

CLINICALLY SIGNIFICANT PHARMACOKINETIC INTERACTIONS OF ANTIEPILEPTIC DRUGS

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Antiepileptic drugs show clinically significant interactions among themselves as well as with other medications, because of a specific pharmacokinetic profile and relatively small therapeutic spectrum. The most significant clinical interactions of AE occur during their metabolism and distribution. In the combined antiepileptic therapy, it is very important to know the order of application of AE because of their influence on liver enzymes and the affinity to attach to plasma proteins. The AE with shorter half-time elimination have a greater potential for interaction which is why therapy monitoring is recommended. Populational pharmacokinetic analysis can provide significant information concerning interactions of AE with other medications. Vulnerable, pediatric population is under a special risk of developing interactions alongside patients with liver and kidney function damage. *Acta Medica Medianae 2007;46(4):55-60.*

Key words: *pharmacokinetic interactions, antiepileptic drugs, interaction potential, clinical significance*

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Introduction

Antiepileptic drugs show clinically significant interactions both with each other and with other medications, because of the specific pharmacokinetic profile and relatively narrow therapeutic range (1,2).

Interactions of antiepileptic drugs (AE) need special attention since the treatment of epilepsy is long lasting and frequently life-long (2). Even though monotherapy is applied, it is often necessary to combine antiepileptic drugs for the reason of controlling the disease itself, AE characteristics and patient specific features. Sometimes it is indicated that epileptic patients take other medications because of the accompanying diseases and states.

Unpredicted changes of the patient's clinical condition with the controlled dosage are mainly caused by the occurrence of interactions. Clinically significant interactions of AE suggest change in the dosage procedure in order to gain and/or reduce toxic effects of medications that often require therapeutic monitoring. Pharmacokinetic

interactions of AE are mainly quantitative and easily predictable. They occur in locations of pharmacokinetic processes and are always followed by changes in the plasma concentration of medications. Compared to pharmacodynamic interactions, they are more studied and more easily identified and quantified (2,3).

Pharmacokinetic processes significant for interaction occurrence

Absorption

Absorption includes releasing a medication from its therapeutic form, its dissolving and entrance into system circulation (3). Medications that influence gastro kinetics also change antiepileptic kinetics. For example, metoclopramide and cisapride accelerate, while propanterol slows down a gastric discharge, change the time needed for release and dissolve medicine from its therapeutic form (4,5). Laxatives shorten transitory time of antiepileptics through the digestive tract, reduce absorption and concentration of the medication in the plasma. Cytostatics damage cells of the intestines, change their flora and reduce absorption of AE (5). The influence of quantity and consistence of gastrointestinal fluid, presence of food, or patient's general condition should not be neglected. Primarily, the presence of the solid food increases gastric circulation and slows down intestinal mobility while the liquid food shows the opposite effect (6). The process of absorption of AE is also influenced by their pharmaco – technological form.

Distribution

Distribution is the process of a medication transfer from the system circulation to utilization location. Amount of distribution of the medication determines its dispersion in the bodily fluids. In the course of the medication distribution, the most prominent are reactions of competitive inhibition of bonding to plasma proteins (Table 1). Most antiepileptics are bonded in blood plasma to albumins and d - glyco protein (6). When the binding of AE is significant (over 90 %), presence of another medication with greater affinity can immensely increase or decrease its plasma concentration, which is the reason why these interactions are of great importance. They can often be predicted and avoided owing to the knowledge of pharmacokinetic characteristics of a medication. For example, vigabatrin combined with phenitoin reduces its bonding to plasma proteins to 30 % and increases the free fraction of phenitoin (79). During the reduction of the medication with a reduced capability of bonding to plasma proteins from the medication-protein complex, its free fraction and clearance increase.

Metabolism

Clinically most significant interactions of AE occur during their metabolism. Most antiepileptic drugs are metabolized by utilization of CYP 2C9, CYP 2C19 and CYP 3A4 - the subtypes of hepatic

enzyme cytochrome P 450 (7). Antiepileptic drugs are capable of inducing or inhibiting CYP liver enzyme, which lead to changes in their metabolic speed and their concentration in the blood. While combining antiepileptic therapy, it is important to know the influence of AE on the function of the liver enzymes. (Table 2). Various combinations of antiepileptic drugs can be encountered clinically, often with carbamazepine, valproate or lamotrigine whereas the use of phenitoin and phenobarbitone is significantly reduced in modern therapy of epilepsy (6,8).

Excretion

Excretion presents the process of elimination of a medication from the human body where there are no clinically significant interactions of AE. Excretion can be influenced by medications that change renal clearance, renal circulation or urine pH, which lead to either slowing down or accelerating the process of elimination. It is well-known that urine is alcalised by Na - bicarbonate after the inebriation with barbiturates in order to eliminate the medication from the body. The concentration of lamotrigine is increased in the consecutive application of valproate whereas their mutual rivalry for the glucuronidation reaction reduces the clearance of lamotrigine.

Table 1. Pharmacokinetics profiles AE drugs significant for interaction

Antiepileptic	Binding for plasma proteins (%)	Metabolics transformation	Renal elimination	Halftime elimination(t _{1/2})(h)
carbamazepine	75	yes	no	16-24
diazepam	98	yes	no	24-48
etosuximide	0	yes	no	40-60
phelbamate	25	yes	yes	13-23
lamotrigine	56	yes	no	22-38
phenobarbiton	50	yes	yes	80-100
vigabatrine	0	yes	yes	5-7
valproate	90	yes	no	8-18
levetiracetam	slabo	no	yes	6-18
clobazam	90	yes	yes	18-42

Table 2. Enzymes in metabolic reactions of antiepileptic drugs

Antiepileptic	Influence of CYP enzymes and UDPGT	Important metabolism enzymes
phenobarbiton	induction	2C9, 3A4
phenitoin	induction	2C9, 3A4
Carbamazepine	induction	2C9, 3A4
Levetiracetam	no influence	hidralases
Valproac acid	inhibition	2C9
Etosuximide	no influence	3A4
lamotrigine	no influence	UDPGT

* UDPGT-uridindiphosphoglukuronic transpherase

Pharmacokinetic profile of the most important antiepileptics

Phenitoin (PHT)

The most important characteristic of the phenitoin metabolism is the activity of the enzymes CYP 2C9 and CYP 2C19 which take part in its oxidation. Consequently, the medication prepares for reaction after the conjugation of hydroxylation in para-position after which it is being eliminated from the body (7,8). Half - time for PHT elimination is 7 - 42 h. Phenitoin shows nonlinear kinetics due to which small changes in dosage can cause significant changes in medication concentration in the blood showing toxic effects. Phenitoin is a strong inducer of microsomal liver enzymes accelerating its own metabolism as well as the metabolism of other medications. The enzymes of importance for their biotransformation are CYP 2C9 and CYP 2C19

Lamotrigine (LTG)

Lamotrigine is rapidly and easily absorbed. It shows a high level of bio-access without significant metabolism of the first passage. After oral application, LTG reaches its maximum concentration in plasma in approximately 2,5 hours. In the process of distribution, 55% of the medication is bonded to plasma proteins. Lamotrigine metabolism takes place in the liver via enzyme UDPGT (uridindiphosphatglucuronic-transferase) (8). After conjugation with glucuronic acid it is eliminated via urine, and only 2% via feces. If the enzyme induction takes place, normal time for half-elimination that of 29 h can be reduced to 14 h or increased to 70 h in combination with valproate (9). Generally speaking, time of the half- elimination is shorter in children (from 7 h to 80 h). Lamotrigine does not affect oxidative metabolic processes in the liver. However, the speed of its metabolism depends on the function of the liver enzymes (7,9). In the second metabolism phase, the variation in enzyme uridin glukonil - transferase is noted, which conjugates with lamotrigine and prepares it for excretion. Patients with Gilbert's syndrome (genetic deficiency of bilirubine conjugation) show approximately 30% less clearance of lamotrigine, leading to its accumulation.

Valproic acid (VPA)

Valproic acid is resorbed rapidly and completely after oral application reaching its maximal concentration in 1-4 hours. Some disorders of the digestive tract and food presence can postpone the beginning of its utilization. VPA is highly bonded to plasma proteins (about 90%), increasing the potential for interactions during the process of distribution. It almost completely undergoes the reactions of oxidation and glucuronidation, so that its unaltered form could remain unidentified in urine or feces (8,9). Metabolite derived from β - and ω - oxidation, 2 propyl 2- pantoic acid and 2 - enalproic acid also show antiepileptic activity, while 2 - enalproic acid is accumulated in plasma and

CNS in clinically significant concentrations. VPA is the inhibitor of microsomal liver enzymes. When combined with other antiepileptics both medications change their concentrations (10). The half - time of elimination, without the influence of other medications is 15 hours (5,7).

Carbamazepine (CBZ)

Carbamazepine shows limited affinity influencing its bio-access and a possibility of a greater influence of food and liquids present in the digestive tract. Maximal concentration of the medication in plasma is achieved in 4 - 8 hours after the oral application that can be prolonged to 24 hours. The medicine is distributed equally throughout the whole body, so that the CNS concentrations could become equal to the plasma concentrations of drugs. CBZ bonds to plasma proteins about 75%. Metabolism takes place in the liver under the influence of oxidative enzymes forming 10,11 epoxide with the antiepileptic activity rapidly conjugated with glucuronic acid and eliminated from the body (6,7,8). CBZ is a potential inducer of microsomal liver enzymes. The time of half - elimination is 10 - 20 hours. It is shortened in the presence of other antiepileptic drugs and inducers of liver enzymes (phenitoin, phenobarbitone). CBZ reduces plasma concentration of lamotrigine, oxcarbamazepine, topiramate, phenobarbitone (9,10).

Phenobarbitone (PB)

Absorption of PB is slow but complete as a result of the maximum concentration, 5 - 15 hours after the oral application. The speed of absorption depends on pharmacological form, quantity, types of food and liquid present in the digestive system. PB bonds to plasma protein up to 50% and slowly passing through the blood-brain barrier. 25% of it is eliminated in the unaltered form allowing a forced diuresis in the case of inebriation. The rest undergoes hydroxylation in para-position thus getting inactive metabolite which is eliminated as free or as conjugate of glucuronic acid via urine. Half - time of elimination differs a lot between children and adults. In adults, the half-time of elimination is 96 - 100, while in children it is 30 - 70 hours (8).

Levetiracetam

Levetiracetam has been in use since 1999 and belongs to the latest generation of antiepileptic drugs. It is extremely an efficient and wide-ranged AE, which does not require a therapeutic monitoring and is applied widely. Therapeutic concentration is 6 - 20 mg/l. LEV with a very favourable pharmacokinetic profile. Its features are a high-level bio-access and a weak bonding to plasma proteins (11). Its bio - transformation takes place in liver where inactive metabolites are produced by hydrolysis. Oxidative liver enzymes do not participate in metabolism of LEV which significantly reduces its potential for interactions. LEV is partially eliminated via kidneys unaltered. Its elimination half - time is 6 - 8 h. In children, the elimination half - time is slightly shortened but prolonged in kidney diseases. The medication kinetics is linear, predictable with pharmacokinetic parameters that stay unaltered

(8,11). LEV does not show interactions with other AE medications.

Gabapentin (GBP)

Gabapentin represents a new generation of antiepileptics which has a characteristic dose-dependent absorption. The process of absorption requires the presence of a carrier, which causes saturation kinetics and proves the necessity of therapeutic monitoring. GBP does not show significant influence on the level of the other antiepileptics, when applied in a combined therapy. Small interaction potential comes from its metabolism.

Clobazame (CLB)

Clobazame is an antiepileptic from the group of benzodiazepine which is mainly added as an adjuvant in therapy. After a rapid and complete resorbtion, maximum concentration of the medication in plasma is completed in 1-4 hours. In plasma, it is highly bonded to plasma proteins (about 90%). Clobazame shows linear kinetics and substantial distribution. The metabolism is achieved via cytochromal enzymes CYP 3A4 and CYP 2C19, during which an active metabolite-norclobazame is produced (8). The elimination time of GLB is 18 hours while for norclobazame it is 42 hours.

Interactions of AEs in a combined antiepileptic therapy

In a combined antiepileptic therapy it is important to know the order of AEs application, because of their influence on liver enzymes and their affinity to bond to plasma proteins (1,5). Tables 3 and 4 show the influence of AE on each other. As the first medication, Carbamazepine, which is the inductor of liver enzymes, significantly decreases the level of valproate, while valproate added to carbamazepine does not significantly change its level, because the initiated enzyme inhibition is partially restored by induction. Clobazame, an adjuvant in antiepileptic therapy, especially in pediatric population, increases the

level and effect of valproate and phenobarbitone at the same time reducing the level of carbamazepine. Clobazame has the unpredictable influence on phenitoin because of its nonlinear kinetics. The latest AEs generally show weaker influence on other antiepileptics, not significantly changing the concentration of the first AE (Table 4). That is the case with lamotrigine, the concentration of which directly depends on the influence of the first antiepileptic. Valproate, by its competitive inhibition in the second phase of metabolism, reduces excretion of lamotrigine due to which its level in plasma grows until the occurrence of undesirable effects, while carbamazepine significantly reduces the level of lamotrigine (12,13). Phenitoin produces interactions, e.g. with topiramate which has the affinity to bind to plasma proteins and increase free fraction of phenitoin (13). Zonisamide has not been studied enough up to now, but it is known that it changes the level of carbamazepine in an unpredictable way requiring therapeutic monitoring. Phelbamate significantly increases the level of valproate while reducing the level of carbamazepine, whereas it has the opposite effect on carbamazepine metabolite, increasing its level and antiepileptic effect. Levetiracetam, which finds a widespread application in the contemporary therapy, shows an ideal kinetics and does not produce interactions with other AEs. Topiramate has clinically significant reduction effect on the level of valproate, because of its effect on liver enzymes (13).

The influence of the second antiepileptic is quite larger if the therapy is begun with an antiepileptic of the latest generation (Table 5). By inducing valproate and phenitoin, the level of lamotrigine is clinically significantly reduced. In contrast, carbamazepine and oxcarbamazepine increase its concentration (12). By adding another antiepileptic, zonisamide and topiramate show a significant reduction in concentration. The inclusion of another antiepileptic has no significant clinical influence on vigabatrin (Table 5). The influence of other AEs on LEV has not been studied sufficiently, because it is rarely used as the first antiepileptic.

Table 3. Change of the concentration of the first antiepileptic (AE I) after the absorption of the second (AE II)

AEDI + AEDII	PB	PHT	PRM	ESM	CBZ	DZP	CZP	VPA	CLB
PB	AI	PHT↑↓	-	ESM↓↑	CBZ↓↓	DZP↓	CZP↓	VPA↓↓	CLB↓↓ NDMC↓↓
PHT	PB↑	AI	PRM↑ PB↑	ESM↓↑	CBZ↓↓	DZP↓	CZP↓	VPA↓↓	CLB↓↓ NDMC↓↓
ESM	↔	↔	NA	■	↔	NA	NA	VPA↓	NA
CBZ	↔	PHT↓↑	PRM↓ PB↑	ESM↓↓	AI	DZP↓	CZP↓	VPA↓↓	CLB↓↓ NDMC↑↑
VPA	PB↑↑	PHT↓↑	PRM↑↑	ESM↓↑	CBZ↓↓	DPZ↑↑	NA	■	NA
CLB	PB↑↑	PHT↓↑	PRM↑↑	NA	CBZ↓	NA	NA	VPA↑	■

* CLB- clobazam, DZP- diazepam, NDMC- N-desmetilclobazam, CBZE – carbamazepam epoxid

CZP- clonazepam, ETS- etosuximid, PRM- primidon, NA- announ, GBP- gabapentin, FBM- felbamat, LEV- levetiracetam, ZNS- zonisamid, OXC- oxcarbamazepam, 10OHOC- 10,11 dihidroxicarbamazepam, AI- autoinduction

↓ plasma concentration decrease, ↓↓ significant plasma concentration decrease, ↑ plasma concentration increase, ↑↑ significant plasma concentration increase ↔ no change in plasma concentration, ?-unkown

Table 4. Influence of the new antiepileptic drugs on the concentration of the old AE

AED I+ AED II	PB	PHT	PRM	ESM	CBZ	VPA
VGT	↔	PHT↓	↔	NA	↔	↔
LTG	↔	↔	↔	↔	↔	↔
GBP	↔	↔	NA	NA	↔	↔
TPM	↔	PHT↑	↔	NA	↔	VPA↓
PGB	↔	↔	NA	NA	↔	↔
FBM	PB↑↑	PHT↑↑	?	?	CBZ↓ CBZE↑	VPA↑↑
TGB	↔	↔	↔	NA	↔	↔
OXC	PB↑	PHT↑	?	?	CBZ↓	↔
LEV	↔	↔	↔	NA	↔	↔
ZNS	↔	PHT↑↑	↔	NA	CBZ↓	↔

Table 5. Influence of the old antiepileptic drugs on the concentration of the new AE

AED I + AED II	VGB	LTG	GBP	TPM	PGB	FBM	TGB	OXC	LEV	ZNS
PB	↔	LTG↓↓	↔	TPM↓↓	↔	FBM↓↓	TGB↓↓	100HOXC↓	↔	ZNS↓↓
PHT	↔	LTG↓↓	↔	TPM↓↓	↔	FBM↓↓	TGB↓↓	100HOXC↓	↔	ZNS↓↓
PRM	↔	LTG↓↓	↔	TPM↓↓	NA	FBM↓↓	TGB↓↓	?	NA	ZNS↓↓
ETS	NA	NA	NA	NA	NA	?	NA	NA	NA	NA
CBZ	↔	LTG↑↑	↔	TPM↓↓	↔	FBM↓↓	TGB↓↓	100HOXC↓	NA	ZNS↓↓
VPA	↔	LTG↓↓	↔	TPM↓↓	↔	↔	↔	↔	↔	ZNS↓↓

Table 6. Significant interactions of the antiepileptic drugs with other drugs

First drug	Second drug	Pharmacokinetic process	Mechanism of interactions	Pharmacodynamics effect
VPA	antacide	apsorption	Adsorption	↓bioaviability, VPA↓
AE	food	apsorption	binding	changeing of bioaviability
VPA	cholestiramin	distribution	binding VPA with cholestiramin	VPA↓
PHT	aspirin	metabolism	metabolism PHT↑	PHT↓
PHT	fluconasol, ketoconasol	metabolism	inhibition CYP 2C9, CYP 2C19	PHT↑ toxic ↑
PHT	insuline	metabolism	inhibition CYP 2C9	PHT ↑
PHT	doxycycline	metabolism	induction liver enzym	doxicyclin↓
PHT	fluoxetin	metabolism	inhibition CYP 2C9, CYP 2C19	PHT↑
CBZ	Cimetidine	metabolism	metabolismCBZ↓	CBZ↑,adverse efect↑
CBZ	doxycycline	metabolism	Induction CYP 3A4	Doxicyklin↓
CBZ	Cortikosteroid drugs	metabolism	Induction CYP 3A4	degrese efect corticosteroids
CBZ	Macrolid antibiotics	metabolism	inhibition CYP 3A4 metabolism CBZ↓	Toxic CBZ↑
LTG	Antituberculotic drugs	metabolism	metabolism LTG↑	LTG↓
VPA	cimetidin	excretion	clirens VPA↓	VPA↑, toxic VPA↑
CBZ	viloxazin	excretion	Inhibition of clirens CBZ	toxic efects CBZ↑
AE	pesticide	metabolism	Induction of liver enzym	pesticide ↓

Interactions of antiepileptics with other medications

Because of the antiepileptic therapy specific features and the impossibility of its sudden discontinuance, practice has showed frequent interactions with medications, the metabolism of which is performed via the same enzymes, such as the case with antibiotics, oral contraceptives, hypoglycemics and antiarrhythmics. It is highly important to know about and prevent possible interactions, in order to minimize undesirable effects.

The use of macrolidic antibiotics (clarytromicine) and carbamazepine leads to clinically significant interaction, caused by slow metabolism, consequent accumulation and the occurrence of toxic effects of carbamazepine (14,15).

Chloramphenicol increases the plasma concentration of phenitoin because of the strong inhibition of liver enzymes, while riphampicine, the powerful inductor of microsomal liver enzymes, accelerates the metabolism of phenitoin and reduces its plasma concentration (14,16).

Insulin activates interaction with phenitoin because of the inhibition of enzymes participating in its hydroxylation, primarily CYP 2C9, due to which the plasma concentration of phenitoin is increased.

The outcome of a detailed research of pharmacokinetics has showed that valproate, lamotrigine, vigabatrine and gabapentine can be combined with contraceptives which contain only progesteron with levonorestrel based implants and medroxyprogesteron injections, without the risk of reduction of the contraceptive effect.

In order to show improved clinically significant interactions of antiepileptics with other medications, their manifestation mechanism and pharmacodynamic effect are shown in Table 6 (16,17,18). Vulnerable pediatric population, as well as patients with damaged liver and kidneys function, require special caution when combining antiepileptics.

Generally speaking, medications with a shorter half-time elimination have a potential to perform interactions, due to which therapeutic monitoring is recommended. According to the literature-obtained data, the time needed for the maximum interaction effects varies in duration from 3-4 days for valproate and carbamazepine, to 12 days for exosuximide, 14 days for phenitoin and 20 days for phenobarbitone. The data is of special significance to epileptologists (7,16).

Populational pharmacokinetic analysis is very significant in studying interactions of antiepileptics both with each other and with other medications. Based on the insufficient data about the plasma

concentrations of antiepileptics and taking into consideration patients from specific population, the analysis can verify the correlation between medications, their interrelated influence and correction in the therapy applied.

This information is relevant for the pediatric population, since they require special caution in the AEs dosage titration. Relevant factors taken into account are: sex, age habits, body weight and medications (3). Populational analysis confirms the necessity of the AE therapeutic monitoring. With this sort of analysis it is possible to confirm the life style effect e.g. smoking, for instance, reduces the effect of antiepileptic therapy. Using the same analytical method, the influence of new antiepileptics has been tested on the reduction of the contraceptives efficiency.

Children and the elderly with chronic diseases require special attention because they have a different therapeutic response to AEs which is the consequence of interactions of antiepileptics with other medications.

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KLINIČKI ZNAČAJNE FARMAKOKINETIČKE INTERAKCIJE ANTIEPILEPTIKA

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Antiepileptici (AE) pokazuju klinički značajne interakcije međusobno i sa drugim lekovima zbog specifičnog farmakokinetičkog profila i relativno male terapijske širine. Klinički najznačajnije interakcije AE se dešavaju tokom njihovog metabolizma i distribucije. U kombinovanoj antiepileptičkoj terapiji od važnosti je poznavanje redosleda primene AE zbog njihovog uticaja na enzime jetre i afiniteta vezivanja za proteine plazme. Veći potencijal interakcije imaju AE sa kraćim poluvremenom eliminacije, zbog čega se preporučuje njihov terapijski monitoring. Populational farmakokinetička analiza može pružiti značajne podatke vezane za interakcije AE sa drugim lekovima. Poseban rizik za nastanak interakcija ima vulnerabilna, pedijatrijska populacija i bolesnici sa oštećenjem funkcije jetre i bubrega. *Acta Medica Medianae* 2007;46(4):55-60.

Ključne reči: farmakokinetičke interakcije, antiepileptici, interakcijski potencijal, klinički značaj