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Review

Levocarnitine induced seizures in patients on valproic acid: A negative systematic review

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ABSTRACT

Objective: Warnings of L-carnitine induced seizures are recorded on product monographs and pharmacy databases, without any referenced literature. This medication can potentially improve the hospital course in those patients with valproic acid (VPA) induced hyperammonemic encephalopathy, but may be withheld because of this warning. The goal was to perform an extensive systematic review of the literature to document the incidence of levocarnitine (L-carnitine) induced seizures in those patients on VPA therapy.

Methods: Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to June 2015), and reference lists of relevant articles were searched. The strength of evidence was to be adjudicated using both the Oxford and GRADE methodology by two independent reviewers.

Results: We failed to identify a single study implicating L-carnitine supplementation leading to seizures in any patient on VPA therapy. This contradicts all quoted, but unsubstantiated, concerns on product monographs and pharmacy databases related to seizure induction/propagation with L-carnitine supplementation.

Conclusion: There is no literature available to support claims of L-carnitine induced seizures during supplementation in patients on VPA therapy for seizures. This contradicts quoted, but not referenced, concerns on the product monograph. In patients suffering from hypocarnitinemia or hyperammonemic encephalopathy while on VPA, L-carnitine supplementation can be considered knowing there is no data to support seizure propagation or induction with administration of this supplement.

1. Introduction

Valproic acid (VPA) is a commonly utilized anti-epileptic drug (AED) in the management of outpatient epilepsy and the emergent treatment of seizures. Recent guidelines from the Neurocritical Care Society on the management of status epilepticus indicate the existence of class IIb level A evidence for the use of VPA in emergent and urgent treatment of status epilepticus (SE) [1]. The mechanism of action of VPA is not exactly clear. However, it is believed that VPA acts via through a variety of mechanisms [2–4].

Side effects of VPA use include hepatotoxicity, pancreatitis, and bone marrow suppression [5]. In addition, VPA has been linked to hyperammonemic encephalopathy leading to cerebral edema and altered level of consciousness (LOC) in the absence of seizure activity [5–7]. The hyperammonemia seen in VPA administration can be seen in both acute toxicity [3], and both short and long term usage in patients with epilepsy [8].

This hyperammonemia is believed to stem from carnitine coenzyme depletion secondary to VPA therapy. The depletion of carnitine leads to a shift from mitochondrial beta-oxidation to microsomal omega-oxidation of VPA and fatty acids [5,7]. The consequence of this shift in oxidative metabolism is an impaired elimination of ammonia [7]. Furthermore, VPA may even lead to renal glutamine uptake, subsequently resulting in increased glutamate and ammonia production [5,9]. The depletion of carnitine

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stores can be seen in acute toxicity as well as short and long term VPA usage [10,11] with some advocating for supplementation for those on chronic VPA [8,12]. Valproate induced hepatoxicity is of concern in patients with mitochondrial dysfunction. Specifically, polymerase-gamma (POLG) mutations have been linked to the development of valproate induced liver toxicity [13,14].

Carnitine is an essential amino acid involved in the beta-oxidation of fatty acids. Its supplementation in acute VPA overdose/toxicity and in chronic VPA usage has been advocated [3–5,8,12] with resolution of hyperammonemic crisis documented during supplementation [3–5]. Furthermore, supplementation with carnitine in the setting of certain mitochondrial disorders may reduce the risk of developing valproate induced complications. Carnitine supplemented either via intravenous (IV) or oral routes via its active form, levocarnitine (L-carnitine). The side effect profile of L-carnitine is broad, most commonly including: gastrointestinal distress, hyper-/hypo-tension, hypervolemia, dizziness, pharyngitis, and rash [15–17].

It has been suggested through both the product monograph [17], and online pharmacy databases [15,16], that L-carnitine supplementation can induce seizure activity in both patients with and without known epilepsy. The drug monograph states: "Seizures have been reported to occur in patients, with or without pre-existing seizure activity, receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported" [17]. However, no reference to literature is quoted in any of these sources. Also, documented complications, as tabulated within the drug monograph [17], fail to indicate seizures have ever been reported. Despite this seeming lack of literature to support the induction of seizures with L-carnitine, caution is noted during the supplementation of this coenzyme.

Given the potential for L-carnitine supplementation to improve hyperammonemic encephalopathy with VPA toxicity, it would be unfortunate for needing patients to have this medication either under-dosed or withheld secondary to concerns over seizure propagation. Thus, the goal of our manuscript was to perform an extensive systematic review of the literature to document the incidence of L-carnitine induced seizures in those patients on VPA therapy.

2. Methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [18] was conducted. The data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19]. The review questions and search strategy were decided upon by the primary author (FZ) and senior author (MW).

2.1. Search question, population, inclusion and exclusion criteria

The question posed for the systematic review was: In patients on VPA therapy for seizures, are there documented cases of L-carnitine supplementation induced seizure activity? For the purpose of this study, seizures were defined as single seizure, epilepsy, SE or RSE in order to capture all potential patients on VPA and receiving L-carnitine supplementation.

All studies, prospective and retrospective of any size based on human subjects were to be included. The reason for an all-inclusive search was based on the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was L-carnitine induced seizure activity. Secondary outcome measures were patient outcome (if reported), and any other adverse events related to L-carnitine supplementation.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, any age category, documented supplementation of L-carnitine in patients on VPA for seizures, and documented seizure activity induced by L-carnitine supplementation. Exclusion criteria were: experimental and not published in English studies.

2.2. Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, SCOPUS, and Cochrane Library from inception to October 2015 were searched using individualized search strategies for each database. The search strategy for MEDLINE can be seen in Appendix A of the supplementary material, with a similar search strategy utilized for the other databases

Finally, reference lists of any review articles or systematic reviews on seizure management were reviewed for relevant studies on L-carnitine induced seizures were missed during the database and meeting proceeding search.

2.3. Study selection

Utilizing two reviewers (FZ and NS), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcome of seizure control was reported in the study. Any discrepancies between the two reviewers were resolved by a third party (MW).

2.4. Data collection

Data was to be extracted from the selected articles and stored in an electronic database. The planned data fields included: patient demographics, type of study (prospective or retrospective), number of patients, dose and route of L-carnitine supplementation, presence of hyperammonemia and serum levels, time to seizure induction with L-carnitine, how many other AED were utilized prior to implementation of L-carnitine, adverse effects besides seizure, and patient outcomes (if documented).

2.5. Quality of evidence assessment

We planned to assess the level of evidence for each included study by a panel of two independent reviewers, utilizing the Oxford criteria [20] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [21] for level of evidence.

Any discrepancies between the grading of the two reviewers (FZ and NS) were to be resolved via a third party (MW).

2.6. Statistical analysis

No analysis was performed due to the absence of literature implicating L-carnitine induced seizures in the setting of VPA therapy.

3. Results

The results of the search strategy across all databases and other sources are summarized in Fig. 1. Overall 793 articles were identified. After removing duplicates, there were 396 articles. By applying the inclusion/exclusion criteria to the title and abstract,