Reduced valproic acid concentrations in patients receiving carbapenems: meta-analysis

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Abstract

Introduction: The administration of valproic acid (VPA) with a carbapenem antibiotic results in reduced VPA concentrations. This article aims to examine the existing literature on the impact of the co-medication between VPA and carbapenem, and conduct VPA model-based dose optimisation using simulated participants.

Methods: A literature review was conducted utilising Medline™ (via PubMed®), ResearchGate®, and Google Scholar™ (using the following search terms: valproate, valproic acid, carbapenem, ertapenem, meropenem, imipenem, and valproate drug-drug interaction), to obtain clinical studies and case reports reporting on the interaction between VPA and carbapenems. Additionally, a manual search of prominent journals for articles cited in PubMed and Google Scholar was performed. Publications were included up to March 2025 with no lower limit enforced. Model-based simulations for sodium valproate were conducted with RxODE2 (R package) using RStudio.

Results and discussion: Our analysis of 13 pharmacokinetics studies and 15 case reports indicates that carbapenem antibiotics, such as meropenem, ertapenem, and imipenem, can reduce the serum levels of VPA, leading to subtherapeutic concentrations and seizures in certain patients. About a 60–90% increase in VPA clearance was observed. Doses of 465–1 053 mg (10–15 mg/kg/day) were shown to be subtherapeutic for patients taking carbapenems, with doses from 1 227–2 725 mg (25 mg/kg/day) only reaching therapeutic targets, and are most likely to increase the drug's side-effects profile.

Conclusions: In general, it is advisable to avoid the concurrent use of carbapenem antibiotics and VPA derivatives due to the possibility of a drug-drug interaction that causes sub-therapeutic valproate serum levels. Alternative antimicrobial agents should be considered instead of carbapenems; however, if the use of a carbapenem is necessary, an additional antiepileptic is suggested.

Keywords: valproate, simulations, case reports, drug-drug interaction, carbapenem

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Introduction

Valproic acid (VPA) is among the most commonly prescribed antiepileptic medications globally.[1] In addition to its use in treating epilepsy, VPA is also indicated for managing migraines and bipolar mood disorder.[1,2] Therapeutic drug monitoring (TDM), which involves measuring the blood levels of a medication to ensure its concentration remains within the therapeutic range, is particularly important for VPA due to the significant variability in dosage requirements and observed plasma concentration among patients treated with VPA.[1–4] Moreover, use of VPA has been associated with common early side-effects such as anorexia, nausea, vomiting, and somnolence. Weight changes, jaundice, and hypoglycaemia have also been reported.[1,3,4]

The absorption of VPA is reported to be about 90–100% from the gastrointestinal tract, with peak levels within 3–8 h.[3–5] Literature suggests that VPA is highly (90–95%) bound to plasma albumin with dose-dependent kinetics at high doses.[3] In addition, its apparent volume of distribution (Vd) is 0.1–0.5 L/kg.[3,5] Moreover, VPA is primarily eliminated *via* hepatic metabolism, mainly by conjugation with glucuronic acid, β-oxidation, and ω-oxidation, with about 3–7% of VPA excreted in urine unchanged.[5] VPA undergoes metabolism *via* glucuronidation and cytochrome P450 (CYPs) 2C9, 2C19, and 2A6 isoenzymes, therefore, VPA metabolism can be altered by medicines that induce or inhibit these enzymes (i.e. phenytoin, phenobarbital).[3,5,6] Following multiple dosing, oral clearance (CL) is variable, ranging from 0.28 to 0.63 L/h, while half-life ($t_{1/2}$) is between 6 and 17 h.[5] Time needed to reach steady-state is 1–3 days. Target VPA concentrations are associated with seizure control, with optimal seizure control achieved with a VPA target serum concentration between 30 and 100 mg/L.[5,7] However, some patients may benefit from concentrations greater than 120 mg/L without experiencing adverse effects.[5]

Carbapenems (meropenem, doripenem, imipenem, and ertapenem) are a subclass of antibiotics that belong to the β-lactam antibiotics, similar to penicillin and cephalosporins. Carbapenems work as cell wall synthesis inhibitors,[8,9] and have a wide spectrum of antimicrobial coverage (Gram-positive, Gram-negative, and anaerobic bacteria). The use of carbapenems has increased as a result of the rising resistance to cephalosporin antibiotics in Enterobacteriaceae (*Escherichia coli, Klebsiella, Enterobacter*,

and related genera).[8,9] However, concomitant therapy between VPA and carbapenems has been demonstrated to significantly increase the CL of VPA due to CYP450 enzyme induction, inherent to carbapenems.[10] This interaction is particularly noteworthy as a series of population analyses have consistently reported that carbapenems enhance the metabolic CL of VPA by a significant 36-41%.[10–16] Studies exploring this pharmacokinetic relationship highlight the implications for therapeutic drug monitoring and dosage adjustments in patients receiving both medications. The increased VPA clearance can potentially lead to subtherapeutic levels of VPA, necessitating careful management to ensure optimal therapeutic efficacy while minimising VPA adverse effects or breakthrough seizures.

The primary objective of this study was to conduct a comprehensive systematic review and analysis of the interactions between VPA and carbapenems by aggregating data from relevant clinical studies and detailed case reports. We aimed to understand the pharmacokinetic and pharmacodynamic relationships between these medications, with a particular focus on how carbapenems may affect the serum levels and overall efficacy of VPA. Additionally, our investigation included a thorough evaluation of model-based simulations designed for optimising VPA dosing strategies in patients concurrently receiving both VPA and carbapenems. This exploration sought to determine whether increasing the VPA dosage could facilitate the attainment of therapeutic levels while ensuring safety and minimising the risk of toxicity and associated adverse effects. Through this research, we aim to provide insights that may guide clinical decision-making and enhance patient outcomes in multi-drug therapies (VPA and carbapenem).

Method

A comprehensive review of population pharmacokinetic studies and case reports involving VPA and carbapenems interaction was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines,[17] on databases including PubMed®, ResearchGate®, and Google Scholar™. The search strategy used a combination of specific keywords and phrases designed to capture relevant literature. The search terms utilised were: ('valproic acid' OR 'sodium valproate' OR 'VPA') AND ('carbapenems' OR 'imipenem' OR 'meropenem' OR 'ertapenem' OR 'drug-drug interaction') AND ('population pharmacokinetic' OR 'pharmacokinetic model*' OR 'nonlinear mixed effect*' OR 'NONMEM') and many more.

Inclusion and exclusion criteria

Identified studies (case reports and articles) were eligible if treatment of VPA and carbapenems was indicated for participants, and the full-text/articles included a published population pharmacokinetic model using nonlinear mixed effect modelling approaches reporting carbapenems as a significant covariate for VPA studies. Studies were excluded from this review if the articles were systematic reviews or focused on methodology/algorithm or software/program considerations and did not report any new data. In addition, studies were excluded if they were conducted in animals, information on methodology or pharmacokinetics on VPA-carbapenem interaction was insufficient, or articles/case reports were incomplete (only abstract available or accessible).

Data extraction

The following information was extracted from each included article or case report: study characteristics (e.g. types of study, sampling time, number of collected samples, dosage regimen and VPA formulations), target population (patients or healthy subjects), population characteristics (e.g. age and weight range, gender, disease, concomitant medication). In addition, information on population pharmacokinetic analyses such as structural models, statistical models (i.e. inter-individual and residual variability), parameter estimates, covariates retained in the model, as well as their criteria for significance, and approaches employed for model evaluation (e.g. internal or external validation).

Simulations for dose selection

Monte Carlo simulations (n = 30 000) were utilised to predict plasma VPA concentrations in patients with typical characteristics under various dosing regimens (10–60 mg/kg/day, children and adults) across paediatric and adult population using RxODE2, an R package (version 3.6). Each simulation followed a 24-h dosing interval. The therapeutic range for VPA is defined as 30–100 mg/L as per South African guidelines.[7] The simulated dataset was generated based on published population pharmacokinetic studies[11,16,18–20] with participants' characteristics summarised in Supplementary Table SI.

Two models were used for dose optimisation and simulation. Model 1 was published by Zhang et al.[16] as a one-compartment model with CL as a parameter affected by six significant covariates: weight (WT), creatinine (Cr), albumin (ALB), gender, carbapenem (CBP), and inducers (IND2), with ηCL representing the between-subject variability on clearance amongst the participants (See equations 1 and 2 below).

$$CL = 0.43 \times \left(\frac{WT}{60}\right)^{0.787} \times \left(\frac{Cr}{50.3}\right)^{-0.253} \times \left(\frac{ALB}{39}\right)^{0.873} \times e^{Gender} \times e^{CBP} \times e^{IND2} \times e^{\eta CL} \quad Eq.1$$

$$Vd = 8.66 \times \left(\frac{WT}{60}\right)^{0.751} \quad Eq.2$$

Model 2 is published in a paper by Botha et al.[11] Botha et al. conducted their study in children and developed a one-compartment model, however, with fewer covariates on CL, with only WT and carbapenem (M) (See equation 3 below).

$$CL = e^{(0.022*WT-1.38)} \times M \quad Eq.3$$

where M = 1.6 for VPA for participants taking carbapenem

Results

Description of the studies

A total of 200 articles and 19 case reports were identified through a database search (Figure 1). From the 200, 52 (26%) duplicate

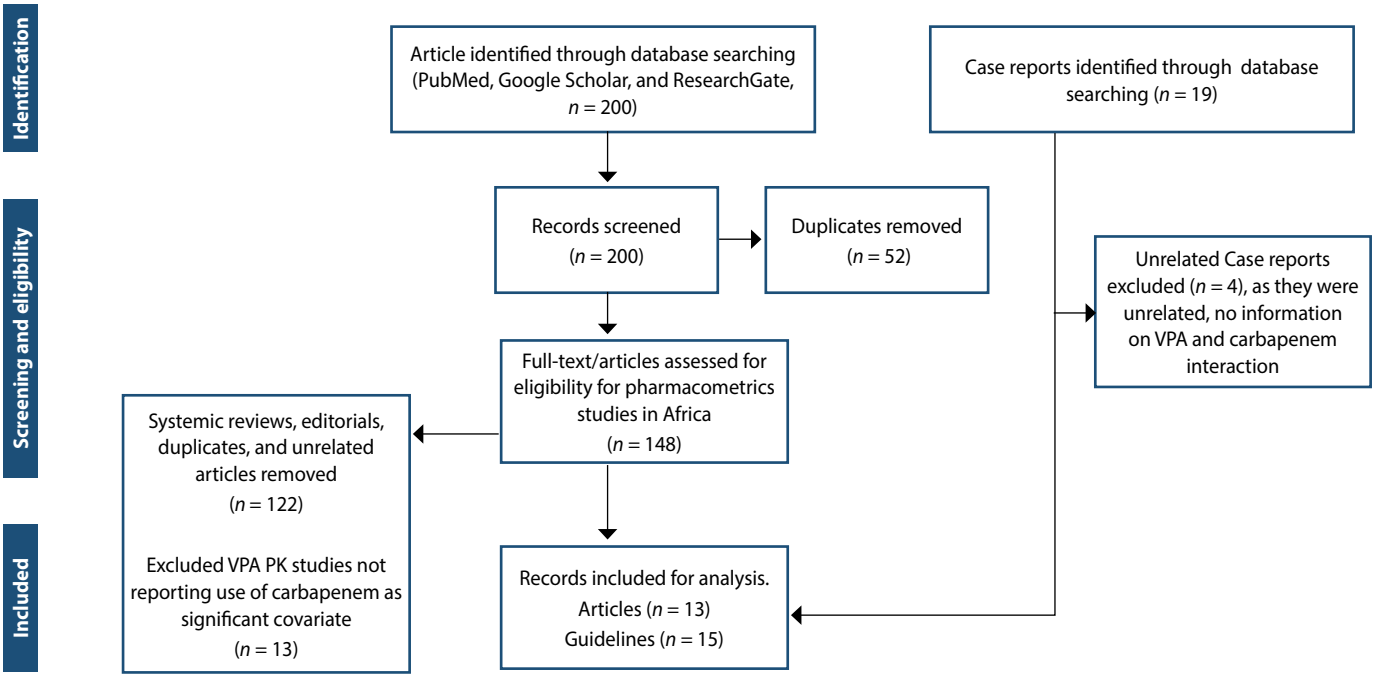

Figure 1: PRISMA diagram for valproic and carbapenem articles and case reports. VPA, valproic acid, PK, pharmacokinetics, n, number of articles or case reports.

articles were removed at the title/authors screening stage. In addition, 135 (91.2%) were removed through abstract and full-text screening. Of the 19 case reports, 4 (21.1%) were excluded as they only reported on VPA, and the patients were not taking a carbapenem. A total of 13 articles and 15 case reports were included for analysis.

Impact of VPA-carbapenem interaction

A total of 24 patients were included from the 15 case reports.[21–35] The case reports were published from 1987–2012, with a total of 88 VPA samples measured from these patients. Of the 88 VPA samples, 50 (56.8%) were below target concentrations

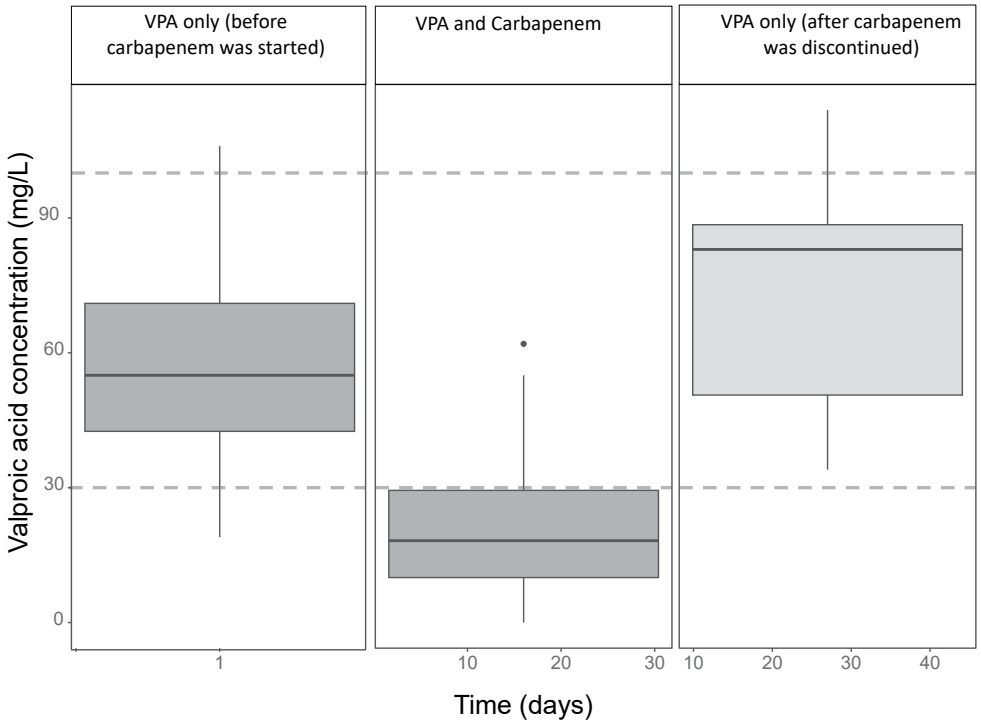

Figure 2: Valproic acid (VPA) and carbapenem interaction: impact on measured plasma concentrations. The horizontal grey dotted lines represent the VPA target concentrations (40–100 mg/L). The X-axis represents time in days: In the VPA-only strata, day 1 corresponds to the day when the first VPA sample was taken prior to initiating carbapenem. In strata 2, which includes both VPA and carbapenem, the days indicate the periods (VPA samples) during which both VPA and carbapenem were administered together. Strata 3 (VPA only-carbapenem discontinued), reflects the days of VPA sampling following the cessation of carbapenem therapy.

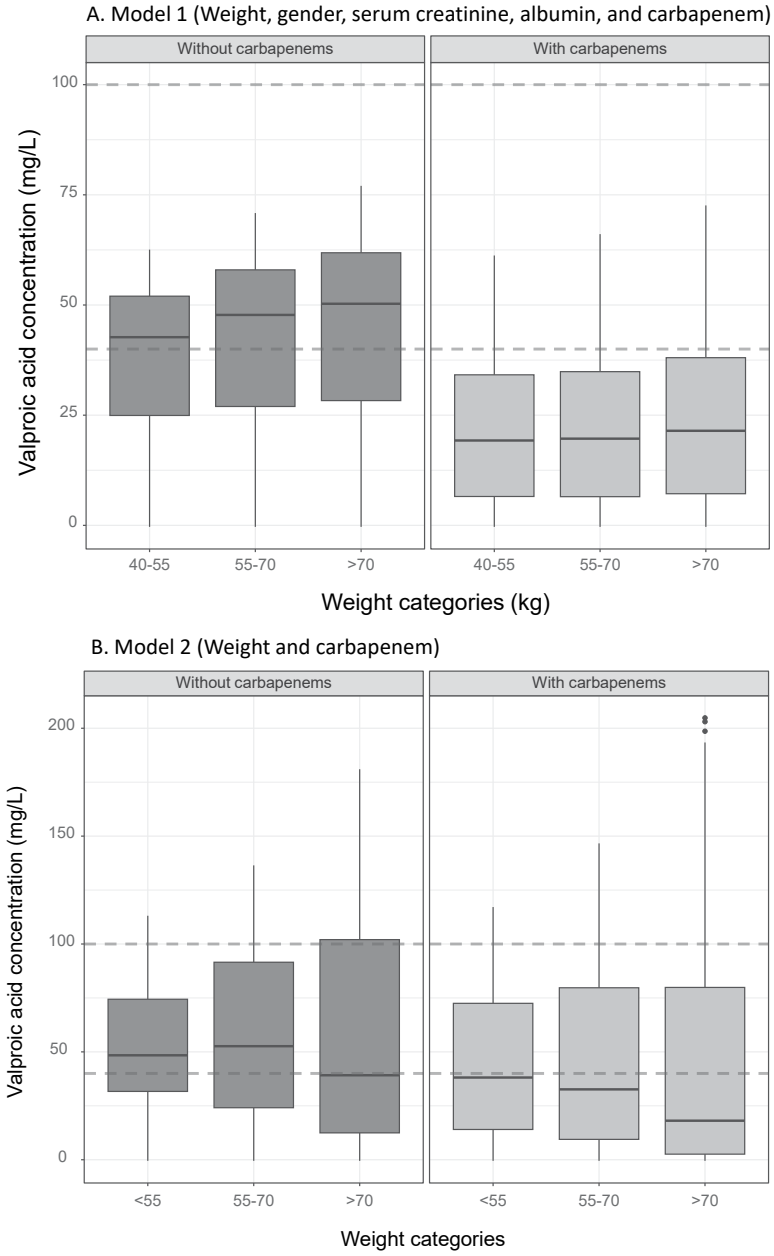

Figure 3: Model-based simulations for participants taking both valproic acid and carbapenem. The horizontal grey dotted lines for both models A and B represent the VPA target concentrations (40–100 mg/L).

(40–100 mg/L), with 44 (88%) of these measured during the co-medication with carbapenems (See Figure 2). Seizures were reported in 7 (29.2%) of the patients receiving carbapenems with measured VPA concentrations below the target (< 40 mg/L). Interestingly, all the 19 patients had VPA levels reaching the target (40–100 mg/L) after carbapenem was discontinued (See Figure 2).

For the 14 population pharmacokinetics articles reporting the interaction of carbapenems and valproic acid, all had sufficient sample size (See Table I). Other significant covariates reported by these articles included age, gender, enzyme induction, co-medication with phenobarbitone, phenytoin, and VPA dose. All of these articles reported that carbapenem increases the CL of VPA (Table I).

Model-based simulations and dose optimisation

The simulated dose of 10–20 mg/kg/day of VPA was shown not to reach the target concentrations in individuals receiving carbapenems, compared to those not on carbapenems, in both models 1 and 2 (See Figure 3A and B). For individuals not taking carbapenem and administered 10 mg/kg/day, dose ranges were seen to be between 465–1 053 mg/day, with targets reached. For individuals taking carbapenem, targets were reached at higher doses of 25 mg/kg/day (1 227–2 725 mg/day) (See Figure S1, stratified according to patient demographics: weight, sex, age, and serum creatinine).

Discussion

This systematic review and meta-analysis evaluated the impact of VPA with concomitant administration of carbapenems. We have reported results from 15 case reports and 13 articles. The impact of carbapenems on VPA plasma target concentration is significant, with more than 80% of the samples measured during this concomitant administration not reaching the target (40–100 µg/ml). The pharmacological treatments of epilepsy have been empirical.[36] The population-based therapeutic range of VPA (40–100 µg/ml) is only a guide to efficacy[16,18,37] and these measurements are also used for assessing adherence.[38] Though these measured or monitored plasma concentrations and doses of VPA are highly correlated,[11,16] there is still notable variability in the optimal VPA concentrations among individuals treated with VPA for epilepsy. In clinical practice, VPA can also be used alone or in combination with other antipsychotic agents to treat mania in bipolar mood disorders[39,40] and to treat aggression in children with attention deficit hyperactivity disorder (ADHD), and chorea.[1] There is also evidence on the use of VPA as treatment and prophylaxis for migraine,[41,42] and potential VPA neuroprotective effects in Alzheimer's patients.[43] However, research is still being conducted for conclusive use and inclusion in package insert or labelling of VPA in migraine and Alzheimer's. Consequently, personalised dosing through therapeutic drug monitoring will be essential for determining the optimal serum VPA concentration necessary to achieve therapeutic targets in all the conditions mentioned above where VPA will be used.

Our analysis of the case reports demonstrated that 29.2% of the patients who received VPA and a carbapenem had poorly controlled seizures. In addition, the attempts to increase the VPA dose failed to achieve target plasma concentrations (40–100 mg/L) for this patient group, and the target plasma concentration was only reached after the carbapenems were discontinued. The literature provides several evidence-based recommendations for managing patients receiving both VPA and carbapenems. Some of the approaches include (i) for low-risk patients, continued VPA

Table I: Pharmacokinetics articles reporting the interaction of carbapenems and valproic acid

Author	Country	Age, mean [range]	Weight (kg), mean	Sample size	VPA formulation	Model structure	Significant covariates
Botha et al.[12]	South Africa	7.6 [1.2–16]	24.2	52	Syrup, tablet, EC tablet	$CL = e^{(0.022*WT-1.38)} \times M$: where M = 1 for VPA monotherapy or VPA with phenobarbital or VPA with phenytoin; M = 1.6 for VPA with carbapenem	WT and co-medication on CL
Yukawa et al. [35]	Japan	15.7 [0.3–54.8]	42.6	207	Tablet, syrup	$CL = 6.06 \times (WT)^{-0.168} \times (\text{VPA dose})^{0.414} \times (\text{carbapenem dose})^{0.095} \times 0.943^{\text{Gender}} \times 1.10^{CO}$ where gender = 0 for males, gender = 1 for females, CO (co-medication) = 0 for VPA + carbapenem, 1 for VPA + carbapenem + one or more antiepileptic drugs	WT, VPA dose, carbapenem dose, gender, co-medication on CL
Yukawa et al.[14]	Japan	11.5 [0.3–54.8]	34.6	400	Tablet, syrup	$CL = 15.6 \times (WT)^{-0.252} \times (\text{VPA dose})^{0.183} \times 0.898^{\text{Gender}} \times CO^{\text{Phenobarbital}} \times CO^{\text{Carbapenem}}$ where gender = 1 for female, $CO^{\text{Phenobarbital}} = 1.1$ if patient treated with phenobarbital, $CO^{\text{Phenobarbital}} =$ 1 if patient not treated with phenobarbital, $CO^{\text{Carbapenem}} = 0.769 *$ carbapenem dose $(\text{mg kg}^{-1} \text{ d}^{-1})^{0.179}$ if patient treated with carbapenem, $CO^{\text{Carbapenem}} = 1$ if patient not treated with carbapenem	WT, VPA dose, gender, co-medication on CL
Blanco-Serrano et al.[15]	Spain	27.3 [14–95]	64.1	208	EC tablet, oral solution	$CL = 0.004 \times (WT) \times (\text{VPA dose})^{0.304} \times (1.363 \times \text{carbapenem}) \times (1.541 \times \text{phenytoin}) \times (1.397 \times \text{phenobarbital})$ (effect of co-medication is bi-therapy, cannot be applied to three or more concomitant medication)	WT, VPA dose, co-medication on CL
Blanco-Serrano et al.[36]	Spain	7.8 [0.1–14]	31.3	255	EC tablet, oral solution	$CL = 0.012 \times (WT)^{0.715} \times (\text{VPA dose})^{0.306} \times 1 + 1.363 \times \text{Carbapenem}$ where carbapenem = 1 if patient treated with carbapenem	WT, VPA dose, co-medication on C
El Desoky et al. [37]	Egyptian	20 [3–58]	48.4	81	EC tablet, oral solution	$CL = 0.105 + 0.151(\text{Carbapenem}) + 0.000248(\text{VPA dose}) + 0.0968(\text{age}/20) + 0.0803(\text{INDI})$ where carbapenem = 1 if patient treated with carbapenem, INDI = 1 if indication for VPA measurement is uncontrolled epilepsy	Co-medication, VPA dose, age, uncontrolled epilepsy on CL
Birnbaum et al.[16]	USA	77 [65–99]	64	146	NR	$CL = 0.843 \times 0.729$ (if female) $\times 1.41$ (if taking carbapenem or phentynol) $\times 1.25$ (if formulation is syrup)	Gender, co-medication, formulation on CL
Jiang et al.[38]	China	8.78 [0.28–16]	33.69	317	NR (have SR formulation)	$CL = 0.106^{(0.98*CO)} + 0.0157$ (age) where CO = 1 when co-medication exists	Formulation on K_a, WT on V_d, co-medication and age on clearance
Jankovic et al.[39]	Serbia	7.21 [1–14]	27.07	58	Film coated tablet or syrup	$CL = 0.137 + 0.00258\,(WT) + 0.159\,(\text{Carbapenem})$ where carbapenem = 1 if patient treated with carbapenem, or otherwise = 0	WT and co-medication with carbapenem on CL
Ogusu et al.[19]	Japan	17.2 [2.2–52.2]	48.8	327	SR tablet	$CL = 0.559 \times (\text{VPA dose}/1000)^{0.596} \times 0.917^{\text{female}}\ 1.19^{\text{Carbapenem}} \times 1.12^{\text{Phenobarbital}} \times 1.43^{\text{Phentynil}} \times 0.906^{\text{Clobazam}}$ where female = 1, male = 0; carbapenem, phenobarbital, phenytoin or clobazam = 1 if drugs were given or otherwise = 0	VPA dose, gender, co-medication with carbapenem, phenobarbital, phenytoin or clobazam on CL/F
Ding et al.[17]	China	5.7 [3 week–14.0]	21.6	902	Syrup, conventional and SR tablet	$CL = 0.3 \times 1.43^{\text{Carbapenem}} \times (WT/70)^{\left(0.791-\frac{90.096*Age^{3.63}}{0.802^{3.63}+Age^{3.63}}\right)} \times \left(1+\frac{(2.8*TDD^{1.68})}{37.4^{1.68}+TDD^{1.68}}\right)$ where carbapenem = 1 for patients co-treated with carbapenem or 0 otherwise. TDD, being the total daily dose of VPA (mg/kg)	WT, age, VPA dose, co-medication with carbapenem on CL/F
Lin et al.[40]	China	26.6 [14–66]	60.2	199	SR and conventional tablet	$CL = 0.1 \times (WT)^{0.7} \times (\text{VPA dose})^{0.2} \times 1.36$ (if co-treated with carbapenem) $\times 1.25$ (if taking with phenytoin) $\times 1.11$ (if co-treated with phenobarbital)	WT, VPA dose and co-medication on CL/F; WT on V/F
Zhang et al. 8	China	32.74 [0.27–84.38]	60.0	443	Oral solution and SR tablet	$CL = 0.43 \times \left(\frac{WT}{60}\right)^{0.787} \times \left(\frac{\text{Creatinine}}{50.3}\right)^{-0.253} \times \left(\frac{\text{Albumin}}{39}\right)^{0.873} \times e^{\text{Gender}} \times e^{\text{Carbapenem}} \times e^{\text{IND2}} \times e^{\eta CL}$ where gender = 0.121 for female, otherwise = 0; carbapenem = 1.50 when combined with carbapenems, otherwise = 0; IND2 = 0.15 when combined with oxcarbazepine, carbamazepine, phenobarbital, or phenytoin, otherwise = 0.	Weight on Vd; weight, gender, enzyme induction (IND), carbapenem, albumin, serum creatinine (Cr) on CL

monitoring, while limiting the duration of carbapenem therapy,[44] (ii) keep VPA, but add a second antiepileptic (e.g. levetiracetam), selected based on seizure type, potential adverse effects, interactions with other medications, and comorbid medical conditions [44] (iii) discontinue VPA and consider an alternative anti-epileptic such as phenytoin, phenobarbital or levetiracetam,[45] and (iv) review microbiological susceptibility profile and consider an alternative antibiotic for the carbapenems.[9,46] In resource-limited facilities (government hospitals in South Africa), there are limited antibiotic options the clinicians can choose from for the treatment of multidrug-resistant Gram-negative (i.e. extended-spectrum ß-lactamases) infections. Therefore, carbapenems eventually become the only available and considered antibiotic of choice for the treatment of these infections.

Carbapenems are stable against hydrolysis by most β-lactamases produced by drug-susceptible organisms. However, the interaction between carbapenem with VPA limits carbapenem use in individuals taking VPA. Carbapenems' mechanism or effect on clearance is said to be related to the hepatic metabolism of VPA. According to Blanco-Serrano et al.,[14] carbapenems enhance the glucuronidation of VPA by increasing uridine diphosphate–glucuronic acid levels, which in turn result in a 60–80% reduction in VPA plasma concentrations. A population pharmacokinetic study by Zhang et al. investigated the influence of coadministration of carbapenems on the CL of VPA, and about 4.9% of participants were co-administered carbapenems (4.1% with meropenem and 0.6% with ertapenem) and VPA. A significant 448.2% increase in VPA CL was observed in participants with carbapenem co-medication.[16] Other studies have reported similar findings, with VPA serum concentrations decreasing significantly by 69.1% with ertapenem and 65.2% with meropenem.[45,47,48]

Our meta-analysis showed that the onset of the interaction can be rapid, as a significant reduction in the serum VPA concentration was observed within 1 to 30 days of co-administration and recovery of plasma levels was noted within 3 days to 2 weeks after carbapenem discontinuation. This suggests that there is a possibility of this interaction being facilitated through multiple mechanisms other than enzyme induction, as enzyme induction may take days to weeks to occur.[21] Other reported mechanisms include absorption (increased perfusion of VPA from the luminal to the vascular perfusate and inhibition of the absorption of VPA at the basolateral membrane of intestinal epithelial cells),[49,50] and distribution (increased erythrocyte distribution of VPA, and the efflux of VPA from erythrocytes inhibited by multidrug resistant-associated proteins).[51,52]

We also evaluated the effectiveness of increasing the dose using model-based simulations in the cohort co-administered carbapenems. A comparable study by Zhang et al. used NONMEM. In Zhang's model, a male weighing 60 kg, aged 33 years, with 50.3 µmol/L Cr and 39 g/L ALB, not taking CBP and IND2, requires a VPA dose ranging from 903 mg (target of 50 mg/L) to 1 795 mg (100 mg/L) every 24 h. These results were also reproducible in our application of the same model by Zhang et al., across individuals weighing 38.8–125kg and 2–70 years of age (See Figure 3A). In contrast, simulations using the model by Botha et al. (model 2, Figure 3B), a different prediction was observed with the high weight category and older participants (showing a significant underprediction), and this can be due to that the model was developed using only children.

Our dose recommendations using both models for individuals taking VPA and carbapenems were similar to those by Zhang et al., and were high (as shown in Figure 3A and B). This can increase the likelihood of VPA side-effects when targets are unattainable and no benefits are observed.[1,16] In addition, VPA clearance is correlated significantly with the VPA daily dose. [12–14,18,20,53,54] An improvement in model fit obtained with the inclusion of the VPA dose has been observed in many pharmacokinetic studies,[12–14,18,20,53–56] which showed that a patient receiving a higher dose has a higher CL rate than a patient receiving a lower dose. In two recent studies that used the same methodology,[12,55] a non-linear relationship was established between CL and the VPA daily dose. Similar findings were also reported by Blanco-Serrano et al.[56] Therefore, increased VPA dose leads to increased total concentration of the drug, consequent increase in its free fraction, and associated increased CL.[53] This indicates that it may be more effective to consider alternative or dual antiepileptic therapy if carbapenems are administered, rather than continuing to increase the VPA dose, as increasing the VPA dose may lead to consistently subtherapeutic levels because of the increased CL of VPA.

Our analysis is based solely on reported VPA concentrations from case reports, which consist of a single post-dose sample. While this sampling method is recommended, it restricts our ability to examine the effect of carbapenem on the entire plasma concentration profile of VPA, from absorption to elimination. Furthermore, the model developed by Botha et al. was specifically designed for the paediatric population, which means it primarily accounts for this demographic. As a result, it tends to underpredict VPA levels in adults, the elderly, and individuals with higher body weights.

Conclusion

Based on our analysis of data from clinical studies and published case reports, the combination of VPA and carbapenem antibiotics should be avoided whenever possible. The reduction in VPA plasma concentration observed in these cases is significant, and this pharmacokinetic interaction may lead to uncontrolled seizures. Increasing the dose VPA, increases VPA plasma concentration: however, VPAs CL also increases. It is advisable to consider alternative antimicrobial agents instead of carbapenems when susceptibility results allow. Additionally, replacing VPA with a non-interacting antiepileptic medication or prescribing an additional antiepileptic agent may be appropriate. When carbapenem-VPA combination therapy is deemed necessary, therapeutic drug monitoring of valproate levels is strongly recommended.

Conflict of interest

We have no conflicts of interest to disclose.

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References

1. Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. Clin Biochem. 2013;46(15):1323-38. https://doi.org/10.1016/j.clinbiochem.2013.06.012.
2. Patsalos PN, Berry DJ, Bourgeois BFD, et al. 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(7):1239-76. https://doi.org/10.1111/j.1528-1167.2008.01561.x.
3. Peterson GM, Naunton M. Valproate: a simple chemical with so much to offer. J Clin Pharm Ther. 2005;30(5):417-21. https://doi.org/10.1111/j.1365-2710.2005.00671.x.
4. McKee PJW, Percy-Robb I, Brodie MJ. Therapeutic drug monitoring improves seizure control and reduces anticonvulsant side-effects in patients with refractory epilepsy. Seizure. 1992;1(4):275-9. https://doi.org/10.1016/1059-1311(92)90037-2.
5. Vučićević K, Miljković B, Pokrajac M, et al. The influence of drug-drug interaction and patients' characteristics on valproic acid's clearance in adults with epilepsy using nonlinear mixed effects modeling. Eur J Pharmaceut Sci. 2009;38(5):512-8. https://doi.org/10.1016/j.ejps.2009.09.017.
6. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev. 2013;2013(10):CD003196. https://doi.org/10.1002/14651858.CD003196.pub2.
7. Scheduling status. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/07/pi-epilim-range_clean_17.08.2022_approved-10.10.2022.pdf. Accessed, 30 March 2025.
8. Breilh D, Texier-Maugein J, Allaouchiche B, Saux MC, Boselli E. Carbapenems. J Chemother. 2013;25(1):1-17. https://doi.org/10.1179/1973947812Y.0000000032.
9. Hawkey PM, Livermore DM. Carbapenem antibiotics for serious infections. BMJ. 2012;344:e3236-e3236. https://doi.org/10.1136/bmj.e3236.
10. Methaneethorn J. A systematic review of population pharmacokinetics of valproic acid. Br J Clin Pharmacol. 2018;84(5):816-34. https://doi.org/10.1111/bcp.13510.
11. Botha JH, Gray AL, Miller R. A model for estimating individualized valproate clearance values in dhildren. J Clin Pharmacol. 1995;35(10):1020-4. https://doi.org/10.1002/j.1552-4604.1995.tb04020.x.
12. Yukawa E, Honda T, Ohdo S, Higuchi S, Aoyama T. Detection of carbamazepine-induced changes in valproic acid relative clearance in man by simple pharmacokinetic screening. J Pharm Pharmacol. 1997;49(8):751-6. https://doi.org/10.1111/j.2042-7158.1997.tb06106.x.
13. Yukawa E, To H, Ohdo S, Higuchi S, Aoyama T. Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: Influence of drug-drug interaction and patient characteristics. J Clin Pharmacol. 1997;37(12):1160-7. https://doi.org/10.1002/j.1552-4604.1997.tb04301.x.
14. Blanco-Serrano B, Otero MJ, Santos-Buelga D, et al. Population estimation of valproic acid clearance in adult patients using routine clinical pharmacokinetic data. Biopharm Drug Dispos. 1999;20(5):233-40. https://doi.org/10.1002/(SICI)1099-081X(199907)20:5<233::AID-BDD179>3.0.CO;2-5.
15. Birnbaum AK, Ahn JE, Brundage RC, et al. Population pharmacokinetics of valproic acid concentrations in elderly nursing home residents. Ther Drug Monit. 2007;29(5):571-5. https://doi.org/10.1097/FTD.0b013e31811f3296.
16. Zhang L, Wu R, Li X, et al. Combined carbapenem resulted in a 4.48-fold increase in valproic acid clearance: a population pharmacokinetic model in Chinese children and adults with epilepsy or after neurosurgery. Front Pharmacol. 2024;15. https://doi.org/10.3389/fphar.2024.1423411.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34. https://doi.org/10.1016/j.jclinepi.2009.06.006.
18. Ding J, Wang Y, Lin W, et al. A population pharmacokinetic model of valproic acid in pediatric patients with epilepsy: A non-linear pharmacokinetic model vased on protein-binding saturation. Clin Pharmacokinet. 2015;54(3):305-17. https://doi.org/10.1007/s40262-014-0212-8.
19. Nakashima H, Oniki K, Nishimura M, et al. Determination of the optimal concentration of valproic acid in patients with epilepsy: A population pharmacokinetic-pharmacodynamic analysis. PLoS One. 2015;10(10):e0141266. https://doi.org/10.1371/journal.pone.0141266.
20. Ogusu N, Saruwatari J, Nakashima H, et al. Impact of the superoxide dismutase 2 Val-16Ala polymorphism on the relationship between valproic acid exposure and elevation of γ-glutamyltransferase in patients with epilepsy: A population pharmacokinetic-pharmacodynamic analysis. PLoS One. 2014;9(11):e111066. https://doi.org/10.1371/journal.pone.0111066.
21. Lee MC, Sun YH, Lee CH, Wu AJ, Wu TW. Interaction between valproic acid and carbapenems: Case series and literature review. Tzu Chi Med J. 2012;24(2):80-4. https://doi.org/10.1016/j.tcmj.2012.02.008.
22. Lee SG, Kim JH, Joo JY, Kwon OH. Seven cases of decreased serum valproic acid concentration during concomitant use of carbapenem antibiotics. Ann Lab Med. 2007;27(5):338-43. https://doi.org/10.3343/kjlm.2007.27.5.338.
23. Gu J, Huang Y. Effect of concomitant administration of meropenem and valproic acid in an elderly chinese patient. Am J Geriatr Pharmacother. 2009;7(1):26-33. https://doi.org/10.1016/j.amjopharm.2009.02.005.
24. Liao FF, Huang YB, Chen CY. Decrease in serum valproic acid levels during treatment with ertapenem. Am J Health-Syst Pharm. 2010;67(15):1260-4. https://doi.org/10.2146/ajhp090069.
25. Hellwig RT, Onisk LM, Chapman AB. Potential interaction between valproic acid and doripenem. Curr Drug Saf. 2011;6(1):54-8. https://doi.org/10.2174/157488611794480007.
26. Lunde JL, Nelson RE, Storandt HF. Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. Pharmacotherapy: J Hum Pharmacol Drug Ther. 2007;27(8):1202-5. https://doi.org/10.1592/phco.27.8.1202.
27. Spriet I, Meersseman W, De Troy E, et al. Meropenem -valproic acid interaction in patients with cefepime-associated status epilepticus. Am J Health-Syst Pharm. 2007;64(1):54-8. https://doi.org/10.2146/ajhp050512.
28. Fudio S, Carcas A, Pinana E, Ortega R. Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. J Clin Pharm Ther. 2006;31(4):393-6. https://doi.org/10.1111/j.1365-2710.2006.00743.x.
29. Cabanes Mariscal MA, Sánchez López P, Álvarez Herranz P, Chamorro Merino G. Pharmacokinetic interaction between valproic acid and ertapenem. Farmacia Hospitalaria. 2006;30(5):313-5. https://doi.org/10.1016/S1130-6343(06)73997-6.
30. Coves-Orts FJ, Borrás-Blasco J, Navarro-Ruiz A, Murcia-López A, Palacios-Ortega F. Acute seizures due to a probable interaction between valproic acid and meropenem. Ann Pharmacother. 2005;39(3):533-7. https://doi.org/10.1345/aph.1E358.
31. Nacarkucuk E, Saglam H, Okan M. Meropenem decreases serum level of valproic acid. Pediatr Neurol. 2004;31(3):232-4. https://doi.org/10.1016/j.pediatrneurol.2004.03.014.
32. Clause D, Decleire PY, Vanbinst R, Soyer A, Hantson P. Pharmacokinetic interaction between valproic acid and meropenem. Intensive Care Med. 2005;31(9):1293-4. https://doi.org/10.1007/s00134-005-2695-0.
33. Yamagata T, Momoi MY, Murai K, et al. Panipenem-betamipron and decreases in serum valproic acid concentration. Ther Drug Monit. 1998;20(4):396-400. https://doi.org/10.1097/00007691-199808000-00008.
34. De Turck BJ, Diltoer MW, Cornelis PJ, et al. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. J Antimicrob Chemother. 1998;42(4):563-4. https://doi.org/10.1093/jac/42.4.563.
35. Nagai K, Shimizu T, Togo A, et al. Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. J Antimicrob Chemother. 1997;39(2):295-6. https://doi.org/10.1093/jac/39.2.295.
36. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. BMJ. 2014;348(feb28 2):g254-g254. https://doi.org/10.1136/bmj.g254.
37. Turnbull DM, Rawlins MD, Weightman D, Chadwick DW. Plasma concentrations of sodium valproate: Their clinical value. Ann Neurol. 1983;14(1):38-42. https://doi.org/10.1002/ana.410140107.
38. Vajda FJE, Eadie MJ. The clinical pharmacology of traditional antiepileptic drugs. Epileptic Disord. 2014;16(4):395-408. https://doi.org/10.1684/epd.2014.0704.
39. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? Epilepsia. 2012;53(s7):26-33. https://doi.org/10.1111/j.1528-1167.2012.03712.x.
40. Vasudev K, Mead A, Macritchie K, Young AH. Valproate in acute mania: is our practice evidence based? Int J Health Care Qual Assur. 2012;25(1):41-52. https://doi.org/10.1108/09526861211192395.
41. Blumenfeld A, Gennings C, Cady R. Pharmacological Synergy: The Next Frontier on Therapeutic Advancement for Migraine. Headache: J Head Face Pain. 2012;52(4):636-47. https://doi.org/10.1111/j.1526-4610.2011.02058.x.
42. Terbach N, Williams RSB. Structure-function studies for the panacea, valproic acid. Biochem Soc Trans. 2009;37(5):1126-32. https://doi.org/10.1042/BST0371126.
43. Zhang XZ, Li XJ, Zhang HY. Valproic acid as a promising agent to combat Alzheimer's disease. Brain Res Bull. 2010;81(1):3-6. https://doi.org/10.1016/j.brainresbull.2009.09.003.
44. Bates D, Parkins M, Duggan K. Ertapenem-induced reduction in valproate levels: Case report and review of the literature. Can J Hosp Pharm. 2010;63(4). https://doi.org/10.4212/cjhp.v63i4.936.
45. Huang C, Lin C, Hsiao S, et al. Drug interaction between valproic acid and carbapenems in patients with epileptic seizures. Kaohsiung J Med Sci. 2017;33(3):130-6. https://doi.org/10.1016/j.kjms.2016.12.001.
46. Al-Quteimat O, Laila A. Valproate interaction with carbapenems: Review and recommendations. Hosp Pharm. 2020;55(3):181-7. https://doi.org/10.1177/0018578719831974.
47. Miranda Herrero MC, Alcaraz Romero AJ, Escudero Vilaplana V, et al. Pharmacological interaction between valproic acid and carbapenem: What about levels in pediatrics? Eur J Pediatr Neurol. 2015;19(2):155-61. https://doi.org/10.1016/j.ejpn.2014.12.010.
48. 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;62:151-6. https://doi.org/10.1016/j.jcrc.2020.12.005.
49. Torii M, Takiguchi Y, Izumi M, Fukushima T, Yokota M. Carbapenem antibiotics inhibit valproic acid transport in Caco-2 cell monolayers. Int J Pharm. 2002;233(1-2):253-6. https://doi.org/10.1016/S0378-5173(01)00916-4.
50. Torii M, Takiguchi Y, Saito F, Izumi M, Yokota M. Inhibition by carbapenem antibiotic imipenem of intestinal absorption of valproic acid in rats. J Pharm Pharmacol. 2001;53(6):823-9. https://doi.org/10.1211/0022357011776171.
51. Ogawa K, Yumoto R, Hamada N, Nagai J, Takano M. Interaction of valproic acid and carbapenem antibiotics with multidrug resistance-associated proteins in rat erythrocyte membranes. Epilepsy Res. 2006;71(1):76-87. https://doi.org/10.1016/j.eplepsyres.2006.05.016.
52. Omoda K, Murakami T, Yumoto R, et al. Increased erythrocyte distribution of valproic acid in pharmacokinetic interaction with carbapenem antibiotics in rat and human. J Pharm Sci. 2005;94(8):1685-93. https://doi.org/10.1002/jps.20338.
53. EL Desoky ES, Fuseau E, EL Din Amry S, Cosson V. Pharmacokinetic modelling of valproic acid from routine clinical data in Egyptian epileptic patients. Eur J Clin Pharmacol. 2004;59(11):783-90. https://doi.org/10.1007/s00228-003-0699-7.
54. Lin WW, Jiao Z, Wang CL, et al. Population pharmacokinetics of valproic acid in adult Chinese epileptic patients and its application in an individualized dosage regimen. Ther Drug Monit. 2015;37(1):76-83. https://doi.org/10.1097/FTD.0000000000000100.
55. Yukawa E. A feasibility study of the multiple-peak approach for pharmacokinetic screening: Population-based investigation of valproic acid relative clearance using routine clinical pharmacokinetic data. J Pharm Pharmacol. 1995;47(12A):1048-52. https://doi.org/10.1111/j.2042-7158.1995.tb03295.x.
56. Blanco Serrano B, García Sánchez MJ, Otero MJ, et al. Valproate population pharmacokinetics in children. J Clin Pharm Ther. 1999;24(1):73-80. https://doi.org/10.1046/j.1365-2710.1999.00202.x.

Reduced valproic acid concentrations in patients receiving carbapenems: meta-analysis

Supplementary files

Supplementary Table SI: Simulated participants characteristics	
Items	**Overall (*n* = 30 000)**
Age (years), median [min, max]	37.0 [2.00, 70.0]
Male, *n* (%)	15 960 (53.2%)
Weight (kg), median [min, max]	72.4 [38.8, 125]
Albumin (g/L), median [min, max]	37.0 [24.0, 52.0]
Enzyme inducers 1, *n* (%)	15 420 (51.4%)
Serum creatinine (micromol/L), median [min, max]	227 [14.0, 446]
On carbapenems, *n* (%)	15 300 (51.0%)

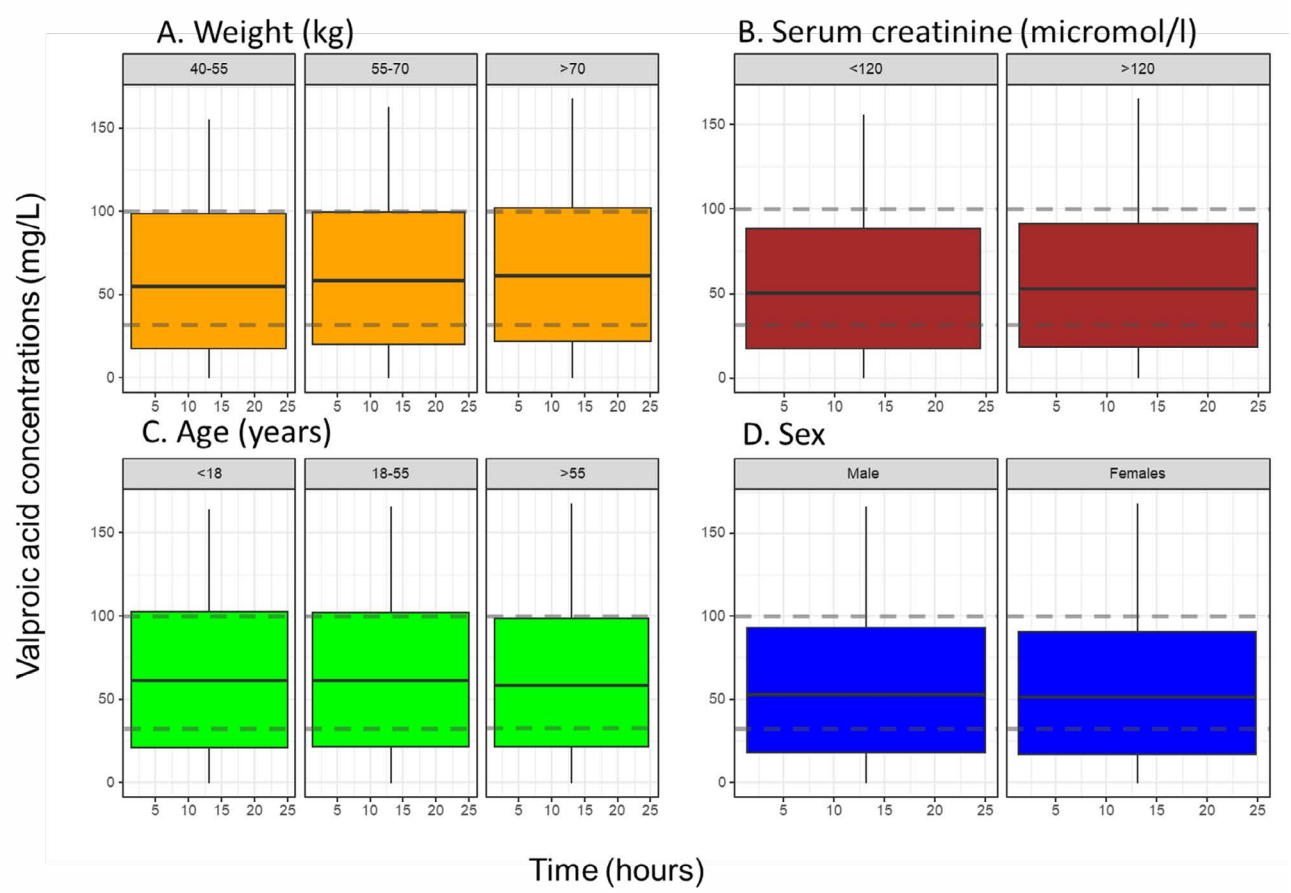

Figure S1: Dose optimisation for 25 mg/kg/day for virtual participants using Model 1. The horizontal dotted lines represents the target valproic acid concentration (40–100 mg/L).