Research Square

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Effect of carbapenem and VPA coadministration on seizure outcomes: a retrospective single-center study

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Abstract

Background

The concomitant use of carbapenem antibiotics and valproate is generally avoided because carbapenems markedly reduce serum valproate concentrations, raising concern about increased seizure risk. However, robust clinical evidence linking this pharmacokinetic interaction to worsened seizure control remains scarce.

Methods

This single-center, retrospective, self-controlled study included 189 patients with epilepsy or status epilepticus who received valproate together with meropenem and/or imipenem. Serum valproate concentrations, seizure incidence, and seizure frequency were compared across the pre-concomitant, concomitant, and post-concomitant periods.

Results

During concomitant therapy, median serum valproate concentration declined by 74.7% (from 48.04 to 12.15 μg/mL). Despite this reduction, no significant increase in seizure rate or frequency was observed. Seizure rates were 28.0% pre-concomitantly, 20.6% during therapy (P = 0.5602), and 8.5% post-therapy (P = 0.0086). Seizure frequency remained 0 (0–0.5), 0 (0–0), and 0 (0–0) per person-week, respectively. No significant differences in valproate concentrations were found between patients with and without seizures.

Conclusions

These findings challenge current precautionary recommendations and support a more nuanced, evidence-based approach to managing this drug combination in clinical practice.

Introduction

Epilepsy is a prevalent chronic neurological disorder that affects an estimated 65 million individuals worldwide, and has an annual incidence of 50–100 per 100,000 population. The incidence is notably higher among infants under one year of age and adults over 85 years[1]. Sodium valproate (VPA) occupies an irreplaceable role in epilepsy management due to its broad-spectrum antiseizure activity, unique multi-target mechanism of action, preferred status in specific epilepsy syndromes, suitability for monotherapy, and well-established pharmacokinetic and safety profile [2, 3].

Bacterial infections of the central nervous system represent one of the most frequent and preventable risk factors for acute symptomatic seizures and acquired epilepsy[4, 5]. Infections can also trigger status epilepticus, a high-mortality condition defined by continuous or recurrent seizures lasting more than five minutes[4]. Carbapenem antibiotics have become cornerstone therapeutic agents for severe infections owing to their broad antimicrobial spectrum and efficacy against multidrug-resistant organisms[6]. Given their pronounced efficacy against multidrug-resistant and Gram-negative bacteria, meropenem and imipenem dominate clinical use and are among the most frequently administered carbapenems in critically ill patients[7].

In clinical practice, managing patients with concurrent infection and epilepsy or those at high seizure risk often necessitates the concomitant use of carbapenems and VPA. However, the safety of this combination, particularly its impact on seizure control, remains a subject of long-standing controversy. The prevailing view posits that carbapenems significantly reduce serum VPA concentrations, primarily by enhancing the clearance of VPA glucuronide conjugates and inhibiting its enterohepatic recirculation, thereby potentially compromising therapeutic efficacy[8, 9]. Several case reports and small observational studies have documented worsened seizure control or even status epilepticus following co-administration[8]. An alternative perspective notes that therapeutic antiseizure activity is primarily mediated by free (unbound) valproic acid. Some preclinical studies found that concomitant use did not decrease free VPA concentrations, suggesting a potentially neutral effect on seizure risk[10, 11].

Despite this, international guidelines generally recommend avoiding the combination or, if unavoidable, implementing close therapeutic drug monitoring of VPA with corresponding antiseizure regimen adjustments. This recommendation poses a significant clinical dilemma: critically ill patients often have a clear indication for carbapenems, while alternative antibiotics may offer limited efficacy or greater toxicity. Furthermore, as time-dependent antimicrobials, insufficient carbapenem exposure increases the risk of infection relapse or treatment failure[12]. Conversely, VPA is crucial for seizure control in many patients, and inappropriate substitution or discontinuation carries substantial risk. More importantly, current evidence suggesting an increased seizure risk from this drug interaction largely stems from case reports and small-scale studies, highlighting a significant gap in large-scale, systematic clinical evidence. Therefore, a large-scale, systematic study to evaluate the true seizure risk associated with concomitant carbapenem and VPA use is urgently needed to address this clinical dilemma and evidence gap.

Materials and methods

Study design

This single-center, retrospective, self-controlled study was conducted through a review of electronic medical records. It aimed to evaluate the effects of concomitant VPA and carbapenem antibiotic (meropenem or imipenem) therapy on serum VPA concentrations and antiseizure efficacy.

Study population

Data source

Inpatients treated at The Third Affiliated Hospital of Sun Yat-sen University between June 2013 and June 2023 were eligible. Meropenem and imipenem were administered intravenously; VPA was administered either intravenously or orally.

Inclusion criteria

Patients were included if they met the following criteria: (1) a confirmed diagnosis of epilepsy or status epilepticus, and (2) concomitant administration of VPA with meropenem and/or imipenem.

Exclusion criteria

Exclusion criteria were: (1) non-concurrent use of VPA and carbapenems or a concomitant duration of less than 24 hours; (2) prophylactic use of VPA; or (3) missing essential clinical or laboratory data.

Methods

Data collection

Data were systematically extracted using a standardized case report form. Clinical information included epilepsy/status epilepticus diagnosis, seizure etiology, indication for carbapenem use, duration and dosage of VPA and carbapenem therapy, seizure activity, VPA discontinuation (and reason if applicable), and number/type of other antiseizure medications. Laboratory data consisted of liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and albumin. The infection markers: white blood cell (WBC) count, neutrophil percentage, C-reactive protein (CRP), and procalcitonin (PCT), measured before and during concomitant therapy.

Data processing

To assess the influence of concomitant therapy, each patient's hospital stay was divided into three intervals: pre-concomitant, concomitant, and post-concomitant (up to 14 days after carbapenem discontinuation). For patients discharged earlier, data were recorded until the discharge date. For each interval, the following were recorded: serum VPA concentration, seizure occurrence (yes/no and frequency), and seizure duration.

Statistical analysis

Analyses were performed using GraphPad Prism 8. Categorical variables are summarized as number (percentage). Continuous variables are presented as mean ± standard deviation if normally distributed, or as median (interquartile range) otherwise. Based on data distribution and design, group comparisons were made using independent or paired t-tests, one-way or repeated-measures ANOVA, or corresponding

non-parametric tests (Mann–Whitney U, Kruskal–Wallis, Wilcoxon signed-rank, or Friedman tests). A two-sided P-value < 0.05 defined statistical significance.

Results

Patient selection and baseline characteristics

We retrospectively analyzed 309 cases from The Third Affiliated Hospital of Sun Yat-sen University (June 2013 to June 2023) involving concomitant use of VPA with meropenem and/or imipenem. Following the application of inclusion and exclusion criteria, 120 cases were excluded: 86 for non-concurrent use of VPA and carbapenems, 29 for a concomitant duration <24 hours, 4 for prophylactic VPA use, and 1 due to missing data. Consequently, 189 patients were included in the final analysis (Figure 1).

Among the 189 included patients, 174 (92.1%) had a diagnosis of epilepsy and 15 (7.9%) had status epilepticus. The distribution of underlying etiologies was as follows: cerebrovascular disease (n = 87, 46.0%), metabolic/toxic/septic encephalopathy (n = 25, 13.2%), encephalitis or meningoencephalitis (n = 24, 12.7%), pre-existing epilepsy (n = 20, 10.6%), traumatic brain injury (n = 14, 7.4%), brain tumor (n = 10, 5.3%), and post-cardiopulmonary-cerebral resuscitation (n = 9, 4.8%). Detailed baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics and diagnoses of included patients (n = 189).

Characteristic	n (%)
Epilepsy diagnosis	
Epilepsy	174 (92.1%)
Status epilepticus	15 (7.9%)
Etiology	
Cerebrovascular Disease	87 (46.0%)
Metabolic/Toxic/Septic Encephalopathy	25 (13.2%)
Encephalitis/Meningoencephalitis	24 (12.7%)
Pre-existing epilepsy	20 (10.6%)
Traumatic brain injury	14 (7.4%)
Brain tumor	10 (5.3%)
Post-cardiopulmonary-cerebral resuscitation	9 (4.8%)

Values are presented as n (%).

The duration and indications for concomitant antibiotic therapy are summarized in Table 2. Meropenem was administered to 151 patients with a median concomitant duration of 8 days (IQR 4-12). Indications included pulmonary infection (n = 120), central nervous system (CNS) infection (n = 23), and other infections (n = 8; e.g., urinary tract infection [UTI], skin infection, sepsis). Imipenem was given to 31 patients for a median of 8 days (IQR 4-14), primarily for pulmonary infection (n = 30), with one case for other infection (postoperative). Seven patients received both imipenem and meropenem concurrently for a median of 21 days (IQR 10-42), all for pulmonary infection.

Table 2. Utilization of meropenem and imipenem. Values are presented as median [IQR].

Item	Meropenem (n = 151)	Imipenem (n = 31)	Imipenem + Meropenem (n = 7)
Median concomitant duration, days	8 (4-12)	8 (4-14)	21 (10-42)
Indication, n (%)			
Pulmonary infection	120 (79.5%)	30 (96.8%)	7 (100.0%)
CNS Infection	23 (15.2%)	0	0
Other Infection	8 (5.3%)	1 (3.2%)	0

Among the 189 patients, 161 (85.2%) received concomitant antiseizure medications (ASMs) in addition to VPA, whereas 28 (14.8%) remained on VPA monotherapy. The median number of concomitant ASMs was 2 (interquartile range [IQR] 1–3). Levetiracetam was the most frequently co-administered agent (n = 113), followed by lamotrigine (n = 47), phenobarbital (n = 42), clonazepam (n = 30), magnesium sulfate (n = 29), topiramate (n = 26), oxcarbazepine (n = 24), and carbamazepine (n = 12) (Table 3).

Table 3. Concomitant use of other antiseizure medications.**Values are presented as median [IQR].**

Category	n (%) / Detail
Patients on other ASMs	161 (85.2%)
Patients on VPA monotherapy	28 (14.8%)
Number of concomitant ASMs, median (IQR)	2 1-3
Specific ASMs used, n	
Levetiracetam	113
Lamotrigine	47
Phenobarbital	42
Clonazepam	30
Magnesium sulfate	29
Topiramate	26
Oxcarbazepine	24
Carbamazepine	12

Impact of concomitant VPA and carbapenem use on laboratory parameters

Serially measured biochemical parameters were analyzed using median values from the pre-concomitant and concomitant periods (Table 4). Assessed serum indices included markers of inflammation—WBC count, neutrophil percentage, CRP, and PCT—and markers of liver function—AST, ALT, ALP, total bilirubin, and albumin. No significant differences were found in WBC count, neutrophil percentage, CRP, or PCT between the two periods. This likely reflects that most patients were not in an active infectious state prior to concomitant therapy and that infections were adequately controlled during treatment. Regarding liver function, ALT levels were significantly higher and albumin levels were significantly lower during concomitant therapy compared to the pre-concomitant period, though both remained within normal clinical limits. Other liver function parameters (AST, ALP, total bilirubin) did not change significantly. Furthermore, comparisons of inflammation and liver function markers between patients with and without seizures during the concomitant period showed no significant differences (Table 5), indicating no clear association between seizure occurrence and these laboratory parameters after initiating combination therapy.

Table 4. Inflammatory and liver function markers before and during concomitant VPA and carbapenem therapy.

Parameter	Pre-concomitant Period	Concomitant Period	P-value
WBC (×10⁹/L), n = 78	9.210（6.910-12.70）	8.830（6.538-12.68）	0.8169
Neutrophil %, n = 76	0.7445（0.6643-0.8316）	0.7595（0.6549-0.8276）	0.9293
CRP (mg/L), n = 96	17.49（6.803-52.23）	30.38（5.750-70.94）	0.6124
PCT (ng/mL), n = 54	0.2025（0.09638-0.5443）	0.3015（0.1083-1.333）	0.8226
AST (U/L), n = 114	24.00（18.00-37.50）	26.00（19.00-39.50）	0.1968
ALT (U/L), n = 116	10.79（5.013-24.75）	17.00（7.959-27.38）	**0.0002**
ALP (U/L), n = 39	76.00（56.00-109.0）	78.00（56.20-99.00）	0.7326
Total bilirubin (μmol/L), n = 71	7.400（4.910-10.99）	7.260（4.700-10.62）	0.2737
Albumin (g/L), n = 111	36.50（33.85-40.20）	34.70（30.15-38.50）	**0.0159**

Values are presented as median [IQR]. Abbreviations: WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Table 5. Inflammatory and liver function markers in patients with and without seizures during concomitant therapy.

Parameter	Pre-concomitant Period	Concomitant Period	P-value
WBC (×10⁹/L), n = 78	9.110（6.655-13.24）	10.12（6.774-12.43）	0.8920
Neutrophil %, n = 76	0.7490（0.6570-0.8220）	0.7733（0.6563-0.8255）	0.5198
CRP (mg/L), n = 96	29.70（8.500-70.93）	23.75（2.255-56.38）	0.1786
PCT (ng/mL), n = 54	0.2540（0.1178-1.353）	0.2025（0.093-0.5084）	0.2397
AST (U/L), n = 114	25.00（19.00-38.00）	29.00（18.00-50.00）	0.2874
ALT (U/L), n = 116	16.00（8.000-31.00）	18.00（7.040-27.50）	0.9503
ALP (U/L), n = 39	72.50（55.00-98.25）	78.00（61.25-117.0）	0.4284
Total bilirubin (μmol/L), n = 71	7.500（4.720-10.95）	7.325（5.530-16.88）	0.4435
Albumin (g/L), n = 111	34.58（29.74-38.38）	37.05（32.70-38.70）	0.0587

Values are presented as median [IQR]. Abbreviations: WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Impact of concomitant VPA and carbapenem use on serum concentrations and seizure control

The median daily VPA dose was 1.0 g (IQR 0.6–1). Concomitant use of meropenem and/or imipenem was associated with a substantial reduction in serum VPA levels, while no clinically significant worsening in seizure control was observed.

Prior to concomitant therapy, the median serum VPA concentration was 48.04 μg/mL (IQR 29.63–73.11; n = 50 measurements) in the overall cohort of 189 patients. Concentrations were 51.64 μg/mL (28.36–73.98; n=33) in the 136 seizure-free patients and 45.30 μg/mL (31.55–71.55; n = 17) in the 53 patients with seizures. During the concomitant period, the median concentration decreased to 12.15 μg/mL (6.283–30.05; n = 58) overall, with levels of 11.49 μg/mL (6.47–29.28; n = 39) in 150 seizure-free patients and 15.09 μg/mL (3.21–32.91; n = 19) in 39 patients with seizures. Within 14 days after discontinuing concomitant therapy, the median concentration was 28.99 μg/mL (11.00–39.31; n = 16) overall, 28.99 μg/mL (14.32–38.34; n = 10) in 173 seizure-free patients, and 32.02 μg/mL (7.995–57.25; n = 6) in 16 patients with seizures.

These data demonstrate that concomitant carbapenem use reduced the median serum VPA concentration from 48.04 μg/mL to 12.15 μg/mL, corresponding to a decline of approximately 74.7%. Although concentrations partially recovered to 28.99 μg/mL within 14 days after discontinuation—a 138.6% increase from the concomitant period—they remained about 39.6% below pre-concomitant levels and did not return to baseline (see Tables 6 and 7). This indicates that the carbapenem-induced reduction in serum VPA is not readily reversible in the short term. No significant differences in VPA concentrations were observed between patients with and without seizures across the pre-concomitant, concomitant, and post-concomitant periods.

Table 6. Serum VPA concentrations across study periods. **Values are presented as median [IQR].**

Observation Period	Serum VPA Concentration (μg/mL)	Change from Pre-concomitant Level
Pre-concomitant (n = 189)	48.04 (29.63–73.11) [n = 50]	—
During concomitant use (n = 189)	12.15 (6.283–30.05) [n = 58]	−74.7%
Within 14 days post-concomitant (n = 189)	28.99 (11.00–39.31) [n = 16]	−39.6%

Table 7. Serum VPA concentrations in patients with and without seizures during concomitant therapy. **Values are presented as median [IQR].**

Observation Period	Serum VPA Concentration (μg/mL)
No seizures during concomitant therapy (n=150)	11.49 (6.47–29.28) [n=39]
Seizures during concomitant therapy (n=39)	15.09 (3.21–32.91) [n=19]

Analysis of seizure outcomes revealed seizure rates of 28.0% in the pre-concomitant period, 20.6% during concomitant therapy, and 8.5% within 14 days after discontinuation (Table 8). No statistically significant difference was observed between the pre-concomitant and concomitant periods ($P = 0.5602$),

whereas the difference between the pre-concomitant period and the 14-day post-concomitant interval was statistically significant ($P = 0.0086$). Seizure frequency was 0 (0–0.5) seizures per person per week in the pre-concomitant period, 0 (0–0) during concomitant therapy, and 0 (0–0) within 14 days after discontinuation (Table 8). No statistically significant difference was found between the pre-concomitant and concomitant periods ($P > 0.9999$), while a statistically significant difference existed between the pre-concomitant period and the 14-day post-concomitant interval ($P = 0.0128$). These results suggest that neither the seizure rate nor the seizure frequency was clearly associated with concomitant carbapenem use.

Table 8. Effect of concomitant use of VPA with carbapenems on seizure control. **Values are presented as median [IQR].**

Observation period	Seizure incidence (%)	Seizure frequency (per person/week)
Pre-concomitant (n = 189)	28.0	0 (0–0.5)
During concomitant therapy (n = 189)	20.6 ($P = 0.5602$)	0 (0–0) ($P > 0.9999$)
Within 14 days after discontinuation (n = 189)	8.5 ($P = 0.0086$)	0 (0–0) ($P = 0.0128$)

Discussion

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, whose associated cognitive decline and psychosocial comorbidities often substantially impair quality of life and impose a considerable burden on patients, families, and society[1]. Pharmacological therapy remains the cornerstone of management, aiming to achieve symptom control and reduce seizure frequency[8]. VPA is one of the most widely used and efficacious antiseizure medications, with a well-established role spanning over five decades in the treatment of generalized, focal, and specific epilepsy syndromes[8].

Infection is a major preventable cause of epilepsy globally. Antibiotic use in patients with epilepsy requires careful consideration of potential interactions with antiseizure drugs and of antibiotic-related effects on seizure threshold[13]. Notably, several antibiotic classes—such as carbapenems, penicillins, cephalosporins, fluoroquinolones, and antimalarials—exhibit proconvulsant properties and may precipitate seizures even in individuals without epilepsy[14, 15]. Among carbapenems, imipenem has long been a first-line option for severe mixed and multidrug-resistant infections due to its broad β-lactamase stability[16]. Meropenem offers enhanced activity against non-fermenting Gram-negative bacilli (e.g., Pseudomonas aeruginosa, Acinetobacter baumannii) and a relatively lower risk of central nervous system toxicity, rendering it preferable for conditions such as meningitis, hospital-acquired pneumonia,

and mixed aerobic/anaerobic infections[17]. Concomitant use of carbapenems with VPA has consistently been associated with a marked decrease in total plasma VPA concentrations, commonly attributed to pharmacokinetic interactions[8]. However, VPA is highly protein-bound (~ 90–95%), and its pharmacological activity is mediated primarily by the free (unbound) fraction. The observed reduction in total concentration may partly reflect methodological limitations in conventional assays. Preclinical studies have shown that although total VPA clearance increases during carbapenem co-administration, the unbound fraction remains stable, suggesting that free VPA concentrations—and thus antiseizure activity—may be preserved[10]. Other evidence indicates that the decrease in total concentration results from inhibition of enterohepatic recirculation, without necessarily reducing free drug levels[18]. These observations raise the possibility that the reported decline in total VPA concentration could represent a methodological artifact, while stable free VPA concentrations may explain maintained seizure control in many patients receiving the combination.

Despite numerous case reports and small studies highlighting reduced VPA concentrations during carbapenem therapy, robust evidence linking this interaction to an increased risk of seizures has been lacking. Large-scale, real-world analyses systematically evaluating clinical seizure outcomes have been notably absent. In this retrospective study of 189 patients receiving VPA with meropenem or imipenem, we confirmed a substantial decrease in total serum VPA concentrations but found no corresponding increase in the seizure rate or seizure frequency. This finding challenges the conventional caution against concomitant use and supports a more nuanced, evidence-based approach to clinical decision-making. Prospective, multicenter studies incorporating therapeutic drug monitoring of both total and free VPA, along with detailed seizure diaries, are warranted to refine risk stratification and guide management. In conclusion, our large real-world analysis indicates that concomitant carbapenem and VPA therapy, while significantly lowering total VPA concentrations, does not increase the risk of seizures.

Despite its contributions, this study has several limitations. First, as a single-center retrospective analysis, it is subject to selection bias and heterogeneity in patient management, which may affect the generalizability of our findings. Second, the majority of patients received concomitant antiseizure medications in addition to VPA, potentially confounding the assessment of VPA-specific seizure control during carbapenem therapy. Third, while total serum VPA concentrations were routinely monitored, free VPA concentrations—which more accurately reflect pharmacological activity—were not measured, limiting our ability to fully elucidate the pharmacokinetic interaction. Finally, the follow-up period was confined to 14 days after carbapenem discontinuation; longer-term outcomes regarding seizure recurrence, VPA concentration recovery, and safety with repeated exposures remain unknown and warrant further investigation in prospective studies.

Conclusions

Concomitant use of meropenem or imipenem with VPA significantly lowers total serum VPA concentrations but does not increase seizure rate or frequency. These findings challenge current precautionary recommendations and support a more evidence-based approach to clinical practice.

Abbreviations

VPA, Valproate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; WBC, White blood cell; CRP, C-reactive protein; PCT, Procalcitonin; ASM, Antiseizure medication; CNS, Central nervous system; IQR, Interquartile range; UTI, Urinary tract infection .

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (Approval No. ZSSYEC II2024-019-01, approved on 17 January 2024). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee in accordance with relevant Chinese regulations and guidelines, including the Measures for Ethical Review of Life Sciences and Medical Research Involving Humans (2023).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request but are not publicly accessible due to data privacy restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FY, XL, LY and MH conducted the research design. FY and WQ participated in the writing of the paper. FY, WQ and LY analyzed and explained the data; LX, LX and WQ collected and helped with analyzing the data of the study. All authors read and approved the final manuscript.

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Clinical trial number

Not applicable.

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Figures

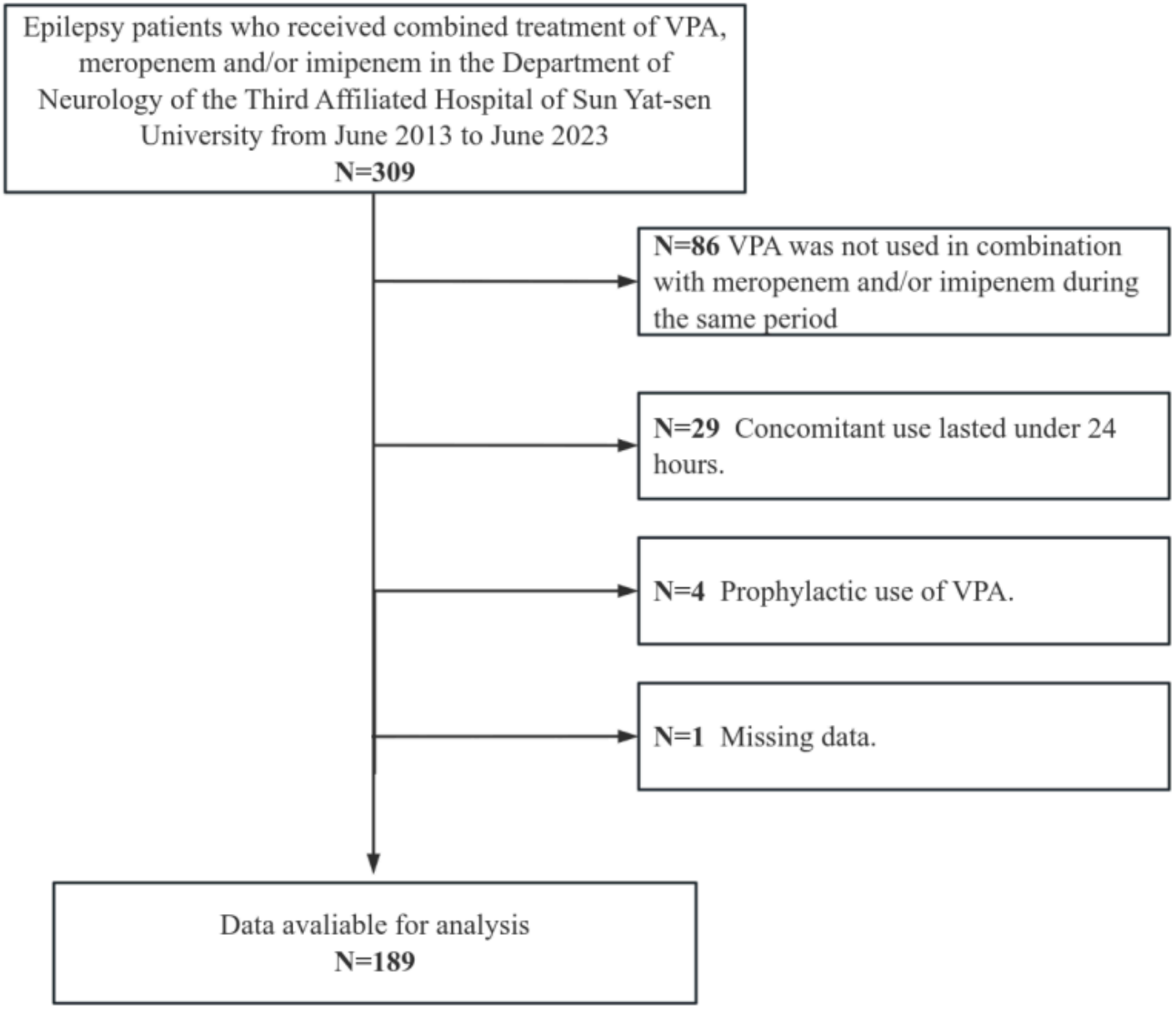


Figure 1

Patient screening process