Chapter 12
Drug Concentration Monitoring

CQ 12-1

When should serum concentrations of antiepileptic drugs be monitored?

Summary

Measurement of serum concentrations of antiepileptic drugs is useful for the following purposes: (1) to establish individual therapeutic ranges when the desired seizure control is obtained; (2) to diagnose adverse effects; (3) to evaluate adherence at the time of poor seizure control or breakthrough seizure; (4) to adjust doses in situations of pharmacokinetic changes (such as in children, elderly patients, comorbid disorders, and change in dosage form); (5) to adjust doses when change in pharmacokinetics is predicted (such as during pregnancy and addition or removal of drugs having interactions); and (6) to adjust doses of drugs having dose-dependent pharmacokinetics (particularly phenytoin).

Comment

Monitoring serum concentrations of antiepileptic drugs is useful in deciding patient's medication regimen, if monitoring is done for a clear purpose and the results are interpreted properly along with other clinical factors. Serum concentrations of antiepileptic drugs should not be monitored routinely without intended purposes. However, they should be measured when there are clinical needs (**Table 1**)[1].

The reference range of serum concentrations of a certain drug is not the same as its therapeutic range. The lower limit of the reference range of serum concentrations is the concentration being more likely to produce an insufficient therapeutic effect, and the upper limit is the concentration being more often associated with adverse effects. That is, the serum concentrations of antiepileptic drugs within the reference range (so-called effective serum concentrations) indicate that they are expected to be effective with fewer adverse effects in most of the patients[1].

The therapeutic range of serum concentrations for a certain patient is the range within which that patient has the best seizure control. In most of the patients, the therapeutic range is within or overlaps with the reference range. However, treatment may be effective even when the serum concentration is lower than the reference range in some cases, or conversely may be effective only when the concentration is higher than the reference range in other cases, because of large inter-individual variability of the therapeutic range. Therefore, it is important to know the therapeutic range for each patient. The dose should not be increased if the patient remains seizure-free at serum concentration lower than the reference range. On the other hand, the dose might be increased to above the reference range if the patient has residual seizures without any adverse effects. The reference range of serum concentration differs depending on age, epilepsy syndrome, and seizure type[1, 2].

The reference range is determined based on the lowest serum concentration (the trough value, which is measured before drug taking in the morning). However, it is difficult to measure the trough value in outpatient clinic, and serum concentration measured at our clinics is usually higher than the trough. Therefore, it is not a concern if the measured value exceeds the upper limit of the therapeutic range. We should interpret the blood concentration considering the blood sampling time, the drug taking time, and the time of maximum concentration (T_{max}) of each drug (**Table 1** in CQ 12-2 on page 104).

Antiepileptic drug exists in two forms in the blood: a protein-bound form and a free form. In patients with hypoproteinemia, pregnancy, hepatic disorders or renal disorders, the amount of drug in the free form is larger than that in healthy subjects even when the measured serum concentration is the same, and the efficacy and adverse effects are not the same as in normal controls. Although the free form possesses antiepileptic effect, measurement of free form is not covered by medical insurance. In general, the total serum concentrations of antiepileptic drugs, including both protein-bound form and free form, are measured and recorded.

References

1) 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): 1239-1276.
2) Johannessen SI, Patsalos PN. Individual approach to laboratory monitoring of antiepileptic drugs. In: Wyllie E, Gidal BE, Goodkin HP, et al eds. Willie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.568-573.

Table 1. General indications for monitoring blood concentrations of antiepileptic drugs.

1. After initiation of treatment or after dose adjustment, when the clinician decides to aim at a target concentration for that patient.
2. Once the desired seizure control state has been achieved, to establish the "individual therapeutic range."
3. To determine the magnitude of a dose increase, particularly with antiepileptic drugs showing dose-dependent pharmacokinetics (most notably, phenytoin).
4. When there are uncertainties in the differential diagnosis of signs or symptoms suggesting drug-related adverse reaction, or when adverse effect is difficult to assess clinically (young children, patients with mental disability).
5. When seizures persist despite an adequate dosage.
6. When change in pharmacokinetics (consequently, required dose also change) is suspected, due to age, pregnancy, comorbidity, or drug interaction.
7. To assess changes in steady state drug concentration when a change in drug formulation or change to generic formulation is made.
8. When there is an unexpected change in clinical response.
9. To conform adherence when poor compliance is suspected.

(Modified from: 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: 1276.)

CQ 12-2

Serum concentration monitoring is useful for which drugs?

Summary

The reference ranges of serum concentrations have been established for carbamazepine, phenytoin, phenobarbital, primidone, valproate, and ethosuximide. Serum concentration monitoring is useful for these drugs. However, for some other drugs, the serum concentration monitoring is not very useful because the reference ranges have not determined for them or they show remarkable fluctuations in serum concentration (Tables 1 and 2)[1-5].

Comment

Because there are large interindividual variabilities in epileptogenesis and response to a given antiepileptic drug, it is difficult to find a general therapeutic range of serum concentrations applicable to all patients. However, it is known that there exists a range of serum concentrations at which seizures are controlled and dose-dependent adverse effects are rarely seen in most of the patients. This range is called the "reference range" (so-called effective blood concentration).

Even for drugs with no established general reference ranges, serum concentration measurement is useful for comparisons within an individual patient. Benzodiazepines play a role as an anti-convulsant by binding with benzodiazepine receptors in the brain. Because the number of benzodiazepine receptors varies from person to person, it is difficult to determine the reference blood concentration range for all persons. The reference ranges for clobazam, nitrazepam and diazepam have not been reported. However, repetitive serum concentration measurements in one patient are useful for monitoring adverse effects such as drowsiness in that patient.

Phenytoin is a drug showing big fluctuations in serum concentration, which requires attention. Because of the non-linear relationship between dosage and serum concentration and the narrow therapeutic window, measurement of serum concentration is critical for setting the optimal dosage. Especially, a rapid rise in serum concentration occurs at high doses[1]. The serum concentration of lamotrigine decreases drastically when used concomitantly with enzyme-inducing drugs (phenytoin, carbamazepine, phenobarbital, and primidone), increases greatly when used in combination with valproate, and declines significantly during pregnancy. Serum level of carbamazepine decreases within 1–3 months after start of treatment, due to enzyme self-induction. Therefore, serum concentration has to be monitored shortly after treatment initiation.

■ References

1) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.376-700.
2) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015, p.593-768.
3) Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.
4) Drugs in Japan Forum, ed. Drugs in Japan: Ethical Drugs 2016 Edition. Tokyo: Jiho Inc., 2015 (in Japanese).
5) Johannessen SI, Johannessen-Landmark C, Perucca E. Pharmacokinetic optimization of therapy. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.124-138.

Table 1. Therapeutic ranges of blood levels and pharmacokinetics of major antiepileptic drugs.

Generic name (abbreviation)		Maintenance dose[a]		Dose increase range		Blood conc. reference range[b] (μg/mL)	$T_{1/2}$: elimination half-life[c] (h)			T_{max}: peak time[c] (h)	
							Adult		Child		
		Adult (mg)	Child (mg/kg)	Adult (mg)	Child (mg/kg)		mono-therapy	with enzyme inducer[d]		Adult	Child
Phenobarbital	PB							almost unchanged			
Primidone	PRM										
Carbamazepine	CBZ						10–26[e]				
Phenytoin[f]	PHT							almost unchanged			
Valproate	VPA										
sustained release	VPA-R									7.5–16[g]	
Ethosuximide	ESM										
Clonazepam	CZP										
Nitrazepam	NZP										
Clobazam	CLB										
N-desmethyl	CLB[h]										
Acetazolamide	AZM										
Potassium bromide	KBr						10–13 days		5–8 days		
Gabapentin	GBP										
Topiramate	TPM										
Lamotrigine[i] (1) with VPA (2) with enzyme inducer[d] (3) with (1) and (2)	LTG										
Levetiracetam[j]	LEV										
Rufinamide	RFN[k]	by weight	by weight								
Stiripentol	STP										
Vigabatrin	VGB										
Perampanel	PER[l]		8–12[l]								
Lacosamide[m]	LCM		200–400[m]								

a: In children, the younger the age, the higher the dose per kg body weight is required to obtain a given blood concentration, the maintenance dose is higher, and half-life and peak time are shorter. In adolescents, pharmacokinetics are almost the same as adults.

b: If effective, blood concentration can stay low, or can be increased to higher than the therapeutic range as long as there is no adverse effect.

c: This is the time for the concentration to decrease by half from the peak. The time until blood concentration decreases by one-half after administration is peak time + half-life. Half-life and peak time are in principle determined for monotherapy with drug taking after meal. In combination therapy, half-life is shortened when the combination lowers blood level through interaction, and is prolonged when the combination increases blood concentration (see "Interaction" in CQ 12-4 on page 109). Peak time is shortened significantly with drug is taken when fasting.

d: Enzyme-inducing drugs: PB, PRM, CBZ and PHT. Increase drug metabolism in the liver, concomitant use shortens half-life of original drug.

e: Value at the time when self-induction is completed (3–4 weeks after starting)

f: For PHT, the higher the blood level, the longer is the half-life. L: low dose (blood level around 5 μg/mL), H: high dose (blood level 10 μg/mL or above)

g: Peak time of VPA sustained release preparation varies depending on the dosage form: 5 to 10 h for Selenica® R fine granule, 7.5 to 10 h for Depakene® R tablet, and 13 to 16 h for Selenica® R tablet.

h: N-DMCLB is a metabolite of CLB. N-DMCLB has anticonvulsive action of approximately 1/4 strength of that of CLB. When classified by CLB:N-DMCLB concentration ratio into three groups of approximately 1:2–3 (10% of the subjects), around 1:10 (80%), and around 1:50–100 (10%), drowsiness occurs at a higher rate as the CLB:NDMCLB concentration ratio increases.

i: In Japan, monotherapy use is approved only for partial seizure (including secondarily generalized seizures) and tonic clonic seizure in 16 year-old and above. To prevent rash (especially Stevens–Johnson syndrome), follow the instructions in the package insert concerning the initial dose, the dose increase range and the maximum dose of LTG.

j: Monotherapy use only for 4 year-old and above with partial seizure.

k: Covered by insurance for 4 year-old and above. Starting dose to maximum dose is as follows: 15 to < 30 kg in weight: 200–1,000 mg, 30 to < 50 kg: 400–1,800 mg, 50 to < 70 kg: 400–2,400 mg, ≥ 70 kg: 400–3,200 mg. Dose increase range is: 15 to < 30 kg: ≤ 200 mg, and ≥ 30 kg: ≤ 400 mg. Official abbreviation is undecided and RUF is also commonly used.
l: Covered by insurance for 12 year-old and above. Official abbreviation is undecided and PRP is also commonly used.
m: Covered by insurance for 6 year-old and above.

(Compiled from: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds.: Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015, p.593–768. / Patsalos PN, Bourgeois BFD: The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010. / Drugs in Japan Forum, ed. Drugs in Japan: Ethical Drugs 2016 edition. Tokyo: Jiho Inc., 2015.)

Table 2. Usefulness of measuring blood concentration.

Usefulness	Antiepileptic drugs
Very useful	Phenytoin, lamotrigine
Useful	Carbamazepine, phenobarbital, valproate, rufinamide, perampanel
Useful to certain extent	Primidone, ethosuximide, zonisamide, topiramate
Limited or undetermined	Clonazepam, clobazam, diazepam, nitrazepam, acetazolamide, gabapentin, levetiracetam, potassium bromide, stiripentol, vigabatrin, lacosamide

(Compiled from: Johannessen SI, Johannessen-Landmark C, Perucca E. Pharmacokinetic optimization of therapy. In: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 4th ed. Chichester: Wiley Blackwell, 2015, p.124–138.)

CQ 12-3

Is serum concentration monitoring a requisite in the treatment of patients with hepatic or renal dysfunction?

Summary

Since the pharmacokinetics of antiepileptic drugs may alter in patients with hepatic or renal dysfunction, conduct treatment based on serum concentrations of drugs. Dialysis reduces serum drug concentrations.

Comment

Antiepileptic drugs are mainly metabolized by the liver and excreted by the kidney. But the ratio of hepatic metabolism and renal excretion varies depending on the drug. In patients with liver or kidney disorders, pay attention to the increase in serum concentrations of antiepileptic drugs, bearing in mind the metabolism and excretion routes and the ratio of hepatic metabolism and renal excretion for each drug. Then, the doses should be reduced if necessary. For drugs that are metabolized by the liver, serum concentrations do not change markedly in acute hepatitis since metabolic enzymes do not decrease, but serum concentrations rise in cirrhosis because metabolic enzyme and hepatic blood flow are both reduced. In patients treated with hemodialysis, the blood levels of some drugs decrease, therefore consider dose increment[1] (**Table 1**)[2-4].

References

1) Singh G. Management of medical comorbidity associated with epilepsy. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.245-258.
2) Spina E, Italiano D. Drug interactions. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2016. p.344-359.
3) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700.
4) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768.

Table 1. Metabolic and excretion routes of major antiepileptic drugs, and dose adjustment of antiepileptic drugs in the case of hepatic and renal impairment.

	Hepatic metabolism (%)	Renal excretion (%)	Adjustment during liver impairment	Adjustment during kidney impairment
Phenytoin	90	< 2	Dose reduction	No need
Carbamazepine	90	< 1	Dose reduction	No need
Valproate	85	< 5	Dose reduction	No need
Phenobarbital	55	25	Slight dose reduction–No need	Slight dose reduction
Primidone	45–60	20–25	Slight dose reduction–No need	Slight dose reduction
Clobazam	> 90	< 1	Dose reduction	No need e
Clonazepam	> 90	< 1	Dose reduction	No need
Zonisamide	70	< 30	Dose reduction	Slight dose reduction
Ethosuximide	70	20	Dose reduction	No need
Potassium bromide	0	100	No need	Dose reduction
Gabapentin	0	100	No need	Dose reduction
Topiramate	< 25	75	No need	Dose reduction
Lamotrigine	90	10	Dose reduction	No need
Levetiracetam	< 3	70	No need	Dose reduction
Rufinamide	85	2	Dose reduction	No need
Stiripentol	75	25	Dose reduction	No need
Vigabatrin	10	90	No need e	Dose reduction
Perampanel	70	30	Dose reduction	No need
Lacosamide	30	40	Dose reduction	Slight dose reduction

(Compiled from: Spina E, Italiano D. Drug interactions. In: Shorvon S, Perucca E, Engel J Jr. eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2016. p.344–359. / Shorvon S, Perucca E, Engel J Jr. eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768.)

CQ 12-4

What are the drugs that interact with antiepileptic drugs?

Summary [1-5)]

When addition or removal of a given non-antiepileptic drug results in an increase in seizures or adverse effects, suspect drug interaction with the antiepileptic drugs being used and consider measurement of serum concentrations of the antiepileptic drugs. Conversely, when an antiepileptic drug is being added or removed, pay attention to the possibility that the therapeutic effects of other drugs may alter, which may result in some changes in comorbid symptoms.

Comment

Drug interactions include interactions between antiepileptic drugs (**Table 1**)[1-3)], interactions between antiepileptic drugs and psychotropic drugs (**Tables 2 and 3**)[1-5)], and interactions between antiepileptic drugs and general drugs other than psychotropic drugs (**Tables 4 and 5**)[1-5)]. Pay special attention when patients are complicated with psychiatric disease or developmental disorder, or elderly people taking various drugs because of comorbidities.

Among antibiotics, clarithromycin and erythromycin inhibit the metabolism of carbamazepine, resulting in a large increase in serum concentration of carbamazepine, causing dizziness, vertigo, and severe drowsiness. Carbapenem antibiotics (panipenem–betamipron, meropen, imipenem–cilastatin, doripenem, biapenem, tebipenem) are contraindicated when taking valproate, as they significantly lower the serum concentration of valproate.

For antithrombotic drugs, warfarin used with phenytoin mutually increase the serum concentrations of each other, and the blood level of rivaroxaban is lowered by carbamazepine, phenytoin or phenobarbital (see CQ 3-8 on page 30).

■ References

1) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700.
2) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768.
3) Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.
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Table 1. Interactions between epileptic drugs.

Added drug	Blood concentration of the original antiepileptic drug																	
	VPA	PB	CBZ	PHT	ZNS	CZP	CLB	ESM	AZM	GBP	TPM	LTG	LEV	RFN	STP	VGB	PER	LCM
VPA		↑↑	↓[a]	↓[b]	↓		↓	↑		→	↓	↑↑	→	↑↑				
PB	↓		↓	→↓	↓	↓	↓	↓		→	↓↓	↓↓	↓	↓↓	↓↓			↓
CBZ	↓↓	↑↓→		↑	↓	↓	↓	↓↓		→	↓↓	↓↓	↓	↓	↓↓	→	↓↓	↓
PHT	↓↓	↑↓	↓↓		↓↓	↓	↓	↓↓		→	↓↓	↓↓	↓	↓↓	↓↓	→	↓↓	↓
ZNS		→	→[c]	→						→		↑						
CZP		→	↓	→						→		→						
CLB	↑↑	↑	↑[d]	↑↑						→		→			↑			
ESM	↓	→	→	↑						→		→						
AZM			↑	↑														
GBP	→	→	→	→	→	→	→	→			→	→	→					
TPM	↓	→	→	↑						→		→		→				
LTG	↓	→	→	→	→	↓	→			→	→		→	→				
LEV	→	→	→	→		→	→			→		→						
RFN	→	↑	↓	↑							→	↓						
STP	↑	↑	↑↑	↑↑			↑↑											
VGB	→	→	→	↓														
PER	→	↓	→	→	→	→	→				→	→	→					
LCM	→		→	→	→					→	→	→	→					

Blood level: ↑ increase, ↑↑ marked increase, ↓ decrease, ↓↓ marked decrease, → unchanged.
In the case of marked increase or marked decrease, consider decrease or increase dose of the original antiepileptic drug.
[a]: Although total concentration decreases, CBZ–epoxide increases and the effect is augmented, no need to increase dose.
[b]: Although total concentration decreases, free drug increases and the effect is augmented, no need to increase dose.
[c]: CBZ-epoxide increases.
[d]: Both CBZ and CBZ-epoxide increase
PRM is metabolized to PB and is the same as PB, therefore is omitted.
(Compiled from: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010)

Table 2. Effects of psychotropic drugs on antiepileptic drugs (AED).

AED	Blood concentration of AED	Psychotropic drugs that influence AED
PB	↑	Tricyclic antidepressant, zotepine, methylphenidate, tetracyclic antidepressant
PRM	↑	Tricyclic antidepressant, zotepine, phenothiazines, methylphenidate
CBZ	↑	Quetiapine, chlorpromazine, paroxetine, haloperidol, fluvoxamine, risperidone
PHT	↑	Tricyclic antidepressant, trazodone, fluvoxamine, methylphenidate, tetracyclic antidepressant
VPA	↑	Chlorpromazine, tricyclic antidepressant, sertraline
CLB	↑	Haloperidol , phenothiazines, fluvoxamine
NZP	↑	Phenothiazines
ZNS	↑	Adverse effects increased by tricyclic antidepressant
	↓	Risperidone
KBr	↑	Phenothiazines (drowsiness, attention, concentration, reduced reflex movement worsened)
LTG	↑	Sertraline
	↓	Olanzapine, risperidone (somnolence enhanced)
TPM	↑	Amitriptyline, lithium

*: Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, and amoxapine. Tetracyclic antidepressants: maprotiline and mianserin. Phenothiazines: chlorpromazine, levomepromazine, fluphenazine, and propericiazine.
**: CZP, AZM, ESM, GBP, LEV, RFN, STP, VGB, LCM: no description.
(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

Table 3. Effects of antiepileptic drugs (AED) on psychotropic drugs.

AED	Blood concentration of psychotropic drugs	Psychotropic drugs that are influenced by AED
PB	↑	Tricyclic antidepressant, zotepine, phenothiazines, tetracyclic antidepressant
	↓	Olanzapine, chlorpromazine, tricyclic antidepressant, paroxetine , haloperidol, tetracyclic antidepressant, risperidone
PRM	↑	Tricyclic antidepressant, zotepine, phenothiazines
CBZ	↑	Lithium
	↓	Aripiprazole, alprazolam, tricyclic antidepressant, sertraline, trazodone, paliperidone, paroxetine, haloperidol , phenothiazines, tetracyclic antidepressant, risperidone
PHT	↑	Tricyclic antidepressant, trazodone, fluvoxamine, tetracyclic antidepressant
	↓	Quetiapine, tricyclic antidepressant, trazodone, paroxetine , tetracyclic antidepressant
VPA	↑	Aripiprazole, chlorpromazine, tricyclic antidepressant, paroxetine
CZP	↑	Effect of phenothiazines enhanced
CLB	↑	Haloperidol, phenothiazines
NZP	↑	Phenothiazines
ZNS	↑	Adverse effects of tricyclic antidepressant increased
KBr	↑	Phenothiazines (drowsiness, attention, concentration, reduced reflex movement worsened↑)
TPM	↑	Amitriptyline, haloperidol, lithium
	↓	Risperidone
RFN	↓	Triazolam

*: Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, and amoxapine. Tetracyclic antidepressants: maprotiline and mianserin. Phenothiazines: chlorpromazine, levomepromazine, fluphenazine, and propericiazine
**: AZM, ESM, GBP, LTG, LEV, STP, VGB, LCM: no description.
(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

Table 4. Effects of general drugs other than psychotropic drugs on antiepileptic drugs (AED).

AED	Blood concentration of AED	General drugs other than psychotropic agents that influence AED
PB	↑	Chloramphenicol, antihistamines (hydroxyzine, diphenhydramine), selegiline
	↓	Antacid
	contraindicated	In the case of PB elixir: cyanamide, disulfiram (enhance alcohol reaction)
PRM	↑	Selegiline, antihistamines
CBZ	↑	Azole antifungals (including miconazole, fluconazole, and itraconazole), isoniazid, omeprazole, Ca channel blockers (including verapamil, amlodipine, nifedipine, and benidipine), quinupristin/dalfopristin, chloramphenicol, salicylic acid, ciprofloxacin, cimetidine, diltiazem, sulfamethoxazole-trimethoprim, selegiline, danazol, darunavir , telaprevir, bicalutamide, verapamil, macrolide antibiotics (including erythromycin, clarithromycin, and josamycin), ritonavir
	↓	Aminophylline, efavirenz, antacid, theophylline, rifampicin
PHT	↑	Azole antifungals (including miconazole, fluconazole, itraconazole, and voriconazole), amiodarone, aminophylline, allopurinol, isoniazid, omeprazole, chloramphenicol, cyclosporine, disulfiram, cimetidine, diltiazem, sulfamethoxazole-trimethoprim, tacrolimus, ticlopidine, theophylline, nelfinavir, para-amino-salicylic acid, fluorouracil-based preparations (including tegafur preparations and doxifluridine), fosfluconazole, warfarin
	↓	Aminophylline, salicylic acid, diazoxide, cisplatin, theophylline, nelfinavir, pyridoxine, vinca alkaloids (including vincristine), rifampicin
VPA	↑	Isoniazid, salicylates (including aspirin), cimetidine, macrolide antibiotics (including erythromycin, clarithromycin, and josamycin)
	↓	Carbapenem antibiotics (panipenem-betamipron, meropen, imipenem-cilastatin, doripenem, biapenem, tebipenem), cholestyramine, cisplatin, naproxen, methotrexate, rifampicin
ESM	↑	Isoniazid
	↓	Rifampicin
CZP	↑	Selegiline
CLB	↑	Cimetidine, drugs metabolized by CYP3A4 (including rifampicin), CYP3A4 inhibitors (including ritonavir, corticosteroid preparations, and macrolide antibiotics), selegiline
NZP	↑	Cimetidine, selegiline
AZM	↑	High-dose aspirin
	↓	Ammonium chloride
GBP	↑	Cimetidine, naproxen, morphine
	↓	Antacid (aluminum hydroxide, magnesium hydroxide)
TPM	↑	Hydrochlorothiazide
LTG	↓	Acetaminophen, atazanavir, oral contraceptives (including ethinylestradiol and norethisterone), ritonavir, rifampicin, lopinavir-ritonavir combination
PER	↑	Ketoconazole

*: ZNS, KBr, LEV, RFN, STP, VGB, LCM: no description.
**: Underlined parts denote concomitant use contraindicated.
(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

Table 5. Effects of antiepileptic drugs (AED) on general drugs other than psychotropic drugs.

AED	Blood concentration of general drugs	General drugs other than psychotropic agents that are influenced by AED
PB	↑	Including thiazide hypotensive diuretics (orthostatic hypotension↑), selegiline, antihistamines (hydroxyzine, diphenhydramine)
	↓	Azelnidipine, aminophylline, imatinib, irinotecan, HIV protease inhibitors (including indinavir, saquinavir, nelfinavir, and lopinavir), chloramphenicol, cyclosporine, tacrolimus, theophylline, doxycycline, PDE5 inhibitors (sildenafil, tadalafil, vardenafil), felodipine, corticosteroids (including dexamethasone), flecainide, verapamil, voriconazole, montelukast etc., estrogen-progestogen preparations (including norgestrel and ethinylestradiol), rivaroxaban, warfarin
PRM	↑	Antihistamines, thiazide hypotensive diuretics (including trichlormethiazide) (orthostatic hypotension↑), selegiline
	↓	Doxycycline
CBZ	↑	Isoniazid (enhance hepatoxicity), cyclophosphamide, selegiline
	↓	Acetaminophen, aprepitant, aminophylline, albendazole, alprazolam, itraconazole, HIV protease inhibitors (including saquinavir, indinavir, nelfinavir, and lopinavir), etravirine, efavirenz, eplerenone, eletriptan, ondansetron, caspofungin, anticancer drugs (axitinib, irinotecan, imatinib, gefitinib, sunitinib, sorafenib, dasatinib, tamibarotene, temsirolimus, toremifene, nilotinib, lapatinib), dienogest, digoxin, dihydropyridine calcium antagonists (including nifedipine, felodipine, and nilvadipine), sildenafil, solifenacin, tadalafil, dabigatran etexilate, theophylline, telaprevir, doxycycline, donepezil, tramadol, nondepolarizing muscle relaxant (including vecuronium), corticosteroids (including prednisolone and dexamethasone), buprenorphine, praziquantel, flecainide, fosaprepitant, voriconazole, maraviroc, mirabegron, meglumine, immunosuppressants (cyclosporine, tacrolimus, everolimus), estrogen-progestogen preparations, rivaroxaban, rilpivirine, warfarin
PHT	↑	Warfarin
	↓	Azelnidipine, aminophylline, itraconazole, imatinib, irinotecan, indinavir, ondansetron, quinidine, hypoglycemic agents (insulin, oral hypoglycemic agents), thyroid hormone preparations (including levothyroxine), saquinavir, cyclosporine, disopyramide, tacrolimus, tadalafil, theophylline, deferasirox, doxycycline, nisoldipine, nifedipine, nelfinavir, nondepolarizing muscle relaxant (including vecuronium and pancuronium), PDE5 inhibitors (tadalafil, sildenafil, vardenafil), felodipine, corticosteroids (including dexamethasone), praziquantel, flecainide, verapamil, voriconazole, mexiletine, estrogen / gestagen preparations (including norgestrel and ethinylestradiol), rivaroxaban, warfarin
VPA	↑	Warfarin
CZP	↑	Selegiline
CLB	↑	Drugs metabolized by CYP3A4 (including rifampicin), selegiline
NZP	↑	Selegiline
AZM	↑	ACTH, antihypertensive drugs, digitalis preparations (digoxin)
TPM	↑	Metformin
	↓	Oral contraceptives (including ethinylestradiol and norethisterone), digoxin, pioglitazone
LTG	↑	Oral contraceptives (including ethinylestradiol and norethisterone)
	↓	Oral contraceptives (including ethinylestradiol and norethisterone)
RFN	↓	Oral contraceptives (including ethinylestradiol and norethisterone)
PER	↓	Oral contraceptives (including ethinylestradiol, and norethisterone)

*: ZNS, ESM, KBr, LEV, STP, VGB, LCM: no description. However, STP has potent inhibitory effect on drug metabolic enzymes in the liver, and may increase the blood concentrations of various drugs.
**: Underlined parts denote concomitant use contraindicated.
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