European Review for Medical and Pharmacological Sciences 2024; 28: 516-524

A prospective study of drug-drug interaction between antiepileptic drugs and meropenem in patients in a tertiary hospital in China from January 2020 to March 2023

Q. YU[1], S.-H. ZHAN[1], H.-Q. LU[1], J. ZHAO[1], Y. JIN[2]

[1]Department of Pharmacy, Tongling People's Hospital, Tongling, Anhui Province, China
[2]School of Pharmacy, Anhui Medical University, Hefei, Anhui Province, China

Abstract. – OBJECTIVE: This study aimed to determine the minimum interaction between different antiepileptic drugs (AEDs) and meropenem (MEPM) for clinical treatment.

PATIENTS AND METHODS: The data of 91 patients enrolled in the neurology department from January 2020 to March 2023 for clinical trials were measured and observed. Self-controlled studies were conducted to monitor the trough concentrations of valproic acid (VPA), carbamazepine (CBZ) and levotiracetam (LEV) before and after MEPM usage. Relevant indicators of liver and kidney function were also monitored.

RESULTS: The serum VPA trough concentrations were 36.25±8.22 μg/ml at 24±12 h and 34.99±11.17 μg/ml at 96±12 h after MEPM use; the difference was significant ($p<0.05$). Decreased CBZ trough concentrations were also identified after MEPM usage (96±12 h), whereas LEV trough concentrations were not affected. An increased liver injury rate ($\chi^2 = 8.744$, $p<0.05$) and a decreased kidney injury rate ($\chi^2 = 5.393$, $p<0.05$) were found in the VPA group only.

CONCLUSIONS: The interaction between VPA and MEPM decreased serum VPA concentrations, increased liver injury rates, and decreased kidney injury rates. In addition, the co-administration of MEPM and CBZ reduced serum CBZ concentrations. Clinicians should be aware of this potential interaction and closely monitor the relevant biochemical indices and number of seizures.

Key Words:
Valproic acid, Carbamazepine, Levetiracetam, Meropenem, Liver injury, Kidney injury.

Introduction

Epilepsy, a common neurological disease, is a clinical syndrome characterized by a highly synchronous abnormal discharge of brain neurons for a variety of reasons[1,2]. Epidemiological data have demonstrated that there are currently approximately 9 million epilepsy patients in China[3]. Epileptic seizures not only seriously reduce patient quality of life, but they affect their mental health, leading to increased mortality rates. The treatment of epilepsy includes surgery and the use of antiepileptic drugs (AEDs), the main treatment method. However, AEDs have different chemical structures and mechanisms of action, and their effectiveness and correlation between multiple mechanisms of action are not fully understood[4]. The concomitant use of AEDs with other drugs may affect their pharmacokinetics, leading to poor seizure control or an increase in adverse clinical events.

Valproic acid (VPA), carbamazepine (CBZ), and levetiracetam (LEV), the most commonly used AEDs in hospitals, are characterized by long medication cycles, significant individual differences in effective doses, narrow treatment windows, and the potential for significant adverse reactions[5-7]. Their target concentrations are as follows: VPA, 50-100 μg/mL; CBZ, 4-12 μg/mL; and LEV, 12-46 μg/mL[5]. An insufficient concentration leads to epilepsy treatment failure, whereas an excessive concentration often leads to adverse reactions. Therefore, serum drug concentrations are typically monitored to ensure treatment safety and efficacy.

Carbapenems are broad-spectrum antibacterial agents that include meropenem (MEPM), biapenem, and imipenem, which have good anti-infective effects against severe infections[8,9]. However, recent studies[10,11] reported that MEPM can reduce serum VPA concentrations. In fact, MEPM reportedly relieves VPA poisoning[12,13]. A summary of product characteristics suggests that combination therapy with VPA and carbapenems is generally not recommended unless necessary. The sudden discontinuation of AEDs therapy is

Corresponding Author: Yong Jin, Ph.D; e-mail: jinyong@ahmu.edu.cn

dangerous and can lead to an increased risk of seizures. Moreover, different AEDs are given for different indications/epilepsy types and are not directly interchangeable. When simultaneous drug use is inevitable, it might be important for clinicians to add appropriate AEDs to ensure continued seizure control. However, there is insufficient medical evidence regarding the interaction between different AEDs and MEPM.

This prospective and self-controlled study aimed to determine interactions between different AEDs (VPA, CBZ, or LEV) and MEPM to answer the following questions: A) whether the use of MEPM can affect the serum trough concentrations of AEDs; B) whether MEPM combined with AEDs can lead to clinical adverse events; C) which AEDs have the least serious interactions with MEPM; and D) if MEPM use affected the serum concentrations of AEDs, was the effect related to the daily dose of MEPM.

Patients and Methods

Study Legitimacy

This prospective self-controlled study was conducted at a single tertiary hospital in China between January 2020 and March 2023. This study was conducted in the the neurological department of the Tongling People's Hospital and approved by the hospital ethics committee. All procedures involving human participants were performed in accordance with the Declaration of Helsinki and its latest amendments[14].

Study Patients

Potential study participants were required to meet the following inclusion criteria: age 18-80 years; weight > 40 kg; ability to act independently; documented history of seizures; currently taking oral VPA, CBZ, or LEV monotherapy at regular intervals; current severe infection; and stable serum AED concentrations upon admission.

The exclusion criteria were as follows: currently pregnant or lactating; requirement for parenteral nutrition support; hemodynamic instability; alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea nitrogen (BUN), and total bilirubin (TBil) levels > 2× the upper limit of normal (ULN), and creatinine clearance rate (CCR) < 60 mL/min. Patients who did not require anti-infective therapy with MEPM during the hospitalization according to the treatment guidelines or who discontinued the AEDs during the hospitalization were also excluded from the study. Before enrollment, each patient provided written consent after being fully informed of the study purpose and procedures.

Study Protocol

This study was designed to compare the effects of MEPM on serum concentrations of VPA, CBZ, and LEV. Clinical response data (including liver and kidney functions and number of seizures) were also collected. The doses of AEDs varied among patients and were not standardized. Prior to therapeutic drug monitoring (TDM), patients were treated with VPA, CBZ, or LEV for at least five half-lives and attained a steady-state serum concentration. To ensure stable serum trough concentrations among the enrolled patients, they underwent TDM twice on admission with AEDs, and those with a serum trough concentration difference (>20%) outside the therapeutic window have been withdrawn from this study. Whether a patient needed to receive MEPM anti-infective therapy was determined by the clinician according to the treatment guidelines and actual situation without interference from clinical trials. The mean value of the two initially monitored serum trough concentrations was designated the baseline level (point 1). After the use of MEPM, subsequent serum trough concentration periods were scheduled at 24±12 h intervals (point 2) and 96±12 h intervals (point 3). Clinical response data, including liver and kidney functions, were collected at the corresponding points (48 h before and after MEPM use). Serum ALT, ALP, BUN, TBil, and CCR levels were monitored using blood biochemical analyses. Clinically, liver injury was defined as an ALT ≥ 3× or 5× the ULN or an ALP ≥ 2× the ULN (>200 U/L), or an ALT ≥ 3× ULN (>120 U/L) and TBil ≥ 2× ULN (>42 μmol/L)[15]. Kidney injury was defined as CCR<90 ml/min[16].

Statistical Analysis

The sample size was estimated by a preliminary experiment. Continuous data are expressed as mean ± standard derivation for normally distributed data or as median (quartile range) for skewed distributed data. Paired *t*-test were performed for comparison when normally distributed. The Wilcoxon rank-sum test was also used to compare the differences between two paired samples when skewed. Serum ALT, AST, BUN, and CCR levels were measured 48 h before and after MEPM administration. All data were analyzed using SPSS 26.0 (IBM Corp, Armonk, NY, USA), and statistical significance was set as $p < 0.05$.

Results

Demographic Data and Drug Interactions in 91 Patients

The demographic data of all enrolled patients who completed the TDM are presented in Table I. Interactions between VPA and MEPM, CBZ and MEPM, and LEV and MEPM were explored separately throughout this study. The mean patient ages were 58.68±10.62 (range, 37-79) years in the VPA and MEPM group, 58.94±14.48 (range, 30-76) years in the CBZ and MEPM group, and 59.04±10.00 (range, 38-79) years in the LEV and MEPM group. Severe pulmonary infection was the prevailing type of infection observed in all three groups. Furthermore, hypertension was the predominant underlying disease in all three groups.

Fluid Volume (L) Changes 48 h Before and After MEPM Usage

To eliminate the potential confounding effects of fluid volume changes on serum drug concentrations and related biochemical indices caused by MEPM administration, we calculated the average intravenous fluid intake 48 h before and after MEPM treatment. An examination of kurtosis and skewness revealed that the three groups of data were normally distributed. A paired *t*-test showed no significant difference ($p>0.05$) in the average amount of intravenous fluid input among the three groups. Therefore, the statistical results eliminated the effects of the differences in venous fluid intake. The average intravenous fluid volume is shown in Table II.

Table I. Demographic data of 91 patients treated with an AEDs (VPA, CBZ, LEV) and MEPM.

Characteristics	VPA Group	CBZ Group	LEV Group
Sex, N (%)			
Male/Female (Total)	25/22 (47)	12/4 (16)	19/9 (28)
Age (Y)	58.68 ± 10.42	58.94 ± 14.48	59.04 ± 10.00
Weight (Kg)	57 (53-66)	58.55 (48.82-68.38)	58.00 (54.12-65.75)
Type of infection, N (%)			
Unidentified site infection	4 (8.51)	/	1 (3.57)
Pneumonia	19 (40.43)	11 (68.75)	12 (42.86)
CNS	14 (29.79)	2 (12.50)	9 (32.14)
UTI	1 (2.13)	/	1 (3.57)
Pneumonia + UTI	4 (8.51)	/	1 (3.57)
Pneumonia + CNS	4 (8.51)	3 (18.75)	4 (14.29)
Pneumonia + CNS+UTI	1 (2.13)	/	/
Underlying disease, N (%)			
None	20 (42.55)	5 (31.25)	15 (53.57)
HTN	18 (38.30)	6 (37.50)	6 (21.43)
HLP	5 (10.64)	4 (25.00)	4 (14.29)
DM	1 (2.13)	/	/
HTN + DM	2 (4.26)	1 (6.25)	3 (10.71)
HTN + CHD	1 (2.13)	/	/
Outcome, N (%)			
Death	2 (4.26)	3 (18.75)	1 (3.57)

Underlying diseases mainly included hypertension, diabetes, hyperlipidemia, and coronary heart disease. AEDs, antiepileptic drugs; VPA, valproic acid; CBZ, carbamazepine; LEV, levetiracetam; CNS, central nervous system; UTI, urinary tract infection; HTN, hypertension; HLP, hyperlipidemia; DM, diabetes; CHD, coronary heart disease.

Table II. The average intravenous fluid intake 48 h before and after MEPM usage.

	Venous fluid volume (L)		
Groups	Before MEPM usage	After MEPM usage	*p*-value
VPA group (n=47)	3.07±1.01	3.10±1.19	0.763
CBZ group (n=16)	2.57±0.84	2.75±0.93	0.572
LEV group (n=28)	3.07±1.04	3.10±1.12	0.860

LEV, levetiracetam; MEPM, meropenem; VPA, valproic acid.

Interactions Between VPA and MEPM

An examination of kurtosis and skewness revealed that the three groups of data were normally distributed. As shown in Figure 1, the mean serum VPA trough concentrations (n=47) were 69.08±8.57 μg/mL at point 1 (before MEPM usage), 36.25±8.22 μg/mL in point 2 (24±12 h after VPA + MEPM usage), and 34.99±11.17 μg/mL at point 3 (96±12 h after VPA + MEPM usage). Compared with point 1, the serum trough concentrations of VPA decreased significantly ($p < 0.05$) at points 2 and 3. However, there was no significant difference ($p > 0.05$) in levels between points 3 and 2. All results showed that the serum VPA trough concentrations decreased significantly after MEPM usage and remained stable within 96 h.

Since the data were normally distributed, paired *t*-test was performed to compare the effects of different daily doses of MEPM on the serum trough concentrations of VPA. No matter the daily doses (unlimited dose/d: 3.0 g/d or 6.0 g/d) of MEPM, the VPA trough concentrations decreased significantly ($p<0.05$) when administered with MEPM. No statistically significant differences ($p>0.05$) were found between the different daily doses at any time point (Figure 2). Therefore, the results showed that the reduction in serum VPA trough concentration had little correlation with the daily dose of MEPM.

Since the data were normally distributed, the Wilcoxon rank-sum test was performed to compare differences in ALT, ALP, BUN, TBil, and CCR levels 48 h before and after MEPM usage. All data were expressed as median (interquartile ranges). There was a statistically significant difference in the ALT, ALP, and CCR levels 48 h before and after MEPM administration (Table III). Liver and kidney injury occurred in 8/47 (17.02%) and 9/47 (19.15%), respectively, at 48 h after MEPM administration. The chi-squared test was also used to compare the liver and kidney injury rates before and after MEPM usage. As shown in Table IV, the liver injury rate was significantly different (χ^2 =8.744, $p<0.05$)

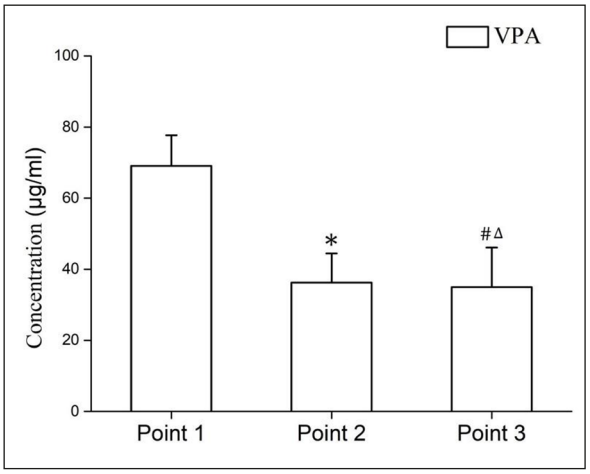

Figure 1. Trend of serum VPA trough concentrations before and after MEPM usage (n=47). Compared to point 1, *p <0.05, #p <0.05. Compared to point 2, Δp >0.05. VPA, valproic acid.

Table III. Changes in ALT, ALP, BUN, TBil, and CCR levels before and after VPA + MEPM usage (n=47).

	Median (quartile range)			
Index	Before MEPM usage	After MEPM usage	Z	*p*-value
ALT (U/L)	25.0 (16.0-39.3)	41.0 (25.0-61.5.0)	-3.991	0.000*
ALP (U/L)	64.0 (47.0-78.0)	75.0 (47.0-96.0)	-3.166	0.002*
TBil (μmol/L)	9.8 (7.0-14.5)	10.4 (7.1-12.9)	-0.18	0.857
BUN (mmol/L)	5.2 (3.7-6.9)	5.5 (4.4-7.1)	-0.305	0.761
CCR (ml/min)	89.7 (73.5-111.6)	106.9 (88.4-129.2)	-3.622	0.000*

Compared to before MEPM usage, *p <0.05. ALP, alkaline phosphatase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CCR, creatine clearance rate; MEPM, meropenem; TBil, total bilirubin.

Table IV. Chi-squared test of pairwise comparison of the liver and kidney injury rates before and after VPA + MEPM usage (n=47).

	Liver injury	Non-liver injury	Kidney injury	Non-kidney injury
Before MEPM usage	0	47	16	31
After MEPM usage	8	39	9	38
χ^2	8.744		5.393	
p	0.003*		0.020*	

Compared to before MEPM usage, *p <0.05. MEPM, meropenem; VPA, valproic acid.

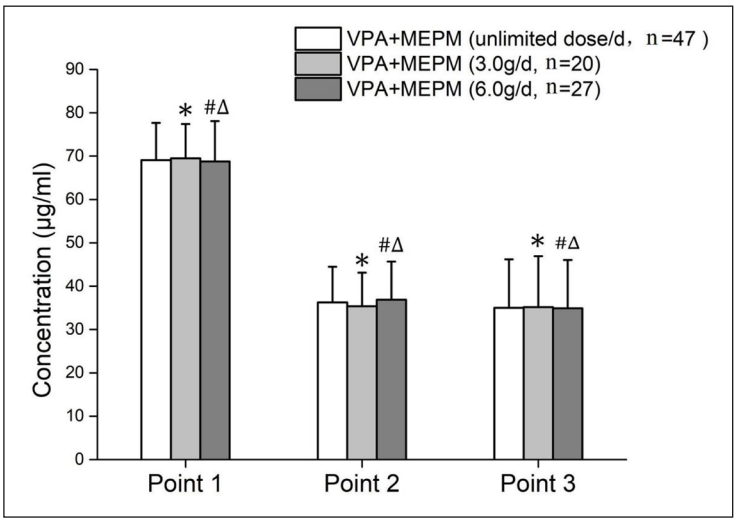

Figure 2. Trend of changes in serum VPA trough concentrations when administered with MEPM at different daily doses. Compared with unlimited dose/d of MEPM group, $^{*}p$ >0.05, $^{\#}p$ >0.05. Compared to 3.0 g/d of MEPM group, $^{\Delta}p$ >0.05. VPA, valproic acid; MEPM, meropenem.

from the kidney injury rate (χ^2 =5.393, p<0.05). The results indicated that the liver injury rate significantly increased but the kidney injury rate decreased after VPA administration with MEPM.

Risk Factors for Interactions between VPA and MEPM

A significant reduction in serum VPA trough concentration after MEPM usage was observed in each patient. Of the 47 patients in the VPA group, serum VPA trough concentrations decreased by more than 50% in 19/47 (40.43%) patients. Binary logistic regression analysis was used to explore sex, age, MEPM dosage, infection type, and underlying disease that may be related to the percentage of serum VPA trough levels that decreased by over 50% within 24 h after MEPM administration (Table V). Age was an independent risk factor related to the percentage of serum VPA trough levels, which decreased by more than 50%.

Interaction between CBZ and MEPM or LEV and MEPM

A statistical analysis of the detection data revealed that the serum CBZ trough concentration (n=16) and serum LEV trough concentration (n=28) data were not normally distributed. On a Wilcoxon rank-sum test, the serum CBZ trough concentrations were 5.36 (4.75-6.92) μg/mL at point 1, 6.12 (4.68-7.15) μg/mL at point 2, and 4.48 (4.16-6.19) μg/mL at point 3 (Table VI). Decreased serum CBZ trough concentrations (-16.42%) were found at 96±12 h after MEPM usage (p=0.039, Z=-2.068). Simultaneously, the serum LEV trough concentrations were 21.60 (19.11-24.90) μg/mL at point 1, 21.35 (18.75-25.30) μg/mL at point 2, and 20.24 (18.48-23.03) μg/mL at point 3. There was no statistically significant difference in serum LEV trough concentrations before and after MEPM usage.

As shown in the CBZ group (Table VII), ALT and ALP levels increased significantly at 48 h after MEPM administration, whereas BUN, TBil, and CCR levels were unaffected. The trends of the relevant indicators were similar in the LEV and CBZ groups.

In the CBZ group (Table VIII), liver and kidney injuries occurred in 4/16 (25.00%) and 6/16 (37.50%), respectively, at 48 h after MEPM administration. The liver and kidney injury rates were analyzed using the chi-squared test. The liver injury rate did not differ significantly (χ^2 =4.571, p>0.05), nor did the kidney injury rate (χ^2 =2.000, p>0.05). The liver and kidney injury rates were not affected by the combination use of CBZ + MEPM.

In the LEV group (Table VIII), liver and kidney injuries occurred in 1/28 (3.57%) and 7/28 (25.0%) at 48 h after MEPM administration, respectively. Similar to the CBZ group, the liver and kidney injury rates were not affected by the combination use of LEV + MEPM.

Discussion

This study found that serum VPA trough concentrations decreased significantly (-47.52%, p<0.05) and almost remained stable within 96±12 h when combined with MEPM. Although this study showed that the serum VPA trough concentrations decreased significantly after its combination use with MEPM was consistent with

Table V. Factors related to the percentage of serum VPA trough levels that decreased >50%.

Factors	*p*	OR	95% CI
Sex	0.368	2.339	0.368-14.848
Age	0.013*	0.870	0.780-0.971
Dose of MEPM	0.200	0.318	0.121-0.834
Type of infection			
Unidentified site infection	0.999	>100	0.000
Pneumonia	0.712		
CNS	0.246	5.087	0.325-79.610
UTI	1.000	>100	0.000
Pneumonia + UTI	0.267	7.992	0.204-312.537
Pneumonia + CNS	0.057	41.623	0.894-1938.339
Pneumonia + CNS+UTI	1.000	>100	0.000
Underlying disease			
HTN	0.870		
DM	1.000	>100	0.000
HLP	0.999	0.000	0.000
HLP + DM	0.566	3.603	0.045
HTN + CHD	0.999	0.000	0.000
None	0.300	0.303	0.032

*p <0.05. CNS, central nervous system; UTI, urinary tract infection; HTN, hypertension; HLP, hyperlipidemia; DM, diabetes; CHD, coronary heart disease.

Table VI. Trend of serum CBZ trough concentrations (n=16) and serum LEV trough concentrations (n=28) before and after MEPM usage.

	Serum CBZ trough concentrations	Serum LEV trough concentrations
Point 1	5.36 (4.75-6.92)	21.60 (19.11-24.90)
Point 2	6.12 (4.68-7.15)	21.35 (18.75-25.30)
Point 3	4.48 (4.16-6.19)*	20.24 (18.48-23.03)

Compared to point 1, *p = 0.039, Z= -2.068. CBZ, carbamazepine; LEV, levetiracetam.

Table VII. Trend of changes in ALT, ALP, BUN, TBil, and CCR levels before and after MEPM usage.

		Median (quartile range)			
Group	Index	Before MEPM usage	After MEPM usage	Z	*p*-value
CBZ group	ALT (U/L)	29.0 (21.5-43.2)	49.0 (39.5-72.2)	-3.518	0.000*
(n=16)	ALP (U/L)	85.0 (67.5-142.8)	137.0 (86.2-196.2)	-2.43	0.015*
	TBil (μmol/L)	11.8 (9.1-20.4)	10.6 (8.8-13.8)	-1.345	0.179
	BUN (mmol/L)	6.0 (3.9-8.3)	7.1 (4.8-10.6)	-1.758	0.079
	CCR (ml/min)	83.4 (66.1-107.0)	93.7 (70.4-119.3)	-0.569	0.569
LEV group	ALT (U/L)	23.0 (17.2-50.0)	40.5 (33.5-71.2)	-3.326	0.001*
(n=28)	ALP (U/L)	74.0 (55.2-107.2)	102.5 (62.0-135.5)	-2.722	0.006*
	TBil (μmol/L)	12.2 (7.3-15.2)	9.4 (7.1-13.6)	-0.661	0.509
	BUN (mmol/L)	5.3 (4.1-6.7)	5.7 (4.1-6.4)	-0.228	0.82
	CCR (ml/min)	86.4 (77.6-106.0)	103.53 (80.2-124.6)	-1.799	0.072

Compared to before MEPM usage, *p <0.05. ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CBZ, carbamazepine; CCR, creatine clearance rate; LEV, levetiracetam; MEPM, meropenem; TBil, total bilirubin.

previous literature reports, the range of decrease was lower than that of previous literature reports of -65.75%[17], -76.06%[18], and -67.7%[19]. Compared to our study, the TDM periods of the above studies varied, which may have led to differences in the results. Simultaneously, serum VPA trough concentrations showed little correlation with the daily dose of MEPM, an important conclusion

Table VIII. Chi-squared test of pairwise comparison of liver and kidney injury rates before and after MEPM usage

Group		Liver injury	Non-liver injury	Kidney injury	Non-kidney injury
CBZ group	Before MEPM usage	0	16	8	8
(n=16)	After MEPM usage	4	12	6	10
	χ^2	4.571		2	
	p	0.101		0.157	
LEV group	Before MEPM usage	0	28	8	20
(n=28)	After MEPM usage	1	27	7	21
	χ^2	1.018		2.517	
	p	1.000		0.109	

CBZ, carbamazepine; LEV, levetiracetam.

of our research. The binary logistic regression analysis showed that age was an independent risk factor related to the percentage of serum VPA trough concentrations, which decreased by over 50% after combination therapy with MEPM.

To date, the exact mechanism of the drug interaction between VPA and MEPM is not well understood. Earlier research[20] reported no differences between VPA and carbapenems in hepatectomized rats. Researchers[21] reported that hydrolytic activity was inhibited by VPA-d6β-D-glucuronide (VPA-G) and inhibited by dolipenem in the rat liver cytoplasm. Further studies[22] identified acylpeptide hydrolase (APEH) as a VPA-G hydrolase in the human liver, where VPA-G hydrolytic activity was achieved. The absence of APEH may result in loss of VPA-G hydrolytic activity. VPA-G is an important VPA metabolite that can be regenerated by VPA-G hydrolases. Therefore, decreased VPA-G deglucuronidation due to the inhibition of APEH by MEPM may be a key mechanism. However, this mechanism was not explored in this study, and the exact mechanism of action was the focus of our follow-up research.

We also found decreased serum CBZ trough concentrations (-16.42%) at 96±12h after MEPM administration ($p<0.05$, $Z=-2.068$), which was not reported until now. Although the sample size was estimated through a preliminary study, the actual sample size of the 16 patients included in the CBZ group was small, and the study's statistical power was relatively poor. Thus, the result of the interaction between CBZ and MEPM in this study is for reference only and requires further validation in large samples. These findings suggest that LEV trough concentrations may not be affected by MEPM usage.

Of the above three groups, an increased liver injury rate ($\chi^2=8.744$, $p<0.05$) and decreased kidney injury rate ($\chi^2=5.393$, $p<0.05$) occurred only in the VPA group. The results predicted that the risk of clinical liver injury would increase after combination therapy with MEPM, a finding that is consistent with that of a previous retrospective study[17]. A recent study[23] showed that augmented renal clearance is a frequent phenomenon in the intensive care unit, with an increased incidence during the first week's stay. All patients enrolled in our study had severe infections. This may explain the reduction in the clinical kidney injury rate after combination use with MEPM in our study.

Conclusions

The following conclusions can be drawn from the questions raised at the beginning of this study. First, the VPA trough concentrations decreased 47.52% and remained stable within 96±12 h after MEPM usage. The CBZ trough concentrations decreased 16.42% 96±12 h after MEPM usage, but further studies are required to validate our findings. The LEV trough concentrations were not affected by MEPM. Second, an increased liver injury rate ($\chi^2=8.744$, $p<0.05$) and decreased kidney injury rate ($\chi^2=5.393$, $p<0.05$) were found in the VPA group only. Third, LEV trough concentrations and liver and kidney injury rates were not affected by MEPM usage. Fourth, the reduction in serum VPA trough concentrations did not correlate with the daily dose of MEPM.

In conclusion, our findings suggest that, when VPA and MEPM are used in combination, it is necessary to closely monitor the relevant biochemical indices and number of seizures. If the VPA trough level falls below the therapeutic levels during MEPM treatment, the addition of other AEDs, such as LEV, might be warranted.

Conflict of Interest

No conflict of interest associated with this work.

Authors' Contributions
We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yu Qing and Jin Yong designed and conducted the study. Zhan Sanhua, Lu Houqing and Zhao Jie supervised data collection analyzed and interpreted the data. Yu Qing and Jin Yong prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript for publication.

Ethics Approval
The study was approved by the Ethics Committee of Tongling People's Hospital (approval No. MR-34-21-009915).

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials
The combined datasets and materials were available upon reasonable request.

Acknowledgement
Thanks to the neurologists and nursing staff for their great support. Thanks to Professor Jin Yong for his guidance on this study. We would like to thank Editage (www.editage.cn) for English language editing.

Funding
This project was supported by science Program grant of Tongling (No. 20200203039).

ORCID ID
Qing Yu: 0009-0000-3197-6899
Sanhua Zhan: 0009-0006-9672-9235
Jie Zhao: 0009-0006-2404-3533
Yong Jin: 0000-0003-3133-7952.

References

1) Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet 2019; 393: 689-701.
2) Beghi E, Giussani G, Sander JW. The natural history and prognosis of epilepsy. Epileptic Disord 2015; 17: 243-253.
3) Lin Y, Hu S, Hao X, Duan L, Wang W, Zhou D, Wang X, Xiao B, Liu X, Wang Y, Zhou L, Fu X, Jiang Y, Zhang J, Deng Y, Wang W, Wu X, Fang X, Hong Z, Li S, Wang Y. Epilepsy centers in China: Current status and ways forward. Epilepsia 2021; 62: 2640-2650.
4) Bialer M. How did phenobarbital's chemical structure affect the development of subsequent antiepileptic drugs (AEDs)? Epilepsia 2012; 53: 3-11.
5) Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008; 49: 1239-1276.
6) Aícua-Rapún I, André P, Rossetti AO, Ryvlin P, Hottinger AF, Decosterd LA, Buclin T, Novy J. Therapeutic Drug Monitoring of Newer Antiepileptic Drugs: A Randomized Trial for Dosage Adjustment. Ann Neurol 2020; 87: 22-29.
7) Cantelmi T, Lepore E, Unfer VR, Unfer V. Safety of inositol supplementation in patients taking lithium or valproic acid: a pilot clinical study. Eur Rev Med Pharmacol Sci 2022; 26: 7269-7276.
8) Badger-Emeka LI, Emeka PM. Genetic fingerprinting and profile analysis of virulence genes in XDR clinical isolates of Klebsiella Pneumoniae. Eur Rev Med Pharmacol Sci 2022; 26: 5233-5244.
9) Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. Clin Infect Dis 2019; 69: S565-S575.
10) Al-Quteimat O, Laila A. Valproate Interaction With Carbapenems: Review and Recommendations. Hosp Pharm 2020; 55: 181-187.
11) Chen IL, Lee CH, Hsiao SC, Shih FY. Interactions between carbapenems and valproic acid among the patients in the intensive care units. J Crit Care 2021; 62: 151-156.
12) 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.
13) 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.
14) World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191-2194.
15) Li RR, Li M, Luo Q, Sun X, Liu CH. Comparative analysis of clinical diagnosis and treatment guidelines for drug-induced liver injury at home and abroad. Zhonghua Gan Zang Bing Za Zhi 2023; 31: 433-439.
16) Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013; 158: 825-830
17) Li Z, Gao W, Liu G, Zhang Z. Interaction between valproic acid and carbapenems: decreased plasma concentration of valproic acid and liver injury. Ann Palliat Med 2021; 10: 5417-5424.
18) Huang CR, Lin CH, Hsiao SC, Chen NC, Tsai WC, Chen SD, Lu YT, Chuang YC. Drug interaction between valproic acid and carbapenems in patients with epileptic seizures. Kaohsiung J Med Sci 2017; 33: 130-136.

19) Wen ZP, Fan SS, Du C, Yin T, Zhou BT, Peng ZF, Xie YY, Zhang W, Chen Y, Xiao J, Chen XP. Drug-drug interaction between valproic acid and meropenem: a retrospective analysis of electronic medical records from neurosurgery inpatients. J Clin Pharm Ther 2017; 42: 221-227.

20) 20. Yamamura N, Imura K, Naganuma H, Nishimura K. Panipenem, a carbapenem antibiotic, enhances the glucuronidation of intravenously administered valproic acid in rats. Drug Metab Dispos 1999; 27: 724-730.

21) Nakajima Y, Mizobuchi M, Nakamura M, Takagi H, Inagaki H, Kominami G, Koike M, Yamaguchi T. Mechanism of the drug interaction between valproic acid and carbapenem antibiotics in monkeys and rats. Drug Metab Dispos 2004; 32: 1383-1391.

22) Suzuki E, Yamamura N, Ogura Y, Nakai D, Kubota K, Kobayashi N, Miura S, Okazaki O. Identification of valproic acid glucuronide hydrolase as a key enzyme for the interaction of valproic acid with carbapenem antibiotics. Drug Metab Dispos 2010; 38: 1538-1544.

23) Egea A, Dupuis C, de Montmollin E, Wicky PH, Patrier J, Jaquet P, Lefèvre L, Sinnah F, Marzouk M, Sonneville R, Bouadma L, Souweine B, Timsit JF. Augmented renal clearance in the ICU: estimation, incidence, risk factors and consequences-a retrospective observational study. Ann Intensive Care 2022; 12: 88.