European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.es/

Original Research Article

Transient Hyperammonemia in a Neonatal Patient Due to a Toxic Dose with Valproic Acid

Article History:

Name of Author:
Felix G.D.R., Eugenia T.S.M., Myriam C.A., Tiscar N.D., Marta H.H. and Jesus D.L.C.M.

Corresponding Author:
Felix G.D.R.

How to cite this article:
Felix G.D.R., et, al. Transient Hyperammonemia in a Neonatal Patient Due to a Toxic Dose with Valproic Acid. *Eur J Clin Pharm.* 2019;1(1);1-4.

Received: 02-01-2019
Revised: 21-01-2019
Accepted: 01-02-2019
Published: 13-02-2019

Abstract: Valproic acid (VPA) toxicity can precipitate transient hyperammonemia in neonates—a serious yet reversible metabolic disturbance. This article reviews the pathophysiology, clinical presentation, diagnostic approach, therapeutic interventions, and outcomes for neonates who develop hyperammonemic encephalopathy after VPA overdose. Recent case reports and observational studies are synthesised, with tables and figures illustrating key features of this rare but critical emergency.

Keywords: Valproic acid toxicity, Hyperammonemia, Neonatal encephalopathy, Metabolic disturbance, Therapeutic interventions.

INTRODUCTION

Neonatal seizures resistant to first-line agents occasionally require second-line therapies such as valproic acid, despite its known risks in this population. VPA toxicity in neonates can lead to acute, transient hyperammonemia, a potentially life-threatening situation unless promptly recognized and managed. Hyperammonemic encephalopathy secondary to VPA is a clinical diagnosis supported by laboratory markers, often manifesting independently of liver dysfunction and potentially reversible with early intervention[1][2][3].

PATHOPHYSIOLOGY

Valproic acid impairs ammonia detoxification through multiple mechanisms:

- **Inhibition of carbamoyl phosphate synthetase I**: disrupts the urea cycle, preventing ammonia conversion to urea.
- **Carnitine depletion**: reduces mitochondrial β-oxidation, promoting accumulation of toxic metabolites.
- **Direct hepatotoxic potential**: may co-exist, but many cases occur with normal hepatic function[2].

Ammonia elevation is not dose-dependent; even therapeutic VPA levels can induce hyperammonemia in predisposed neonates, although toxicity is more likely with overdose[3].

CLINICAL PRESENTATION

Typical features include:

- Rapid onset of neurological dysfunction—somnolence, irritability, poor feeding, vomiting, seizures, and occasionally progression to coma[2][3][4].
- Absence of jaundice or overt hepatic failure.

Key Laboratory Findings:

- Markedly elevated serum ammonia (often >150µmol/L, sometimes >700µmol/L)[4].
- VPA levels can vary; toxicity can occur even within therapeutic range, but are usually elevated after overdose.
- Normal or mildly altered liver enzymes[2][3].

Case Examples

Case Reference	Ammonia Level (µmol/L)	VPA Level (µg/mL)	Clinical Course	Outcome
Pokorna et al.[1]	279	268.6	Somnolence, impaired consciousness	Full recovery after VPA stop
Fernández Colomer[2]	327	157	Encephalopathy, progressive decline	Full recovery; carglumic acid
Oh et al.[5]	715	N/A	Coma, vomiting	Recovery with interventions
Unal et al.[4]	279	268.6	CNS depression, no hepatic failure	Fatal (cerebral edema)

Diagnostics

- **Laboratory**: Blood ammonia, VPA levels, liver function tests, metabolic screening to exclude urea cycle disorder.
- **Imaging**: Brain MRI/CT is typically normal or may show transient findings if severe.
- **Electroencephalography (EEG)**: Diffuse slowing or changes correlating with encephalopathy[1].

Diagnostic Rule-Out:

- Inborn errors of metabolism (urea cycle defects)
- Birth asphyxia
- Sepsis

MANAGEMENT

Prompt intervention is crucial to prevent irreversible CNS damage or death.

Therapeutic Strategies

- **Immediate cessation of VPA**: Most critical intervention, rapidly halts further ammonia accumulation[1][2][3].
- **Ammonia-lowering agents**:
  - **L-carnitine**: 50–100mg/kg/day IV/PO; replenishes carnitine stores, enhances ammonia excretion, particularly effective if carnitine is low[3][4].
  - **Lactulose**: Reduces ammonia absorption from the gut.
  - **Carglumic acid**: Analog of N-acetylglutamate, stimulates the urea cycle, effective in severe or resistant cases[2].
- **Supportive therapy**: Maintenance of fluids, correction of electrolyte/acid-base imbalance, seizure control if required.
- **Renal replacement (dialysis)**: Considered for severe, refractory hyperammonemia (>400-500µmol/L)[5].

Treatment Modality	Mechanism
VPA withdrawal	Stops further ammonia production
L-carnitine	Restores β-oxidation, removes ammonia
Lactulose	Gut ammonia sequestration

Carglumic acid	Activates carbamoyl phosphate synthetase
Dialysis	Physically removes ammonia

Outcomes

- With rapid recognition and intervention, *prognosis is very favorable*; most neonates fully recover without neurological deficits[1][2][3].
- Delayed intervention or massive overdose may result in seizures, cerebral edema, permanent brain injury, or death[4].
- Hyperammonemia is generally transient and reversible after stopping VPA and starting ammonia-lowering therapy.

Graph: Ammonia Decline After VPA Withdrawal

Time Post-Intervention (days)	Ammonia (µmol/L)
0	327
1	180
2	100
3	50

Data based on representative cases illustrating prompt fall in ammonia after stopping valproic acid and supportive therapy[2][3].

DISCUSSION

VPA-induced hyperammonemia in neonates is rare but serious. It is not reliably predicted by VPA levels or liver enzyme abnormalities. Routine monitoring of serum ammonia is advocated when neurologic deterioration occurs in neonates on VPA[2][3].

Clinical pearls:

- High index of suspicion for unexplained CNS depression in neonates receiving VPA.
- Early and aggressive management ensures best outcomes.
- Carnitine supplementation may be considered for all neonates on long-term or high-dose VPA.

CONCLUSIONS

Transient hyperammonemia from VPA toxicity in the neonatal period is a reversible cause of metabolic encephalopathy. Early cessation of VPA and use of ammonia-lowering agents, including L-carnitine and carglumic acid, yield excellent recovery with minimal risk of sequelae. Prompt diagnosis is essential to avoid serious CNS outcomes.

Tables

Table: Summary of Neonatal VPA-Induced Hyperammonemia Cases

Case/Author	Age	VPA Dose	Ammonia Level	Intervention	Outcome
Pokorna et al.[1]	Term	25mg/kg x 2/day	279µmol/L	VPA stop, L-carnitine	Full recovery
Fernández Colomer[2]	20d	30mg/kg x 2/day	327µmol/L	VPA stop, carglumic acid	Complete response
Baudou et al.[3]	1–10d	Various	157–327µmol/L	VPA stop	Full recovery
Unal et al.[4]	6d	310mg/kg (OD)	279µmol/L	Supportive	Death (late)

Recommendations

- Avoid VPA use in neonates unless absolutely necessary.

- Monitor ammonia and carnitine if VPA is used.
- Have protocols for rapid discontinuation and ammonia-lowering interventions for any neonate with CNS symptoms on VPA.
- Consider metabolic consultation for neonates with persistent hyperammonemia or poor response to therapy.

REFERENCES

1. Pokorna, P., et al. "Valproic acid—induced hyperammonemic encephalopathy in a full-term neonate: a brief review and case report." *European Journal of Clinical Pharmacology*, vol. 73, no. 5, 2017, pp. 647–649.
2. Fernández Colomer, B., et al. "Valproate-induced hyperammonaemic encephalopathy in a neonate: Treatment with carglumic acid." *Anales de Pediatría*, vol. 81, 2014, pp. 251–255.
3. E. Baudou, et al. "Adverse Effects of Treatment with Valproic Acid during the Neonatal Period." *Neuropediatrics*, vol. 50, no. 01, 2019, pp. 31–40.
4. Unal, E., et al. "Fatal valproate overdose in a newborn baby." *Human & Experimental Toxicology*, vol. 26, 2007, pp. 453–456.
5. Oh, Yeon Kyun. "Transient hyperammonemia in neonates: case analysis." *Korean Journal of Pediatrics*, vol. 53, no. 4, 2010, pp. 598–602.

