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ORIGINAL RESEARCH

Development and Validation of a Population Pharmacokinetics Model of Perampanel for Pediatric Epilepsy Patients for Optimized Dosing

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Background: Perampanel exhibits substantial interindividual variability, and pharmacokinetic data in pediatric patients are scarce. The aim of this study was to develop a population pharmacokinetic (PPK) model to optimize the dosing of perampanel in children with epilepsy.

Methods: The PPK model was developed via a nonlinear mixed-effects modeling approach, utilizing a dataset comprising 454 plasma concentrations of perampanel obtained from 151 pediatric patients with epilepsy, 120 (79.5%) of whom were aged < 12 years. Goodness-of-fit plots and bootstrap analysis were employed to evaluate the final model. Monte Carlo simulations were utilized to suggest perampanel dosing strategies using a reference plasma concentration range of 100–1000 ng/mL.

Results: In the final PPK models of perampanel, linear centralized age, coadministration of oxcarbazepine (OXC), carbamazepine (CBZ), and valproic acid (VPA) were covariates of clearance (CL/F), and log-transformed body weight was a covariate of the apparent distribution volume (V). The CL/F was estimated via the formula $CL/F=0.177*((age+10)/8.8)^{1.31}*1.51^{OXC}*0.745^{VPA}*1.88^{CBZ}$. The relative standard errors (RSEs) for each fixed effect parameter were 15.2%, 14.2%, 12.0%, 7.92%, and 16.3%, respectively. The V was estimated via the formula V=227*LGBW with an RSE of 14.1%. The model demonstrated good robustness according to goodness-of-fit plots and bootstrap analysis. The simulation analysis resulted in a dosing regimen stratified by covariates.

Conclusion: A reliable perampanel PPK model for pediatric patients was successfully developed. This result could be helpful for dosing optimization in pediatric patients receiving perampanel, especially those aged under 12 years.

Keywords: perampanel, epilepsy, NONMEM, therapeutic drug monitoring, population pharmacokinetic model

Introduction

Epilepsy is one of the most common chronic neurological problems in children and adolescents, with approximately 3/4 of epilepsy cases occurring in childhood.[1–3] It can seriously affect the physical and mental health of children. Pharmacological treatment remains the major option for childhood epilepsy. However, 25–30% of pediatric patients still have poor treatment outcomes and develop refractory epilepsy.[4] Therefore, novel antiseizure medications (ASMs) are sorely needed.

Perampanel is a third-generation ASM that is approved as an adjunctive treatment for focal-onset seizures with or without secondary generalization and for primary generalized tonic–clonic seizures in patients with idiopathic generalized epilepsy.[5,6] The broad-spectrum efficacy, favorable cognitive profile, once-daily formulation, and unique mechanism of action of perampanel make it particularly suitable for pediatric patients.[7]

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Perampanel has a narrow therapeutic index and exhibits significant pharmacokinetic variability in pediatric patients, leading to significant variation in its serum concentration.[8–10] Some guidelines have suggested the use of therapeutic drug monitoring (TDM) to maintain the concentration of perampanel within a certain range.[11] Therefore, there is an urgent need to personalize the dosage regimen for each pediatric patient to improve the efficacy and tolerability of perampanel early, especially for hospitals in which TDM is not available.[12,13]

However, pharmacokinetic data concerning perampanel in pediatric patients are scarce, especially for those aged under 12 years. The phase I/II/III studies of perampanel were carried out in adults or patients aged over 12 years. Although some population pharmacokinetic (PPK) models are available, these models seldom include pediatric patients aged under 12 years, and the results are contradictory.[14–16] Moreover, perampanel is metabolized mainly by CYP3A4 and CYP3A5. The coadministration of enzyme-inducing antiseizure medications (EIASMs) and enzyme-inhibiting ASMs affects the pharmacokinetics of perampanel and increases the variability of drug concentrations.[14–16]

Considering the need for precision dosing of perampanel in young pediatric patients, this study aimed to develop a PPK model for perampanel in pediatric patients (especially those aged under 12 years) with epilepsy and to identify patient characteristics in terms of perampanel pharmacokinetic parameters, which might facilitate its use in clinical practice.

Methods

Study Design and Ethics Approval

This was a retrospective study. Ethics approval was obtained from the ethics committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University (reference number 2024–0117). The requirement for obtaining informed consent from the patients was waived because of the retrospective nature of the study. This study complied with the Declaration of Helsinki. Patients' personal information was accessible only to authorized investigators and was not disseminated.

Patient Inclusion

Pediatric patients who had received perampanel from February 2021 to September 2023 in our hospital were retrospectively included according to preset criteria. The inclusion criteria were as follows: (1) pediatric patients who had a diagnosis of epilepsy; (2) patients who received perampanel orally; and (3) patients who underwent TDM during treatment and had at least one perampanel concentration. The exclusion criteria were as follows: (1) age >18 years and (2) insufficient data (lack of BW, height or laboratory examination data during perampanel treatment).

In this study, a comprehensive set of patient data was collected, including demographic characteristics (age, sex, weight and height), blood test results (erythrocytes, albumin, hemoglobin, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, etc), details of the administration regimen of perampanel (dosage, frequency, time of sampling), coadministration of ASMs, and plasma concentrations of perampanel. The plasma concentration of perampanel was obtained from routine TDM data. In our hospital, perampanel TDM is usually performed 3 weeks after the initiation of perampanel treatment, as perampanel achieves a steady state after 19 days of dosing.[17] Blood samples were collected in the morning, approximately 12 h after the previous dose, and the plasma perampanel concentration was determined by the clinical laboratory via a validated HPLC method.[18] The range of the method is 15–1500 ng/mL.

PPK Modeling and Validation

The perampanel plasma concentration data were analyzed through the PPK approach via nonlinear mixed effects modeling with the software NONMEM (version 7.5.0, ICON Early Phase, San Antonio, TX, USA) coupled with PsN (version 5.4.0) and Pirana (version 23.1.2, Certara, Radnor, PA, USA) on a personal computer (AMD Ryzen 7 PRO 4750U processor, 16 GM RAM). The first-order conditional estimation method with interaction (FOCE-I) was used for the parameter estimation and model construction process. The selection of the model relies on the minimum objective function value (OFV), and the model is evaluated by means of a goodness-of-fit (GOF) plot. A one- or two-compartment model of primary absorption and elimination was used to describe the pharmacokinetics of perampanel.

The covariates were selected via forward inclusion and backward elimination strategies. The screened covariates included sex, age, weight, height, BSA, BMI, albumin, total protein, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and the perampanel dosing regimen. In addition, the effects of enzyme-induced ASMs (including carbamazepine, oxcarbazepine, and phenytoin), enzyme-inhibited ASMs (sodium valproate), and other ASMs (lacosamide, levetiracetam, zonisamide, etc) were studied. Correlation analyses were performed before covariate modeling. If the correlation coefficient between two variables was > 0.3, one of the variables was selected for inclusion in the model on the basis of whether it was clinically relevant or easy to apply. The effects of continuous covariates were modeled via a median standardized model, whereas the effects of categorical covariates were described via a power model, with covariates included in the model on the basis of a decrease in OFV of 3.84 ($p < 0.05$) for forward inclusion and an increase in OFV of greater than 10.83 ($p < 0.001$) for backward exclusion. The final model and parameter estimates were evaluated via GOF plots, bootstrap analysis and visual predictive check (VPC).

Simulation and Dosing Regimen Optimization

On the basis of the final model, Monte Carlo simulations were performed via NONMEM software to optimize the dosing regimen. The lowest dose of perampanel used in clinical practice is 2 mg/d, and a 2 mg/d increment was suggested for adjusting the dose by label. Thus, simulations with different dosing regimens (2 mg/d, 4 mg/d, 6 mg/d, 8 mg/d, 10 mg/d, and 12 mg/d) were performed in pediatric patients stratified by covariates. Each condition was simulated 1000 times. The target stable serum concentration was 100–1000 ng/mL.[19] In addition, an optimal dosing was selected when its probability target attainment (PTA) was over 90%.

Results

Patient Inclusion and Characteristics

In total, 454 plasma concentrations from 151 patients were eligible and included in the development of the PPK model. The demographic characteristics of the included patients are shown in Table 1. No included patients had severe hepatic or renal impairment. Notably, 120 (79.5%) patients were aged < 12 years.

Table 1 Characteristics of Studied Pediatric Patients

Variable	Total[a]	Aged <12 Years[a]	Aged 12–18 Years[a]	Min-Max[b]
No. of subjects	151	120	31	
No. of concentration measurements	454	343	111	
Age (years)	9.00(6.34,11.88)	6.70(4.07–8.87)	13.3(12.8–14.3)	0.58–17.9
Sex (M/F)	96/55	74/46	22/9	
BW (kg)	28.1(21.2,41.0)	22.7(16.9,28.0)	54(45.8,59.8)	9.00–89.0
Height(cm)	134 (120,151)	120(103,134)	160(157,170)	68.0–182
BMI (kg/m^2)	16.6(15.1,19.0)	16.0(14.8,17.8)	21.5(17.7,23.3)	7.40–34.7
BSA($m^{2)}$	1.06(0.84,1.27)	0.89(0.69,1.06)	1.53(1.37,1.65)	0.42–2.23
Daily dose (mg)	2.00(2.00,4.00)	2.00(2.00,4.00)	2.00(2.00,4.00)	1.00–8.00
PER concentration (ng/mL)	242(144,340)	287(215,423)	296(220,408)	30.0–1082
WBC (10^9 /L)	6.40(5.50,7.40)	6.45(5.30,7.70)	6.40(5.60,7.15)	2.50–16.10
HGB (g/L)	133(127,140)	130(125,136)	141(133,149)	101–188
ALB (g/L)	43.1(41.2,45.0)	43.0(40.1,44.2)	43.1(41.8,44.7)	32.6–108
ALT (U/L)	15(13,18)	15(12,20.3)	16(13,21)	2–67
AST (U/L)	27(24,31)	27(25,35)	25(19,27)	11–70
TBIL (μmol/L)	7.2(5.6,9.0)	6.5(5.2,7.6)	7.2(6.6,8.8)	2.1–20.1
SCr (μmol/L)	43.4(40.0,46.6)	42.0(32.6,43.4)	43.4(43,52.5)	9.0–109
CrCl(mL/min)	149(128,169)	151(126,168)	186(167,227)	76.2–432

(*Continued*)

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Table 1 (Continued).

Variable	Total[a]	Aged <12 Years[a]	Aged 12–18 Years[a]	Min-Max[b]
Comedications (used, %)				
Enzyme inducers				
Carbamazepine	8(5.30%)	6(5.00%)	2(6.45%)	
Oxcarbazepine	26(17.2%)	20(16.7%)	6(19.3%)	
Phenobarbital	2(1.32%)	2(1.67%)	0	
Topiramate	28(18.5%)	25(20.8%)	3(9.68%)	
Enzyme inhibitors				
Sodium valproate	53(35.1%)	43(35.8%)	10(32.3%)	
Magnesium valproate	1(0.66%)	1(0.83%)	0	
Not enzyme inducers/inhibitors				
Lacosamide	10(6.62%)	5(4.17%)	5(16.1%)	
Levetiracetam	42(27.8%)	33(27.5%)	9(29.0%)	
Zonisamide	6(3.97%)	1(0.83%)	5(16.1%)	
Vigabatrin	3(1.99%)	3(2.50%)	0	
Nitrazepam	10(0.66%)	7(5.83%)	3(9.68%)	
Clonazepam	9(5.96%)	4(3.33%)	5(16.1%)	
Lamotrigine	13(8.61%)	5(4.17%)	8(25.8%)	
Clobazam	7(4.64%)	2(1.67%)	5(16.1%)	
Type of epilepsy				
Focal	77(51.0%)	61(50.8%)	16(51.6%)	
Generalized	70(46.4%)	56(46.6%)	14(45.2%)	
Focal with generalized	4(2.65%)	3(2.50%)	1(3.23%)	

Notes: [a]The presented data were baseline data. [b]These indicate the maximum and minimum data during the whole study period.
Abbreviations: BW, body weight; BMI, body mass index; BSA, Body Surface Area; WBC, white blood cell; HGB, Hemoglobin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; SCr, serum creatinine; CrCl, creatine clearance.

PPK Model Development

A one-compartment model with volume of distribution (V) and clearance (CL) as first-order elimination parameters better describes perampanel plasma concentrations. After forward inclusion and backward exclusion of covariates (Table S1), the final model had three covariates on CL/F and one covariate on V, which can be described via equations (1) and (2):

$$\mathrm{CL/F(L/h)} = 0.177 * ((\mathrm{Age} + 10)/8.8)^{1.31} * 1.51^{\mathrm{OXC}} * 0.745^{\mathrm{VPA}} * 1.88^{\mathrm{CBZ}} \quad (1)$$

$$\mathrm{V(L)} = 227 * \mathrm{LGBW} \quad (2)$$

where 0.177 (L/h) is a typical CL/F (L/h) and 227 (L) is a typical V (L) value. Age is the age in years, and OXC, VPA and CBZ represent comedications of oxcarbazepine, sodium valproate and carbamazepine, respectively; these variables (comedication) take a value of 0 when absent and 1 when the drug is administered simultaneously with perampanel. LGBW is the log value of body weight. The detailed parameter estimates of the final model are shown in Table 2.

Model Validation

The final model was evaluated via GOF plots and bootstrap analysis. The GOF plots revealed acceptable visual bias (Figure 1). The parameter estimates of 1000 bootstrap runs of the final model are presented in Table 2, which are close to the final model estimates and indicate the robustness of the final model. VPC result was shown in Figure S1, which also indicated that the model was reliable.

Simulation and Dosing Regimen Optimization

Table 3 shows the simulated mean steady-state plasma trough concentrations of perampanel for each daily dose simulated according to age and body weight, as well as the coadministration regimens. The mean steady-state plasma trough

Table 2 Final Model Estimation Parameters and Bootstrap Analysis results

Parameter	Final Model			Bootstrap Analysis				
	Estimate	SE	[RSE (%)]	Median estimate	SE	[RSE (%)]	2.5% CI	97.5% CI
CL/F (L/h)	0.177	0.0269	15.2	0.177	0.0271	15.3	0.130	0.234
V (L)	227	31.9	14.1	226	62.3	27.5	95.9	362
KA[a]	3.37 FIXED	/	/	3.37 FIXED	/	/	/	/
AGE	1.31	0.186	14.2	1.31	0.186	14.2	0.975	1.68
Oxcarbazepine	1.51	0.181	12.0	1.51	0.190	12.5	1.23	1.98
Sodium valproate	0.745	0.0590	7.92	0.743	0.0614	8.27	0.638	0.883
Carbamazepine	1.88	0.306	16.3	1.90	0.358	18.8	1.44	2.77
ωCL	0.0963		20.2	0.0920	0.0197	21.4	0.0552	0.133
σ	0.130		11.4	0.129	0.0145	11.3	0.102	0.159

Notes: The success rate was calculated as 99.8% (998/1000). [a] KA was fixed referred to[20] Fujita Y et al. Ther Drug Monit. 2023;45(5):653–659.
Abbreviations: CL/F, typical apparent clearance; V, typical apparent volume distribution; KA, the first-order rate constant of absorption; ω, interindividual variance for CL; σ, residual variability for proportional error; SE, standard error; RSE, residual standard error; CI, confidence interval.

concentrations in patients not coadministered EIASMs were within the therapeutic range when the perampanel dose range was 2–6 mg/d. For a daily dose of 4 mg, all simulation scenarios reached the effective concentration range. The combined use of sodium valproate reduces perampanel clearance with a greater probability of being above the therapeutic range. For patients aged under 4 years, a daily dose of 2 mg seems to be appropriate from the perspective of plasma concentration.

Discussion

This retrospective study successfully developed a PPK model for perampanel in pediatric patients. The pharmacokinetics of perampanel were described by a single-compartment model of first-order absorption and elimination, which included age, body weight, concomitant medication, and hepatic function as covariates. This result could be helpful for dosing optimization in pediatric patients receiving perampanel, especially those aged under 12 years.

Pediatric patients of different ages have distinct physiological characteristics and drug in vivo. Compared with other available PPK models, we found that this is the only model that includes a majority of patients aged under 12 years. Renfroe et al developed a PPK in pediatric patients via pooled Phase II and III data.[21] This model included 194 patients, but only 41 were aged under 12 years. The median weight was 49.2 kg, with a range of 12.2–121 kg. Takenaka et al developed a PPK model on the basis of data from 1318 patients, of whom only 210 patients were aged 12–18 years.[16] Fujita et al developed a PPK model for full ages (0–76 years). However, the sample size was limited (64 patients). The number of pediatric patients in this model is unclear, but the median weight was 50.3 kg, which was closer to that of adults. Thus, these results would be less informative for young children.[20] Recently, Li et al published a PPK model focused on pediatric patients. However, the median age and body weight in our study were lower than those in Li's model, which made our model more informative for young pediatric patients.[14] We also included a small portion of patients aged 12–18 years for broader pediatric modeling.

The typical CL/F in our population was 0.177 L/h, which is approximately 50–70% lower than the typical CL/F estimated by Villanueva et al[15] (0.729 L/h) and Takenaka et al[16] (0.668 L/h) and Silva et al[22] (0.419 L/h). This is due to the expression style of the covariate of age. When the median age was used, the typical CL/F was 0.439 L/h, which was close to the reported estimates.

Owing to the large variability of covariates in pediatric patients, we transformed the covariates according to degree of variation. Age was linearly centralized, and body weight was log-transformed and then successfully included in the final model of perampanel in this study. Age is the only physiological parameter that serves as a covariate for CL/F. Li et al's model included body weight as a covariate for CL/F.[14] We believe that these results are in accordance with our findings, as age and body weight are always linearly related in pediatric patients. Other models focused on adults or patients over 12 years of age did not include age or weight as covariates, possibly because of the distribution of patient characteristics.[16,20,21] Clearly, V is affected by body weight, and the influence of body weight on V is not negligible

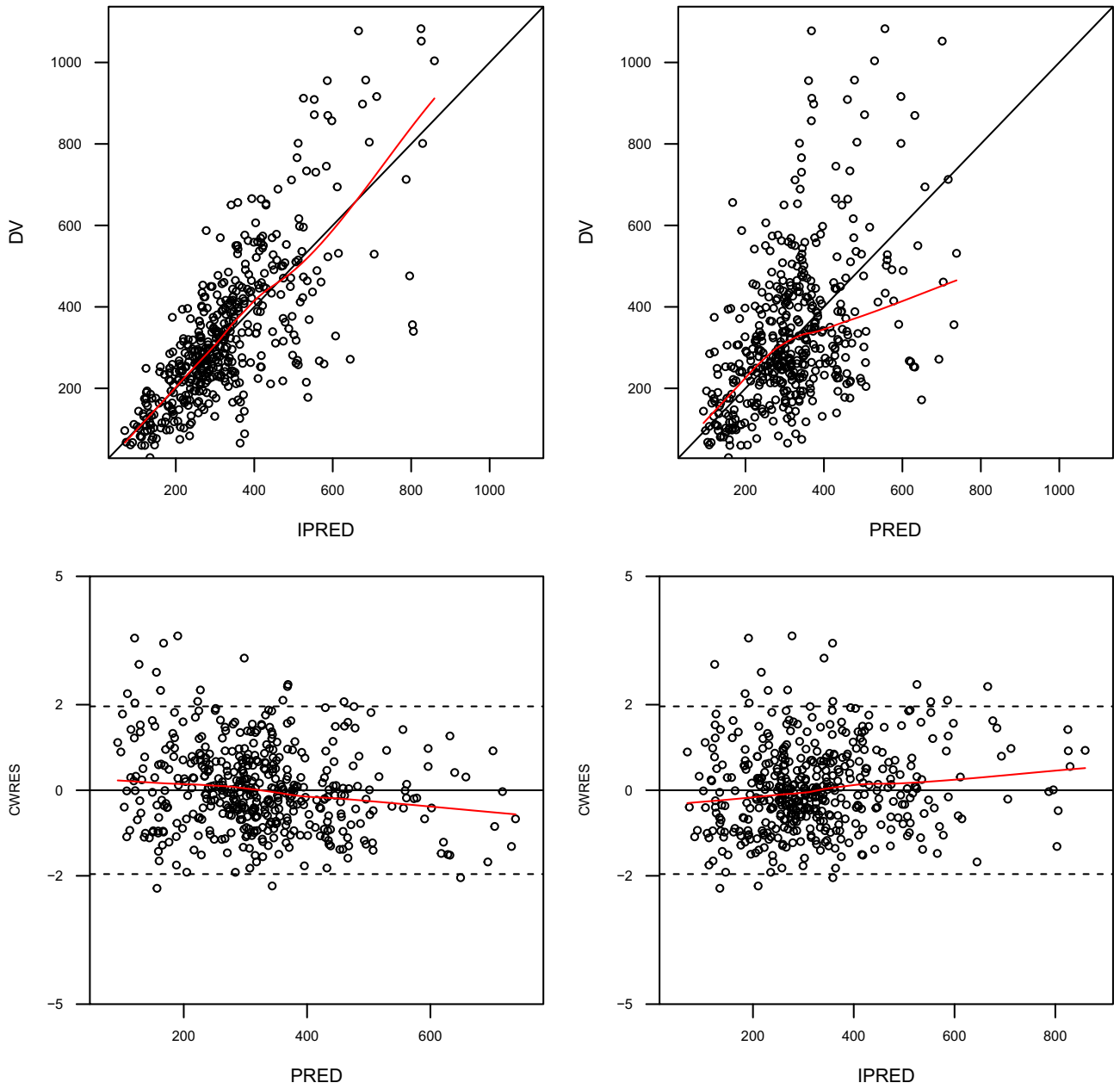

Figure 1 Goodness-of-fit figures for the final PPK model of perampanel.

in pediatric patients. Owing to the simple nature of current studies, it is difficult to estimate the interindividual viability of V. Some models have fixed V to a reported value or included no covariate on V.[14,16,20,21] This approach may be suitable for adult models but is inappropriate for pediatric patients. The Vs of patients aged under 4 years and those aged over 12 years are clearly different. Our study included log-transformed body weight as a covariate for V, which is reasonable and suitable for pediatric patients. This result is supported by published models.[22]

The interaction between ASMs is an important factor affecting the pharmacokinetics of perampanel. In this study, we found that combining oxcarbazepine and carbamazepine increased the CL/F of perampanel and that combining sodium valproate decreased the CL/F of perampanel. The reason is that perampanel is metabolized predominantly by the cytochrome P450 (CYP) isoform CYP 3A4/5,[23–26] and its clearance could be affected by ASMs (and other drugs) that can inhibit or induce CYP3A4/5, which has been extensively characterized and reported in PK analyses in epilepsy patient populations.[27–29] Oxcarbazepine and carbamazepine are strong CYP3A4 enzyme inducers that significantly

Table 3 Median Steady-State Plasma Concentrations (ng/mL) at Different Daily Doses of Perampanel Simulated According to Age, Body Weight and Co-Administration

AGE	DOSE mg/d	Without					With oxcarbazepine					With carbamazepine					With Sodium valproate				
		BW					BW					BW					BW				
		10 kg	20 kg	30 kg	40 kg	50 kg	10 kg	20 kg	30 kg	40 kg	50 kg	10 kg	20 kg	30 kg	40 kg	50 kg	10 kg	20 kg	30 kg	40 kg	50 kg
2	2	321	314	/	/	/	212	208	/	/	/	171	167	/	/	/	430	422	/	/	/
	4	641	637	/	/	/	425	422	/	/	/	341	339	/	/	/	860	855	/	/	/
	6	955	940	/	/	/	632	623	/	/	/	508	500	/	/	/	1282	1262	/	/	/
	8	1259	1236	/	/	/	834	819	/	/	/	670	658	/	/	/	1690	1659	/	/	/
	10	1599	1591	/	/	/	1059	1054	/	/	/	851	846	/	/	/	2147	2136	/	/	/
	12	1888	1918	/	/	/	1251	1270	/	/	/	1005	1021	/	/	/	2535	2575	/	/	/
4	2	261	263	260	254	256	173	174	172	168	169	139	140	138	135	136	351	353	348	340	343
	4	512	502	510	510	506	339	332	338	338	335	273	267	271	271	269	688	673	684	684	680
	6	764	771	764	785	766	506	511	506	520	507	407	410	406	418	408	1026	1035	1025	1054	1028
	8	1018	1040	1023	1010	1029	674	689	678	669	681	542	553	544	537	547	1366	1395	1373	1356	1381
	10	1299	1272	1289	1286	1297	860	842	853	852	859	691	677	686	684	690	1743	1707	1730	1726	1741
	12	1537	1549	1524	1544	1568	1018	1026	1010	1022	1039	818	824	811	821	834	2063	2079	2046	2072	2105
12	2	142	144	142	140	146	94	95	94	93	97	75	77	75	74	78	190	193	190	187	196
	4	283	276	285	282	283	188	183	189	187	188	151	147	152	150	151	380	370	383	378	380
	6	426	423	421	423	415	282	280	279	280	275	227	225	224	225	221	572	568	564	568	558
	8	575	565	576	564	569	381	374	382	373	377	306	301	306	300	303	771	758	773	756	764
	10	714	709	695	711	702	473	470	461	471	465	380	377	370	378	373	959	951	933	955	942
	12	852	845	839	847	848	564	559	556	561	562	453	449	446	451	451	1143	1134	1126	1137	1138
18	2	/	/	/	103	103	/	/	/	68	69	/	/	/	55	55	/	/	/	139	139
	4	/	/	/	209	210	/	/	/	139	139	/	/	/	111	112	/	/	/	281	282
	6	/	/	/	309	307	/	/	/	204	203	/	/	/	164	163	/	/	/	414	412
	8	/	/	/	422	423	/	/	/	279	280	/	/	/	224	225	/	/	/	566	568
	10	/	/	/	515	514	/	/	/	341	340	/	/	/	274	273	/	/	/	691	689
	12	/	/	/	616	617	/	/	/	408	409	/	/	/	328	328	/	/	/	827	828

Notes: Dose regimen with percentage of target concentration attainment over 90% (therapeutic range of 100–1000 ng/mL) are shown with green background. Median concentration out of the range are shown in brown background. Others are shown in white back ground.

increase perampanel clearance, which is consistent with previous studies.[23,30,31] Sodium valproate, an enzyme-inhibiting antiepileptic drug, was previously shown to affect the pharmacokinetics of perampanel, which is consistent with the findings of a published study.[32]

De Liso et al suggested that the optimal pediatric dosage range for perampanel is 4–12 mg/d, with 8 mg/d most often used.[7] US approval of perampanel was based on the results of three multicenter, double-blind, randomized, parallel-group, placebo-controlled Phase III studies at doses of 2, 4, 8 and 12 mg.[33–35] The incidence and severity of adverse events (including psychiatric symptoms) can be reduced by starting at a low dose and titrating slowly.[7,36] The International League Against Epilepsy and International Consensus Guidelines recommend a therapeutic window for perampanel of 180–980 ng/mL.[11,37] The Norwegian Clinical Pharmacology Association has newly established a treatment range of 100–1000 ng/mL.[19] Therefore, until more clinical information was available, a wider range of 100–1000 ng/mL was used in this study as the optimal concentration range for perampanel treatment. To achieve blood levels within the therapeutic range, a maintenance dose of 4 mg per day is recommended for pediatric patients who are not coadministered other ASMs. On the other hand, a daily dose of 2 mg is suitable for patients aged under 4 years.

This study had several limitations. Owing to the retrospective, observational nature of this study, some bias may exist. There is no absorption constant available for pediatric patients, and an adult constant was applied in modeling. In addition, the limited sample size hindered comparisons between groups of patients who received perampanel and those who received each type of ASM. Epilepsy types were not included in the analyses. Finally, this model lacks a large number of patients for external validation, which is needed in the future.

Conclusions

A PPK model of perampanel for pediatric patients with epilepsy has been successfully developed. This model included linear centralized age and comedication as covariates for CL/F and log-transformed body weight as covariates for V. This result would be helpful for dosing optimization in pediatric patients receiving perampanel, especially those aged under 12 years.

Data Sharing Statement

All the data are within the manuscript, and further inquiries can be directed to the corresponding authors (Zhenwei Yu and Haibin Dai).

Ethics Approval Statement

Ethics approval was obtained from the ethics committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University (reference number 2024-0117). This study complied with the Declaration of Helsinki. Patients' personal information was accessible only to authorized investigators and was not disseminated.

Patient Consent Statement

The requirement for obtaining informed consent from the patients was waived as a part of the ethical approval because of the retrospective nature of the study.

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Disclosure

The authors report no conflicts of interest in this work.

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