in dose selection occur most commonly. This type of preventable errors most probably led to the observed dose-dependent ADRs, which could have been avoided. Due to the importance of this drug in the treatment of malnourished and cardiopathic neonates, our results supported the establishment of an L-carnitine rational use policy at the NICU of the hospital under study. Nevertheless, more evidence on L-carnitine safety and effectiveness in neonatal pathologies is needed in order to produce first-hand evidence to enable its rational use and the approval of its current off-label indications.

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Conflict of Interest / Disclosure
All authors declare no conflict of interest**.**

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