Meropenem as an antidote in severe valproic acid poisoning

Meropenem como antídoto en la intoxicación grave por ácido valproico

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Valproic acid (VPA) is a carboxylic acid that inhibits sodium channels and increases γ-aminobutyric acid levels. It is primarily used as an antiepileptic drug[1,2] and is implicated in severe intentional poisonings.[3] Carbapenems have been proposed as antidotes for VPA poisoning.[4-13] The therapeutic concentration of VPA ranges from 50 to 150 mg/L. It has a low volume of distribution (0.1–0.5 L/kg) and is absorbed enterally, reaching peak concentrations within 1–4 hours, although this may take more than 24 hours in overdose. VPA protein binding is concentration-dependent (~80% at concentrations < 150 mg/L) and decreases as serum concentrations increase, resulting in a higher free fraction (~35% at 300 mg/L and ~15% at concentrations > 1,000 mg/L). VPA is metabolized primarily through glucuronidation and β-oxidation, with a smaller contribution from cytochrome P450.1,2 Its half-life is 9–19 hours and may exceed 30 hours in severe poisoning, which can cause hyperammonemic encephalopathy, coma, shock, and death.[2]

In VPA poisoning, supportive care is the cornerstone of clinical management. Activated charcoal is indicated within the first few hours after ingestion, and L-carnitine is recommended despite limited evidence. At serum VPA concentrations > 300 mg/L, extracorporeal treatment (ECTR) is effective because of the increased unbound plasma fraction. ECTR is recommended in cases of refractory hypotension, severe acidosis, respiratory failure, cerebral edema, hepatic dysfunction, or concentrations ≥ 900 mg/L, although no clinical trials support its use.[1,2] Carbapenems, particularly meropenem (MEPM), have been proposed as antidotes for severe VPA poisoning because of their ability to reduce serum VPA concentrations by 50%–80%, increase its clearance (191%), and shorten its half-life from 15 to 4 hours, potentially achieving nontoxic concentrations within 24 hours.[4-15] The MEPM–VPA interaction is multifactorial and complex: it increases hepatic glucuronidation, reduces enterohepatic recirculation, and enhances excretion.[10,14] These mechanisms support the off-label use of MEPM as an antidote for VPA poisoning.[4-13] However, its administration to patients with epilepsy may complicate seizure management, and it may be ineffective in patients with liver disease and impaired glucuronidation.[14,15]

A 49-year-old woman with epilepsy and a psychiatric disorder was admitted, intubated, to the intensive care unit (ICU) following intentional poisoning with VPA, quetiapine, clonazepam, and diazepam. She presented with profound coma, shock, oliguria, and a requirement for norepinephrine (0.48 µg/kg/min). The exact time of ingestion and quantities ingested were unknown. Arterial blood gas analysis revealed respiratory acidosis with hyperlactatemia (pH, 7.25; pCO_2, 63 mmHg; lactate, 2.1 mmol/L). She had acute kidney injury (creatinine, 124 µmol/L), elevated VPA concentrations (668 mg/L), and hyperammonemia (125 µmol/L). Electrocardiography showed QTc interval prolongation (520 ms). Treatment with activated charcoal and L-carnitine was initiated, and cranial computed tomography ruled out cerebral edema or

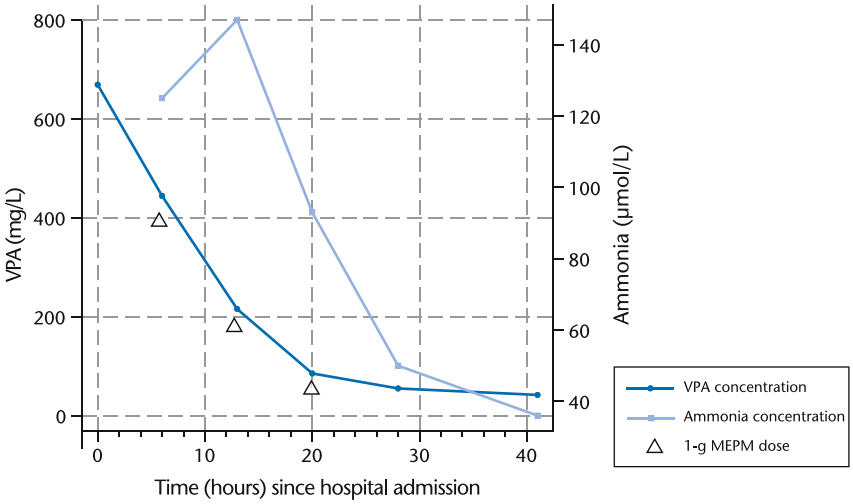


Figure 1. Serum valproic acid and ammonia concentrations during hospitalization. VPA: valproic acid; MEPM: meropenem.

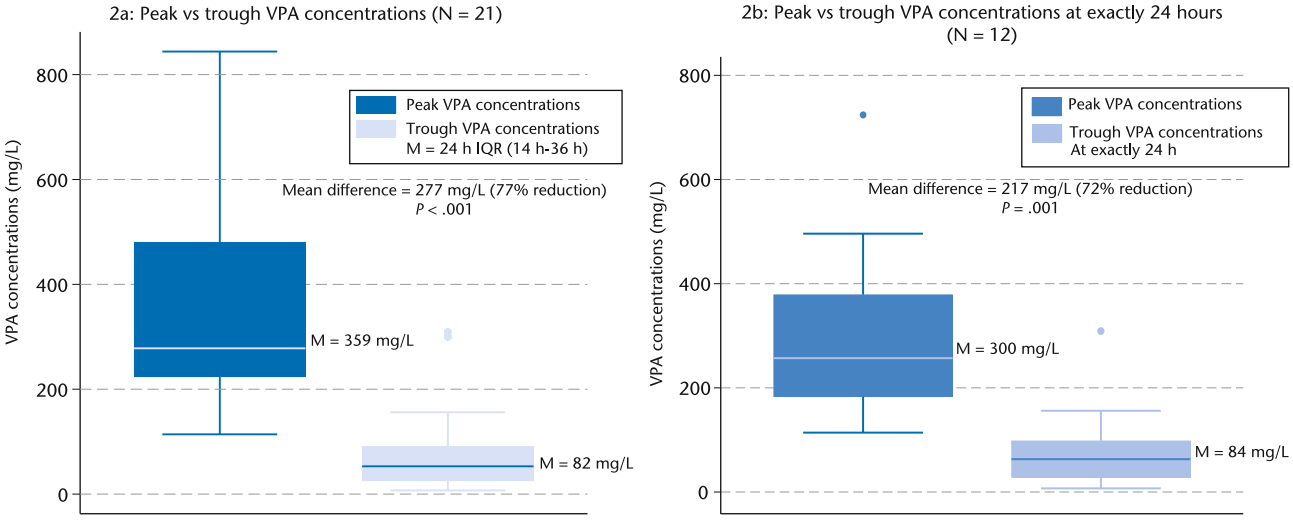


Figure 2. Peak and trough serum valproic acid (VPA) concentrations in the case series.

other acute lesions. Given the severity of her condition, MEPM was administered off-label as an antidote (1 g every 6 hours; total dose, 3 g), and prophylactic levetiracetam was initiated. Following supportive measures and two doses of MEPM, the patient improved rapidly, regaining consciousness and renal function, with VPA concentrations decreasing to 85 mg/L within 20 hours (Figure 1). ECTR was not required. She was discharged from the ICU after 48 hours without complications.

We conducted a structured literature search in MEDLINE, the Cochrane Central Register of Controlled Trials, and Google Scholar, identifying 10 indexed publications involving 20 patients with VPA poisoning treated with carbapenems.[4-13] Relevant data are shown in Table 1 (Supplementary data: https://revistaemergencias.org/extra/5381.pdf). Given the heterogeneity of the data, initial VPA and ammonia concentrations were defined as the first available measurements, and peak concentrations as the highest recorded values. Trough concentrations were defined as the post-carbapenem measurements obtained closest to 24 hours after the initial assessment. VPA concentrations below 150 mg/L were considered nontoxic. Continuous variables were compared using Student's t-test, and categorical variables using the chi-square test. Variables with more than 50% missing data were excluded. The robustness of the paired mean difference between peak and trough VPA concentrations was assessed using bootstrap resampling (5,000 iterations). Confidence intervals (CIs) were calculated using the normal, percentile, bias-corrected (BC), and bias-corrected and accelerated (BCa) methods. When reliable concentration–time data were available, the VPA elimination half-life was estimated using linear regression, assuming that no additional VPA doses had been administered. Statistical analyses were performed using Stata version 18.0.

The review showed that most patients were women (71%), 62% had psychiatric comorbidities, 76% had ingested multiple substances, and 67% were unconscious. MEPM was administered to 18 patients (86%). Activated charcoal and L-carnitine were administered to 8 patients (38%). The mean peak VPA concentration was 359 mg/L (SD, 202), and the mean trough concentration after carbapenem administration decreased to 53 mg/L (SD, 88). Trough measurements were obtained at a median of 24 hours (14–36 hours). Nontoxic trough concentrations were achieved in 18 patients (81%). Thirteen patients (62%) met clinical criteria for ECTR, none based on VPA concentration, but ECTR was performed in only one patient, who was the only patient to die.[2]

Paired analysis demonstrated a 77% reduction in VPA concentrations following carbapenem administration (from 359 mg/L to 82 mg/L), corresponding to a mean difference of 277 mg/L (Figure 2a). In the analysis restricted to trough measurements obtained strictly at 24 hours (n = 12), the reduction was similar (72%) (Figure 2b). Bootstrap analysis confirmed the robustness of the effect across the different CIs (normal: 200–355 mg/L; percentile: 204–360 mg/L; BC: 206–362 mg/L; BCa: 210–368 mg/L), with a mean difference of 277 mg/L (77% reduction; $P < .001$). The VPA elimination half-life was estimated in 16 patients; 11 (69%) had a shorter half-life than expected in a nonpoisoned adult (≤ 9 vs 9–19 hours), and 10 of these patients received MEPM. Only 1 case had a half-life above the range expected in nonpoisoned adults. For the overall case series, the median VPA elimination half-life was 8 hours (range, 2–23 hours).

In this analysis, we contextualize the clinical usefulness of MEPM as an antidote for severe VPA poisoning by reviewing its toxicokinetics, the carbapenem–VPA interaction, and the indexed cases reported to date. In our patient, the addition of MEPM to standard supportive therapies was associated with an 87% reduction in VPA concentrations, clinical improvement, no adverse events, and no need for ECTR. Consistent with the existing literature, our analysis showed that adjunctive MEPM administration resulted in a 72%–77% reduction in peak VPA concentrations.[10,14] In this case series, ECTR was performed in only 1 patient, despite 13 patients (62%) meeting clinical criteria for its use.[2] Following carbapenem administration, 86% of patients achieved nontoxic trough concentrations. Clinical outcomes in this case series were favorable, with no reported adverse events or seizures and only 1 death.[9] All patients treated with MEPM had a VPA elimination half-life equal to or shorter than that expected in nonpoisoned adults,[1,2,14] supporting the hypothesis that MEPM administration might obviate the need for ECTR in highly selected patients under close monitoring.

Table 1. Summary of the case series

	N = 21 n (%)	Missing data n (%)
Epidemiological variables		
Female sex	15 (71)	–
Age (years) [mean (SD)]	43.5 (13)	–
Medical history		2 (10)
Epilepsy	3 (14)	
Psychiatric disorder	13 (62)	
Both	2 (10)	
Liver disease	0 (0)	
Other drugs involved		
Mixed-drug poisoning	16 (76)	–
Benzodiazepines	5 (24)	
Antipsychotics	3 (14)	
Both (BZD and AP)	4 (19)	
Other	4 (19)	
Clinical characteristics of the poisoning episode		
Coma	13 (62)	1 (5)
Need for intubation	11 (52)	1 (5)
Use of vasoactive drugs	7 (33)	4 (19)
Metabolic acidosis	5 (24)	16 (76)
Estimated VPA dose ingested (g) [mean (SD)]	28 (18)	6 (29)
VPA concentrations (mg/L)		
Initial VPA concentration	316 (204)	–
Peak VPA concentration	359 (202)	–
Trough VPA concentration*	82 (84)	–
Nontoxic trough VPA concentrations [n (%)]	18 (86)	–
Time to trough ammonia concentration measurement (hours) [median (min–max)]	24 (14-36)	1 (5)*
Ammonia concentrations (µmol/L) [median (IQR)]		
Initial ammonia concentration	61 (27-115)	13 (62)
Peak ammonia concentration	115 (80-147)	16 (76)
Trough ammonia concentration	51 (37-77)	17 (81)
Time to trough ammonia concentration measurement (hours) [median (min–max)]	24 (18-26)	18 (86)
Carbapenems		
Meropenem	18 (86)	–
Other	3 (14)	–
MEPM dose administered (g) [median (IQR, 25th–75th percentile)]	3 (1-3)	–
Other antidotes		
L-Carnitine	8 (38)	–
Activated charcoal	8 (38)	–
Flumazenil	3 (14)	–
Naloxone	4 (19)	–
Outcome data		
Duration of IMV (days) [median (IQR, 25th–75th percentile)]	2 (1-4)	5 (24)
ICU length of stay (days) [median (IQR, 25th–75th percentile)]	3 (2-5)	13 (62)
Hospital length of stay (days) [median (IQR, 25th–75th percentile)]	4.5 (2-12.5)	17 (81)
Seizure episodes	0 (0)	–
Mortality	1 (5)	–
ECTR		
ECTR performed	1 (5)	–
Overall indication for ECTR†	13 (62)	–
Recommended	6 (29)	–
Suggested	7 (33)	–

Percentiles were rounded to the nearest integer and continuous variables to one decimal place.
AP: antipsychotics; BZD: benzodiazepines; ECTR: extracorporeal treatment; ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; MEPM: meropenem; SD: standard deviation; VPA: valproic acid.
*Sanivarapu *et al.*[11] did not report the exact time of trough concentration measurement, which was estimated graphically.
†According to the EXTRIP recommendations,2 ECTR is recommended if: (1) serum VPA concentration > 1,300 mg/L or (2) cerebral edema or shock attributable to VPA toxicity. ECTR is suggested if: (1) serum VPA concentration > 900 mg/L, (2) coma or respiratory depression requiring mechanical ventilation, (3) acute hyperammonemia, or (4) pH < 7.10.

Our investigation provides a sound pharmacokinetic rationale for using MEPM as an adjunctive antidote to supportive therapies in severe VPA poisoning, a rigorously documented new case illustrating its safe use, and a pooled analysis supporting its clinical plausibility. Of note, the sample size is limited and that bootstrap analysis provides probabilistic support but does not replace the need for larger samples. Heterogeneity and partially missing reported data, together with confounding variables that make it difficult to isolate the effect of MEPM and the absence of control groups inherent to observational studies, limit the generalizability of these findings.

In this context, sufficiently powered prospective trials are unlikely to be feasible. Therefore, the present analysis is the most comprehensive to date on the use of MEPM as an adjunctive antidote in the treatment of severe VPA poisoning. Given the existing toxicokinetic evidence and the consistency of this analysis, we cautiously suggest the off-label use of MEPM as an antidote in severe VPA poisoning, in addition to standard supportive and decontamination measures. We also strongly recommend obtaining informed consent, closely monitoring for complications, maintaining readiness to escalate treatment, and comprehensively documenting and reporting relevant data.

References

1 Sztajnkrycer MD. Valproic Acid Toxicity: Overview and Management. J Toxicol Clin Toxicol. 2002;40:789-801.
2 Ghannoum M, Laliberté M, Nolin TD, MacTier R, Lavergne V, Hoffman RS, et al. Extracorporeal treatment for valproic acid poisoning: Systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015;53:454-65.
3 Greene SC, Wyatt K, Cates AL, Weiss S. Anticonvulsant fatalities reported to the American Association of Poison Control Centers 2000 - 2019. Seizure. 2023;106:1-6.
4 Khobrani MA, Dudley SW, Huckleberry YC, Kopp BJ, Biggs AD, French RNE, et al. Intentional use of carbapenem antibiotics for valproic acid toxicity: A case report. J Clin Pharm Ther. 2018;43:723-5.
5 Smolders EJ, Ter Heine R, Natsch S, Kramers K. Meropenem to Treat Valproic Acid Intoxication. Ther Drug Monit. 2022;44:359-62.
6 Dreucean D, Beres K, McNierney-Moore A, Gravino D. Use of meropenem to treat valproic acid overdose. Am J Emerg Med. 2019;37:2120.e5-2120.e7.
7 Thomas C, Priano J, Smith TL. Meropenem as an antidote for intentional valproic acid

overdose. Am J Emerg Med. 2020;38:690.e1-690.e2.
8 Muñoz-Pichuante D, Villa-Zapata L, Lolas R. Meropenem for management of valproic acid overdose: a case report. Drug Metab Pers Ther. 2020;35:20190028.
9 Perkovic Vukcevic N, Mijatovic Jovin V, Vukovic Ercegovic G, Antunovic M, Kelecevic I, Živanovic D, et al. Carbapenems as Antidotes for the Management of Acute Valproic Acid Poisoning. Pharmaceuticals (Basel). 2024;17:257.
10 Doad G, Mcmanus D, Topal J, Lopez F. Utilizing the carbapenem-valproic acid drug interaction in the management of valproic acid overdose. Crit Care Med. 2018;46:450.
11 Sanivarapu R, Sharma R, Akella J. Thinking out of the box: management of valproic acid toxicity with carbapenems. BMJ Case Rep. 2021;14:e240140.
12 Cunningham D, Clark K, Lord K. Treatment of valproic acid overdose with meropenem in an epileptic patient. Am J Emerg Med. 2022;53:284.e1-284.e3.
13 Romero-Carratala M, Pérez De Amezaga Tomás L, Sala Carazo M, Rialp Cervera G. Meropenem for the management of valproic acid intoxication: a case report and a review of the literature. Med Intensiva (Engl Ed). 2024;48:620-2.
14 Haroutiunian S, Ratz Y, Rabinovich B, Adam M, Hoffman A. Valproic Acid Plasma Concentration Decreases in a Dose-Independent Manner Following Administration of Meropenem: A Retrospective Study. J Clin Pharmacol. 2009;49:1363-9.
15 Spriet I, Willems L. No Interaction Between Valproate and Meropenem in a Cirrhotic Patient. Ann Pharmacother. 2011;45:1167-8.

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