L-Carnitine for Acute Valproic Acid Overdose: A Systematic Review of Published Cases

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OBJECTIVE: To review the evidence supporting the efficacy and safety of L-carnitine in the management of acute valproic acid overdose.

DATA SOURCES: MEDLINE (1950–May 2010), EMBASE (1980–May 2010), and Google Scholar (to May 2010) were searched, using the terms carnitine, valproic acid, and carnitine for valproic acid overdose. Reference citations from identified publications were reviewed.

STUDY SELECTION AND DATA EXTRACTION: Full-text publications evaluating the use of L-carnitine for management of valproic acid overdose in humans were sought. All studies, regardless of design, case series, and case reports reporting efficacy or safety endpoints were included. All languages were included. Two authors extracted primary data elements including patient demographics, presenting features, clinical management, and outcomes.

DATA SYNTHESIS: Seven articles discussing 8 patients and 1 reporting safety data from records of 674 patients were reviewed. Reports covered both pediatric and adult patients with acute exposures to valproic acid mono- and polydrug overdose who were treated with various regimens of L-carnitine. All patients recovered clinically and no adverse effects were noted.

CONCLUSIONS: Published evidence of the efficacy and safety of L-carnitine as an antidote for acute valproic acid overdose is limited. Based on the available evidence, it is reasonable to consider L-carnitine for patients with acute overdose of valproic acid who demonstrate decreased level of consciousness. We recommend intravenous administration of 100 mg/kg once, followed by infusions of 50 mg/kg (to a maximum of 3 g per dose) every 8 hours thereafter, continuing until ammonia levels are decreasing (if they were elevated initially) and the patient demonstrates signs of clinical improvement or until adverse events associated with L-carnitine occur.

KEY WORDS: L-carnitine, overdose, poisoning, toxicology, valproic acid.

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Valproic acid is a broad-spectrum antiepileptic medication that is also used for a number of nonseizure conditions including bipolar disorder, panic disorder, and peripheral neuropathy.[1] The antiepileptic mechanism of action is not fully known; however, it is thought to potentiate the brain's γ-aminobutyric acid system, directly act on neuronal membranes, or reduce excitatory transmission by excitatory neurotransmitters.[1,2] Valproic acid is readily absorbed from the gastrointestinal tract, with an oral bioavailability of 80–90%, and generally reaches peak concentrations within 4 hours.[3] There are documented cases of delayed peak concentrations following acute overdose.[3] It is highly protein bound to serum albumin, with an unbound fraction of ~10–20% at therapeutic concentrations, but protein binding is saturable, whereby the unbound fraction increases as the concentration increases. This may be especially relevant with overdose; the increased unbound concentration of drug may contribute to toxicity and can be a target for accelerated clearance through interventions such as hemodialy-

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sis.[3] Valproic acid is metabolized through mitochondrial oxidation (β-oxidation), microsomal oxidation (Ω-oxidation), as well as through hepatic phase II enzymes to form glucuronide metabolites. More detailed descriptions of metabolism are well described in other reviews.[2-4] The antiepileptic therapeutic window for serum valproic acid is 50–100 mg/L and is typically achieved with total daily doses of 500–2500 mg in adults or 10–30 mg/kg in children.[1,2]

While generally considered a safe medication, valproic acid is associated with a number of adverse effects with therapeutic use.[1] These include skin reactions (eg, Stevens-Johnson syndrome), hematologic effects (myelosuppression), hepatotoxicity, reproductive effects (eg, increased rates of neural tube defects), and metabolic effects (eg, hyperammonemia and carnitine deficiency). In overdose, valproic acid does not produce a readily identifiable toxidrome. Typically, it causes central nervous system (CNS) depression that can progress to coma; cerebral edema; metabolic derangements such as hyperammonemia; cardiovascular instability (hypotension); pancreatitis; and hepatic failure.[3]

In the 2008 American Association of Poison Control Centers' annual report, there were 8462 reported cases of valproic acid overdose, including 3444 single exposures (an overdose with a single ingestion of the drug, as opposed to an overdose by multiple doses).[5] These represent 19% and 16% of all reported anticonvulsant exposures, respectively. Approximately 59% of these cases were treated in health-care facilities, compared with 52% for all anticonvulsant overdose cases. The patients in 56% of these cases were older than 19 years of age. Of the 3444 exposures examined, only 56 (2%) patients were reported as having a "major" outcome (ie, one that was life-threatening or resulted in significant residual disability or disfigurement) and 1 patient died.

Prognostically, significantly elevated serum valproic acid concentrations have been associated with a more severe clinical course. In one case series that correlated symptoms with valproic acid serum concentrations in patients with single-agent ingestion, a peak valproic acid serum concentration above 450 mg/L was statistically significantly associated with progressing to a moderate or major outcome (ie, symptoms that were more pronounced or lasted longer than a minor outcome and typically required treatment, or were life-threatening, or resulted in significant residual disability or disfigurement).[6] Peak valproic acid serum concentrations above 850 mg/L were associated with an increased risk of development of coma, respiratory depression, aspiration, and metabolic acidosis. Importantly, in these cases of acute ingestion, peak valproic acid serum concentrations did not occur for a mean of 7.4 hours from the time of ingestion, with ~15% of concentrations peaking at greater than 10 hours postingestion. No statistical correlations between serum ammonia levels and symptoms, valproic acid serum concentrations, or clinical course were found.[6]

Following valproic acid overdose, it has been postulated that hepatic L-carnitine stores are depleted, impairing the ability of the mitochondria to transport valproic acid across the mitochondrial membrane via the carnitine shuttle, thus leading to a shift to the microsomal Ω-oxidative pathway, resulting in an increase in production of oxidative metabolites with toxic effects.[4] Within other tissues, including the CNS, it has been proposed that the impaired mitochondrial function may cause local tissue dysfunction. Additionally, the loss of the carnitine shuttle impairs ammonia uptake into the urea cycle, likely contributing to the development of hyperammonemia. As a result, L-carnitine has been considered as a potential antidote to restore mitochondrial function, reduce the production of toxic metabolites, and counter or reverse the toxic effects of valproic acid.[4]

L-Carnitine is commercially available in North America under the brand Carnitor. It is indicated in pediatric and adult patients for the treatment of primary carnitine deficiency, secondary carnitine deficiency due to inborn errors of metabolism, and for prevention and treatment of carnitine deficiency in patients with end-stage renal disease undergoing hemodialysis.[7] It is available both as oral tablets and solution (330-mg tablet; 100-mg/mL solution) as well as intravenous solution (200 mg/mL). L-Carnitine has limited oral bioavailability (~15%), is minimally protein bound, and is predominantly excreted unchanged by the kidneys.[7] Additionally, L-carnitine appears to be significantly cleared by hemodialysis, though the implications of this property for its use as an antidote have not been evaluated.

The objective of this article is to review the evidence supporting the efficacy and safety of L-carnitine for acute valproic acid overdose, with the aim of making a therapeutic recommendation based on the best available evidence.

Data Sources

A systematic search of MEDLINE (1950–May 2010), EMBASE (1980–May 2010), and Google Scholar (to May 2010) was performed to identify full-text publications evaluating the use of L-carnitine in the management of valproic acid overdose in humans. Search terms were carnitine and valproic acid, limiting to references flagged as poisoning, toxicity, drug toxicity, or overdose for MEDLINE and EMBASE. Google Scholar was searched using the phrase carnitine for valproic acid overdose. No language restriction was applied to the search. Additional published reports were identified through a manual search of references from retrieved articles.

Study Selection

Citations identified following literature review were evaluated independently by 2 authors (JP, PJZ) for inclusion, using title and abstract. If questions remained regard-

ing eligibility for inclusion, the full-text article was reviewed. All studies, regardless of study design, case series, and case reports reporting efficacy or safety endpoints were included. Reports of the use of L-carnitine for toxicity associated with chronic therapeutic dosing of valproic acid and of animal or metabolic models of toxicity were excluded. All languages were included.

Data Extraction

Data elements for all included reports were evaluated independently by 2 authors (JP, PJZ). Primary data elements extracted included patient demographics and presenting features, quantity of valproic acid ingested, serum valproic acid concentration on presentation, coingestants, L-carnitine regimen administered, additional acute management, and patient outcomes, including any adverse effects.

Data Synthesis

A total of 451 titles were screened for relevance; from these, 17 full-text articles were retrieved, resulting in 7 unique references describing 8 individual cases and 1 report of safety data from a series of 674 patient records. Reference lists of recently published review articles were manually screened for additional references, yielding no further results. Figure 1 details the search results.

The 8 cases reported are summarized in Table I.[8-14] Patients ranged in age from 15 months to 41 years and ingested from 400 mg/kg in the 2 pediatric exposures up to 100 g in 1 adult. Supportive care was provided for all patients, as well as various strategies to reduce absorption and attempt to increase clearance. L-Carnitine was dosed in widely different manners in these cases; in most it was administered intravenously (specific technique not discussed),[8,12-14] while in 2 it was administered by nasogastric tube.[9,10] The route of administration was not reported in 2 cases.[4,11] In the majority of these published cases, the duration of L-carnitine therapy was guided by the patient's level of consciousness and/or by serum ammonia levels; therapy with L-carnitine was continued until improvement in one or both parameters occurred. All patients were reported to fully recover and no adverse events attributable to L-carnitine were recorded.

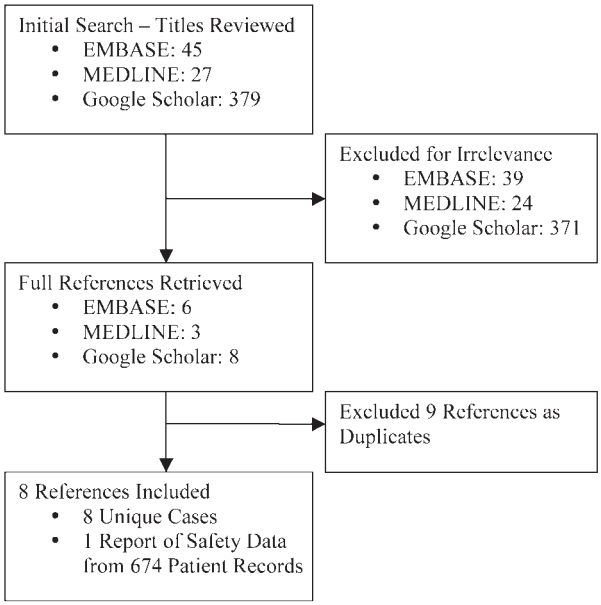

Figure 1. Search strategy flow diagram.

One additional reference, by LoVecchio et al., examined the records of a Phoenix, AZ, area poison center with the aim of gathering safety data on patients who had received L-carnitine to treat valproic acid overdose.[15] More than 300,000 charts were screened, identifying 674 patients with acute valproic acid overdose. Both single-agent and mixed overdoses were included, and a total of 251 doses of L-carnitine were identified as having been given for these cases, though the actual regimen (ie, dose/interval) or routes of administration were not reported. The safety outcomes of interest in this study were hypotension after the administration of L-carnitine or allergic reaction (hives, wheezing). The investigators found no episodes of either event in any of the cases they reviewed and did not report any effectiveness data.

Discussion

Despite the pathophysiologic rationale of using L-carnitine for acute valproic acid ingestion, reporting on the clinical experience associated with its use remains limited. All reported data were derived from the 8 cases we reviewed, and despite the good patient outcomes reported in these cases, they are subject to publication bias and represent a heterogeneous patient population that received varied L-carnitine dosing and treatment duration. Unfortunately, no comparative clinical trials, cohort studies, or case series have evaluated whether any clinical endpoints are improved with L-carnitine following valproic acid overdose.

There is wide variation in the doses and routes of administration used for L-carnitine, making it challenging to identify the optimal dosing strategy. Other indications for L-carnitine supplementation, including chronic hemodialysis and cancer-related fatigue, prevention of hyperammonemia and hepatotoxicity with chronic valproic acid use, and carnitine deficiency states, have used doses in the range of 20–40 mg/kg/day intravenously or after each hemodialysis session or simple 3-g/day dosing.[4,16-18] Given the differences in indication and pathophysiology/etiology, extrapolating these dosing regimens may not be appropriate for patients with acute valproic acid toxicity. The Carnitor product monograph provides administration instructions for intravenous dosing for metabolic disorders as 50

Table 1. Summary of Cases of L-Carnitine for Valproic Acid Overdose

Reference	Pt. Age (y), Sex, Weight (kg)	Valproic Acid Ingested, g (mg/kg)	Coingestant	Initial Valproic Acid Concentration, mg/L (time since ingestion, h)	Peak Ammonia Level, µmol/L (time from admission, h)	GCS: On Admission, at Worst (time from admission, h)	L-Carnitine Dose	Other Care	Outcome
Ishikura (1996)[8]	16 mo, M, 9.7	4 (412)	None	1316 (3)	NR	Deep coma on admission, NR	100 mg/kg initially, then 250 mg q8h for 4 days; route not specified	Gastric lavage, activated charcoal, intravenous fluids, urinary alkalinization	Recovered LOC on day 4, discharged home on day 8 without sequelae
Murkami (1996)[9]	15 mo, M, 10	4 (400)	None	1316 (2)	49 on admission	NR, NR	100 mg/kg NG daily for 3 days	Gastric lavage, intravenous fluids	Recovered LOC on day 3, discharged home on day 8 without sequelae
Houghton (2003)[10]	29, F, NR	NR	Acetaminophen, propoxyphene, diphenhydramine, diazepam, ethanol	337(2)	200 at admission	11, 3 (~8)	100 mg/kg NG daily	Activated charcoal, naloxone, *N*-acetylcysteine, supportive measures	Recovered LOC on day 3, discharged to psychiatric care on day 6 without sequelae
Minville (2004)[11]	36, M, NR	>60	None	560 (NR)	NR	7, NR	50 mg/kg daily for 4 days; route NR	Gastric lavage, hemodialysis	Recovered; discharged from intensive care at 48 h; admitted to psychiatric care
Chan (2007)[12]	Case 1: 14, F, 50	20 (400)	None	288 (10)	74 at admission	15, 14 (18)	3 g iv for 3 doses over 24 h	NR	Recovered LOC at 30 h post-ingestion; discharged home on day 2 without sequelae
	Case 2: 19, M, NR	NR	None	950 (unknown)	65 (28)	10, NR	3 g iv q8h for 4 days	Activated charcoal, supportive measures	Recovered LOC at day 2; discharged home on day 7 without sequelae
Sikma (2008)[13]	41, M, NR	100	None	1308 (>10)	NR	3, 3 (0)	NR	Intravenous fluids, activated fluids	Recovered LOC at 36 h from admission, discharged home on day 17 without sequelae
Jung (2008)[14]	23, F, NR	24	None	1159 (4)	226 (day 2)	3, 3 (0)	20 mg/kg iv q8h for 2 days, then 200 mg/kg iv q8h for 1 day, then 100 mg/kg iv q8h for 1 day	Activated charcoal, activated charcoal hemoperfusion, lactulose	Improved by day 16

GCS = Glasgow Coma Scale; LOC = level of consciousness; NG = nasogastric; NR = not reported.

mg/kg intravenous bolus over 2–3 minutes or by intravenous infusion.[7]

Intravenous administration is the route of choice in significant valproic acid toxicity, given the limited oral bioavailability of L-carnitine.[7] In addition, following drug overdose, many patients are not taking anything by mouth and may have also been given activated charcoal or another form of gastric decontamination; thus, the oral route is not an option. The loading dose of L-carnitine most commonly reported in the references is 100 mg/kg,[8-10] although lower loading doses have also been used. Maintenance dosing is required to treat toxicity due to ongoing or delayed absorption of valproic acid, although published dosing intervals also vary significantly, from every 4 hours to every 24 hours. Based on dosing intervals used in these case reports and those recommended by toxicology textbooks,[19,20] we recommend a dosing interval of every 8 hours. The maintenance dose also varied from 15 mg/kg to 100 mg/kg. While not definitively known whether seizures are a dose-related adverse effect, the risk of invoking seizures may make clinicians hesitant to give large doses. In order to administer an adequate dose in the context of an overdose, without substantially increasing the risk of an adverse event, a maintenance dose of 50 mg/kg (to a maximum of 3 g/dose) appears reasonable but, again, this is not based on especially strong evidence.

LoVecchio et al. demonstrated the general safety of the intervention; however, they potentially failed to include all relevant safety outcomes.[15] Though rarely reported in studies of L-carnitine in other populations (eg, hemodialysis patients), infrequent yet serious adverse events with intravenous administration of L-carnitine have been described, including tachyarrhythmias (6–9%), hypertension (20–21%), and hypotension (3–14%).[7,16] Seizures have been reported in patients receiving L-carnitine supplementation, even in the absence of an underlying seizure disorder, and are listed on the product monograph[7]; however, no references to the original reports are provided, nor could they be identified in a superficial search of the literature.

Case reports represent one of the least rigorous levels of evidence and, generally, should only be relied upon to be hypothesis generating for future research.[21] In cases such as this, in which case reports provide the only evidence available aside from animal and metabolic models, one must be careful in broadly applying the findings. This type of evidence is highly subject to publication bias, with unsuccessful treatment cases unlikely to be published. Additionally, because these reports lack placebo or comparator groups, we are not able to determine the optimal dosing regimen or magnitude of effect. Given that most valproic acid overdose patients recover eventually, regardless of antidote therapy administered, the use of a comparator arm in studies is necessary to clearly define the contribution of the antidote to patients' outcomes.

Based on the sparsity of high-quality evidence surrounding this topic, it is impossible to definitively ascertain the efficacy and safety of L-carnitine therapy for acute valproic acid overdose. Future research on the topic is needed for further clarification. Ideally, these studies would be prospective observational cohort or randomized controlled trials to best reduce confounding factors and bias, and would aim to demonstrate improvements in clinically meaningful outcomes such as recovery of normal mental status.

Based on what is known about the prognosis and toxicologic effects of acute valproic acid overdose, L-carnitine may have a role in select cases. Given that the true clinical significance of hyperammonemia and mitochondrial dysfunction in this setting is unknown, and that it may contribute to the development of CNS depression and cerebral edema, it may still be reasonable to consider L-carnitine for cases of severe intoxication in which level of consciousness is depressed. Additionally, patients demonstrating significantly supratherapeutic concentrations of valproic acid (ie, >850 mg/L) could be considered for empiric use of L-carnitine, although this approach has never been examined. The presence or absence of hyperammonemia likely should not be used as the sole parameter for the consideration of L-carnitine. As well, the low cost of intravenous L-carnitine is unlikely to be a significant barrier to its use.

Summary

Published evidence of the efficacy of L-carnitine as an antidote for acute valproic acid overdose is limited. It is clear that more rigorous studies and experience in acute valproic acid overdose are required to define the effect of L-carnitine on clinically relevant outcome measures, such as recovery of normal mental status. However, it may be reasonable to consider this intervention in patients demonstrating the most severe symptoms following acute valproic acid overdose. Ammonia levels do not appear to correlate with clinical outcome, but they may serve as a surrogate marker of the patient's metabolic status. Thus, we recommend that they only be used in conjunction with the patient's clinical status and that they not be used as the sole variable in determining management in patients following valproic acid overdose.

Based on the reports reviewed here, we suggest that L-carnitine be considered for patients with large, acute ingestions of valproic acid (ie, >100 mg/kg; doses that could be expected to produce peak concentrations >450 mg/L) who are demonstrating decreased level of consciousness. We recommend initiating therapy with intravenous L-carnitine 100 mg/kg (bolus over 2–3 minutes or infusion over 15–30 minutes), followed by 50 mg/kg (to a maximum of 3 g/dose) intravenously (bolus over 2–3 minutes or inter-

mittent infusion over 15–30 minutes) every 8 hours thereafter. L-Carnitine should be continued until ammonia levels are decreasing (if they were elevated initially) and the patient demonstrates signs of clinical improvement or adverse events occur. In the reported cases, up to 4 days of L-carnitine therapy have been required.

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References

1. Fagundes SBR. Valproic acid: review. Revista Neurosciencias 2008;16:130-6.
2. Perucca E. Properties of valproate: a summary after 35 years of clinical experience. CNS Drugs 2002;16:695-714.
3. Sztanjnkrycer MD. Valproic acid toxicity: overview and management. J Toxicol Clin Toxicol 2002;40:789-801. DOI 10.1081/CLT-120014645
4. Lheureux PER, Penaloza A, Zahir S, et al. Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? Crit Care 2005;9:431-40.
5. Bronstein AC, Spyker DA, Cantilena LR, et al. 2008 annual report of the American Association of Poison Control Centers' national poison data system (NPDS): 26th annual report. Clin Toxicol 2009;47:911-1084. DOI 10.3109/15563650903438566
6. Spiller HA, Krenzelok EP, Klein-Schwarts W, et al. Multicenter case series of valproic acid ingestion: serum concentrations and toxicity. Clin Toxicol 2000;38:755-60.
7. Product monograph. Carnitor (levocarnitine). Gaithersburg, MD: Sigma-Tau Pharmaceuticals, 2004. www.carnitor.com/downloads/VIFS_6.pdf (accessed 2010 Jan 24).
8. Ishikura H, Matsuo N, Matsubara M, et al. Levels of evidence. In: Oxford Centre for Evidence Based Medicine (March 2009). Valproic acid overdose and L-carnitine therapy. J Anal Toxicol 1996;20:55-8.
9. Murakami K, Sugimoto T, Woo M, et al. Effect of L-carnitine supplementation on acute valproate intoxication. Epilepsia 1996;37:687-9.
10. Houghton BL, Bowers JB. Valproic acid overdose: a case report and review of therapy. MedGenMed 2003;5(1). www.medscape.com/viewarticle/445062 (accessed 2010 Jan 24).
11. Minville V, Roche Tissot C, Samii K. Haemodialysis, L-carnitine therapy and valproic acid overdose. [French, translated with Google Translate] Ann Fr Anesth Reanim 2004;23:357-60. DOI 10.1016/j.annfar.2003.11.018
12. Chan YC, Tse ML, Lau FL. Two cases of valproic acid poisoning treated with L-carnitine. Hum Exp Toxicol 2007;26:967-9. DOI 10.1177/0960327107087799
13. Sikma MA, Mier JC, Meulenbelt J. Massive valproic acid overdose, a misleading case. Am J Emerg Med 2008;26:110e3-6. DOI 10.1016/j.ajem.2007.06.020
14. Jung J, Ahn K. A case of hemoperfusion and L-carnitine management in valproic acid overdose. Am J Emerg Med 2008;26:388e3-4. DOI 10.1016/j.ajem.2007.07.032
15. LoVecchio F, Shriki J, Samaddar R. L-Carnitine was safely administered in the setting of valproate toxicity. Am J Emerg Med 2005;23:321-2. DOI 10.1016/j.ajem.2005.02.015
16. Brass EP, Adler S, Sietsema KE, et al. Intravenous L-carnitine increases carnitine, reduces fatigue, and may preserve exercise capacity in hemodialysis patients. Am J Kidney Dis 2001;37:1018-28. DOI 10.1053/ajkd.2001.23647
17. Cruciani RA, Dvorkin E, Homel P, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. J Pain Symptom Manage 2006;32:551-9. DOI 10.1016/j.jpainsymman.2006.09.001
18. Arduini A, Bonomini M, Savica V, et al. Carnitine in metabolic disease: potential for pharmacological intervention. Pharmacol Ther 2008;120:149-56. DOI 10.1016/j.pharmthera.2008.08.008
19. Goldfrank LR, Nelson LS, Howland MA, Lewin NA, Flomenbaum NE, Hoffman RS, eds. Goldfrank's toxicologic emergencies. 8th ed. New York: McGraw-Hill, 2006.
20. Olsen KR, Benowitz NL, Blanc PD, eds. Poisoning and drug overdose. 5th ed. New York: McGraw-Hill, 2006.
21. Centre for evidence based medicine. www.cebm.net/index.aspx?o=1025 (accessed 2010 Jan 20).

L-Carnitina para Sobredosis Aguda de Ácido Valproico: Una Revisión Sistemática de Casos Publicados

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EXTRACTO

OBJETIVO: Revisar la evidencia que apoya la eficacia y seguridad de L-carnitina en el manejo de sobredosis aguda de ácido valproico.

FUENTE DE DATOS: Se llevó a cabo una búsqueda en MEDLINE (1950–mayo 2010), Embase (1980–mayo 2010), y Google Scholar (hasta mayo 2010), usando los términos carnitina y ácido valproico, y carnitina para sobredosis de ácido valproico. Las referencias citadas en las publicaciones identificadas fueron revisadas.

SELECCIÓN DE ESTUDIOS: Se obtuvieron los textos completos de las publicaciones que evaluaban el uso de L-carnitina para el manejo de sobredosis de ácido valproico en humanos. Todos los estudios, independientemente del idioma, diseño de estudio, series de casos e informes de casos que reportaron criterios de valoración de eficiencia o seguridad fueron incluidos.

EXTRACCIÓN DE DATOS: Dos autores extrajeron elementos de datos primarios incluyendo variables demográficas de pacientes, características presentadas, manejo clínico, y resultados.

SÌNTESIS DE DATOS: Siete referencias que discutían 8 pacientes y una referencia que reportaba datos de seguridad de los récords de 674 pacientes, fueron revisados. Los reportes cubrieron exposiciones agudas de pacientes pediátricos y adultos a sobredosis de ácido valproico sólo o con otros medicamentos, que fueron tratados con varios regímenes de L-carnitina. Se reportó que todos los pacientes recuperaron clínicamente y no se notaron efectos adversos.

CONCLUSIONES: La evidencia publicada sobre la eficacia y seguridad de L-carnitina como un antídoto para sobredosis aguda de ácido valproico es limitada. Basado en la evidencia disponible, es razonable considerar L-carnitina en pacientes con sobredosis aguda de ácido valproico que presenten un nivel de conciencia disminuido. Recomendamos una sola dosis de 100 mg/kg iv, seguida de ahí en adelante por 50 mg/kg (hasta un máximo de 3 g por dosis) iv cada 8 horas, de forma continua hasta que los niveles de amoníaco disminuyan (si estaban elevados inicialmente), y el paciente demuestre señales de mejoría clínica o se produzcan eventos adversos.

Traducido por Ana E Vélez

Utilisation de la L-Carnitine dans les cas de Surdosage aigu à l'Acide Valproïque: Une Revue Systématique des cas Publiés

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RÉSUMÉ

OBJECTIF: Revoir les évidences cliniques supportant l'efficacité et l'innocuité de l'utilisation de la L-carnitine dans le traitement des cas de surdosage aigu à l'acide valproïque (AV).

PROVENANCE DES DONNÉES: Une recherche des banques de données MEDLINE (1950 à mai 2010), Embase (1980–mai 2010), et Google Scholar (jusqu'à mai 2010) a été effectuée en utilisant les termes carnitine et valproic acid, et carnitine pour l'acide valproique surdosage. Les publications identifiées ont été revues.

SÉLECTION DES ÉTUDES: Les publications rapportant l'utilisation de la L-carnitine dans le traitement du surdosage aigu à l'AV chez l'humain ont été retenues. Toutes les études, peu importe la langue de publication ou le devis expérimental (y compris les séries de cas et les observations uniques) ont été inclues dans l'analyse.

EXTRACTION DES DONNÉES: Deux des auteurs ont extrait les donnée telles que la démographie, les caractéristiques de l'événement, la gestion clinique, et l'évolution de la condition.

RÉSUMÉ: Sept publications discutant de 8 patients et une publication rapportant l'analyse de 674 dossiers patients sont inclues dans cette revue. Les cas rapportés incluent des cas pédiatriques et des cas chez l'adulte, et l'administration d'acide valproïque en mono ou en poly thérapie. Bien que les régimes posologiques varient, il n'est fait mention d'effets secondaires dans aucun des cas rapportés et tous les patients ont récupéré.

CONCLUSIONS: La littérature médicale concernant le traitement du surdosage aigu à l'AV par la L-carnitine est assez restreinte. Compte tenu des évidences disponibles, il est raisonnable de considérer l'utilisation de L-carnitine chez les patients présentant un surdosage aigu à l'AV avec diminution de la vigilance. Une dose d'attaque de 100 mg/kg iv, suivie de 50 mg/kg (maximum 3 g par dose) IV aux 8 heures jusqu'à ce que les niveaux d'ammoniaque diminuent (si ils étaient élevés au départ) et que le patient démontre des signes d'amélioration clinique ou qu'il développe des effets secondaires apparait comme raisonnable.

Traduit par Suzanne Laplante