In the name of God

Annal of Intensive Care

L-carnitine does not improve valproic acid poisoning management: a cohort study with toxicokinetic and concentration/effect relationships

- **Annal of Intensive Care**
- **P**ublished in 2022

Introduction

- Sodium valproate (VPA), synthetic 2-propylpentanoic acid, an antiepileptic, mood-stabilizer, antipsychotic, anti-migraine and analgesic drug.
- VPA poisoning is responsible for central nervous system manifestations : ataxia, sedation and lethargy to coma, respiratory depression, seizures & intracranial hypertension.

Introduction

- Administering L-carnitine in the presence of coma, hyperammonemia and hyperlactatemia attributed to VPA-related toxicity and/or if VPA concentrations are > 850 mg.
- In the acute poisoning setting, no data support the ability of L-carnitine to alleviate VPA induced central nervous system and liver dysfunction..

Aim Of Study

Little is known about L-carnitine-related benefits limiting acute VPA toxicity, we designed this study in VPA-poisoned patients :

➔To describe VPA toxicokinetic.

➔To analyze the relationships between plasma VPA concentrations and VPA-related effects on lactatemia.

➔Evaluate L-carnitine effects on VPA elimination, blood lactate level normalization, and organ failure progress.


CHRONO 500
Release Tablets
Sodium Valproate
Epilim®
CHRONO 500
Controlled Release Tabl
SANOFI


NATURE'S BOUNTY
L-Carnitine
500mg
Supports Heart Health &
Fat Metabolism*
HEART HEALTH

MATERIALS AND METHODS

- **18-year single-center cohort study(2002–2020)**
- According to Helsinki principles.
- Approved by the ethics committee of the French Society of Intensive Care.
- All VPA-poisoned adults admitted to ICU with history and at least one plasma VPA concentration>100 mg/L .

MATERIALS AND METHODS

- The **Simplified Acute Physiology Score** (SAPS) II was determined on admission.
- The **Sequential Organ Failure Assessment** (SOFA) score was calculated on admission and each day during the five following days.
- **Acute kidney injury** was graded according to the KDIGO classification.

MATERIALS AND METHODS

- The Physicians measure plasma VPA concentrations.
- L-carnitine dose regimen, IV 100mg/kg loading dose followed by a maintenance dosing up to 3 g/day in 3 divided doses for 3 days (or until ICU discharge)

RESULTS

- Sixty-nine VPA-poisoned patients (40F/29 M ; age, 41 years ,body-mass index, 24.2 kg/m2) were included.
- 49 (71%) were chronically treated with VPA.
- VPA ingested dose was 15.0 g ,rarely as sustained release formulation .
- Multi-drug ingestion involving benzodiazepines ,ethanol ,antipsychotics and hypnotics.

RESULTS

- On ICU admission, GCS= 6 was the main clinical manifestation.
- Elevations in blood lactate level (2.9 mmol/L and ammonia (96 μmol/L)
- Plasma VPA concentration was 231 mg/L.
- The SOFA score was 4.

RESULTS

- During ICU stay, the patients developed coma , agitation , seizures and brain edema by CT-scan.
- Blood lactate and serum ammonia concentrations increased in 38% and 30% of the patients, peaking at 3.9 mmol/and 127 mmol/L
- Plasma VPA concentration increased in 27% of the patients peaking at 248 mg/L within the first 24 h from admission in almost all cases.

RESULTS

- Acute kidney injury with mild elevation in median serum creatinine(81 µmol/L was classified as KDIGO stage 1 ,stage 2 ,and stage 3 .
- Management : invasive mechanical ventilation , activated charcoal , sedation , intravenous L-carnitine norepinephrine , blood transfusion and Hemodialysis.

RESULTS

- No adverse effect was attributed to L-carnitine administration.
- The length of ICU stay was 3 days, 3 patients died in the ICU.
- L-carnitine-treated and non-treated patients significantly differed regarding coma onset (P=0.007),blood bicarbonate(P=0.003), blood lactate level (P=0.0013), Hb(P=0.043), WBC count (P=0.027)

Discussion

- Based on the multivariate analysis, the peak blood lactate level was the only parameter associated with L-carnitine administration.
- VPA poisoning is responsible for severe and even fatal presentations.
- L-carnitine administration was not associated with significant alteration in VPA elimination.
- No significant clinical or metabolic benefit of L-carnitine.

DISCUSSION

- Carnitine is an essential cofactor in VPA metabolism , transport across the mitochondria membrane and permitting ammonia elimination.
- A lack of carnitine contribute to hyperammonemia and L-carnitine, the levorotatory form of carnitine, was suggested as possible treatment to lower ammonium in long-term VPA-treated patients.
- The proportion of Patients receiving L-carnitine did not change over time during the study period.

DISCUSSION

- **Evidence** to support effectiveness of L-carnitine in improving VPA poisoning is **poor.**
- Based on a matched comparative study, L-carnitine administration was unable to accelerate VPA clearance, speed blood lactate level normalization or limit organ dysfunction.

DISCUSSION

- Findings suggest **limiting** L-carnitine administration to the most severe VPA-poisoned patients (brain edema)
- considering alternative therapies that more effectively such as **hemodialysis** or **meropenem** infusion.

Limitations

- Its limited sample size.
- The prolonged study duration , may introduced **confounding** factors.
- Non-identified **co-ingested** drugs & risk of drug-drug interactions.
- The multivariate analysis of the effectiveness of L-carnitine in VPA poisoning should be interpreted.
- Due to its excellent tolerance and low cost, L-carnitine administration should considered in the meantime on a case-by-case.

Conclusions

- This study suggest no benefits of L-carnitine administration on VPA clearance, hyperlactatemia resolution or organ function improvement.
- The definitive evaluation of L-carnitine benefits requires a multicenter **randomized controlled trial**.

Thank you