Chapter 31

Pharamacokinetic interactions between antiepileptic drugs

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Classically, a drug interaction is regarded as a modification of the effect of one drug by prior or concomitant administration of another. Interactions can be divided into two broad types, namely pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions occur as a consequence of an effect at the site of drug absorption, plasma protein binding, metabolism or elimination and are associated with changes in blood concentrations (levels). Pharmacodynamic interactions occur as a consequence of an effect at the site of action of a drug, are not associated with any change in blood concentrations and are concluded by default.

Commonly, drug interactions have been discovered as a result of unexpected changes in the clinical status of patients upon addition or withdrawal of a drug from existing medication. A clinically significant drug interaction can be defined as one that results in the need to adjust dosage regimens in the majority of patients. However, the end result in individual patients needs also to be considered. For example, a modest or even marked elevation of a low plasma antiepileptic drug (AED) concentration consequent to an interaction may merely improve seizure control, and a small elevation of a nearly toxic concentration may precipitate toxicity. Similarly, a marked interaction in an unusually susceptible individual receiving drug polytherapy that causes little change in the majority of patients is equally significant.

Table 1 shows the various AEDs and the expected changes in plasma concentrations when an AED is added to a concomitant AED regimen.

The pharmacokinetic interactions that are most significant clinically can be attributed to interactions at the metabolic level, and the best examples relate to inhibition or induction of the hepatic monooxygenase enzyme system (cytochrome P450, CYP) involved in drug metabolism. Induction involves the synthesis of new enzyme, and requires protein synthesis. Consequently, it may take many days before induction is complete and results in an increased drug metabolism, reduced plasma concentrations and an attenuated pharmacological effect (if no active metabolite is present). The process goes in reverse when the inducer is withdrawn with an increase in plasma concentrations of the target drug and hence an increased potential for toxic side effects.

Commonly, inhibition results from competition between drugs for the same active site on an isoenzyme of CYP, while induction involves production of more isoenzyme and therefore more binding sites. Circulating concentrations of the inhibited drug increase to a new steady state between four and six half-lives after the interaction has begun. Consequently, potential pharmacological effects will occur quickly if a drug has a short half-life and more slowly if it has a long half-life. The minimum elapsed-time for maximum potentiation is carbamazepine 4 days, ethosuximide 12 days, phenytoin 14 days, phenobarbitone 20 days, and valproate 3 days.

Of the AEDs illustrated in Table 1, four (carbamazepine, phenytoin, primidone and phenobarbital) are potent enzyme inducers. Valproate and stiripentol are potent inhibitors. Phenytoin has some rather unique characteristics in that in addition to being an enzyme inducer, it is only loosely bound to CYP isoenzymes. It also exhibits saturation metabolic characteristics making it particularly susceptible to inhibitory interactions. Of the newly licensed AEDs, gabapentin, lacosamide, levetiracetam, pregabalin and vigabatrin uniquely do not appear to affect the concentrations of other AEDs. In contrast eslicarbazepine acetate, lamotrigine, felbamate, oxcarbazepine, tiagabine, topiramate and zonisamide are associated with numerous clinically significant interactions.

Finally, in the past few years, interactions relating to the selective inhibition of the metabolism of carbamazepine to its epoxide metabolite, or subsequent metabolism of the epoxide, have been described. These may have considerable clinical significance, particularly since there is increasing evidence to suggest that the epoxide may contribute not only to the efficacy of carbamazepine but also to its toxicity. Carbamazepine epoxide plasma concentrations can be quadrupled in some patients by valproate, usually in the absence of changes in carbamazepine, and precipitating toxicity. With the more widespread availability of therapeutic monitoring of the epoxide, these interactions are increasingly being identified.

Further reading

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Table 1. Interactions between antiepileptic drugs (AEDs): Expected changes in plasma concentrations (levels) when an AED is added to a pre-existing AED regimen.

AED added \ PRE-EXISTING AED	*CBZ*	*CLB*	*CZP*	*ESL-a*	*ESM*	*FBM*	*GBP*	*LCM*	*LTG*	*LEV*	*OXC*	*PMP*	*PB*	*PHT*	*PGB*	*PRM*	*RTG*	*RFN*	*STP*	*TGB*	*TPM*	*VPA*	*VGB*	*ZNS*
CBZ	AI	CLB⇓ DMCLB⇑	CZP⇓	ESL↓	ESM⇓	FBM⇓	↔	↔	LTG⇓	LEV↓	H-OXC↓	PMP⇓	↔	PHT↑↓	↔ PB↑	PRM↓	RTG↓	RFN↓	STP⇓	TGB⇓	TPM⇓	VPA⇓	↔	ZNS⇓
CLB	CBZ↑ CBZ-E↑	—	NA	↔	NA	NA	NA	NA	↔	↔	↔	↔	↔	PHT↑	NA	PRM↑	NA	↔	STP↑	?	NA	VPA↑	NA	NA
CZP	↔	NA	—	NA	NA	↔	NA	NA	↔	↔	NA	↔	↔	PHT↑↓	NA	↔	NA	NA	NA	?	NA	↔	NA	↔
ESL-a	↔	↔	NA	—	NA	NA	↔	NA	LTG↓	↔	NCCP	?	↔	PHT↑	NA	NA	?	NA	NA	NA	TPM↓	VPA↓	NA	?
ESM	↔	NA	NA	NA	—	NA	NA	NA	↔	↔	NA	?	↔	↔	NA	PRM↑	NA	NA	NA	NA	NA	VPA↓	NA	NA
FBM	CBZ↓ CBZ-E↑	CLB⇓ DMCLB⇑	CZP↑	?	?	—	NA	NA	LTG↑	↔	↔	?	PB⇑	PHT⇑	NA	?	?	?	?	?	?	VPA⇑	VGB↓	NA
GBP	↔	NA	NA	↔	NA	FBM↑	—	NA	↔	↔	NA	NA	↔	↔	PGB↓	NA	NA	↔	NA	NA	↔	↔	NA	NA
LCM	↔	NA	↔	NA	NA	NA	↔	—	↔	↔	H-OXC↓	?	NA	↔	NA	NA	NA	NA	NA	NA	↔	↔	NA	↔
LTG	↔	↔	CZP↓	↔	↔	↔	NA	↔	—	LEV↓	↔	↔	↔	↔	↔	↔	RTG↑	↔	NA	NA	↔	VPA↓	NA	↔
LEV	↔	↔	↔	↔	↔	NA	↔	↔	↔	—	NA	↔	↔	↔	↔	↔	NA	NA	NA	NA	↔	↔	↔	NA
OXC	CBZ↓	?	?	NCCP	?	?	NA	↔	LTG↓	LEV↓	—	PMP⇓	PB↑	PHT↑	NA	?	?	RFN↓	?	?	TPM↓	↔	NA	NA
PMP	CBZ↓	CLB↓	↔	?	?	?	NA	NA	LTG↓	↔	OXC**	—	↔	↔	NA	?	?	?	?	?	↔	VPA↓	NA	↔
PB	CBZ⇓	CLB⇑ DMCLB⇑	CZP⇓	?	ESM⇓	↔	↔	LCM↓	LTG⇓	LEV↓	H-OXC↓	↔	AI	PHT↑↓	↔	NCCP	RTG↑	RFN↓	STP⇓	TGB⇓	TPM⇓	VPA⇓	↔	ZNS⇓
PHT	CBZ⇓	CLB⇓ DMCLB⇑	CZP⇓	ESL↓	ESM⇓	FBM⇓	↔	LCM↓	LTG⇓	LEV↓	H-OXC↓	PMP⇓	PB↑	AI	PGB↓ PB↑	PRM↓	RTG↓	RFN↓	STP⇓	TGB⇓	TPM⇓	VPA⇓	↔	ZNS⇓
PGB	↔	NA	NA	NA	NA	NA	↔	NA	↔	↔	NA	NA	↔	↔	—	NA	NA	NA	NA	TGB↓	↔	↔	NA	NA
PRM	CBZ⇓	?	CZP⇓	?	ESM⇓	?	NA	?	LTG⇓	↔	?	?	NCCP	↔	NA	—	?	RFN↓	STP⇓	TGB⇓	TPM⇓	VPA⇓	↔	ZNS⇓
RTG	↔	NA	NA	?	NA	NA	**NA**	**NA**	LTG↓	NA	?	?	PB↑	↔	NA	NA	—	NA	NA	NA	↔	↔	NA	NA
RFN	CBZ↓	↔	NA	NA	NA	NA	NA	NA	LTG↓	NA	NA	?	PB↑	PHT↑	NA	NA	NA	—	NA	NA	↔	↔	NA	NA
STP	CBZ⇑	CLB⇑ DMCLB ⇑	?	?	ESM↑	?	NA	NA	?	NA	?	?	PB⇑	PHT⇑	NA	PRM⇑	?	?	—	?	?	VPA⇑	NA	?
TGB	↔	NA	NA	NA	NA	NA	NA	NA	↔	↔	NA	NA	NA	↔	NA	NA	NA	NA	NA	—	NA	VPA↓	NA	NA
TPM	↔	?	?	ESL↓	NA	?	NA	↔	↔	↔	↔	PMP⇓	↔	PHT↑	↔	↔	↔	↔	NA	?	—	VPA↓	NA	NA
VPA	CBZ-E⇑	↔	?	↔	ESM↑↓	FBM↑	↔	↔	LTG⇑	↔	↔	↔	PB⇑	PHT↓*	↔	PB⇑	↔	RFN↑	↔	↔	TPM↓	—	↔	↔
VGB	CBZ↑↓	NA	NA	NA	NA	↔	NA	NA	↔	↔	NA	NA	↔	PHT↓	NA	↔	NA	RFN↓	NA	NA	NA	↔	—	NA
ZNS	CBZ-E↑	?	?	NA	?	?	NA	NA	↔	NA	?	↔	↔	↔	NA	↔	?	?	?	NA	NA	↔	NA	—

CBZ = carbamazepine; CBZ-E = carbamazepine-10,11-epoxide (active metabolite of CBZ); CLB = clobazam; CZP= clonazepam; DMCLB = N-desmethylclobazam (active metabolite of CLB); ESLa = eslicarbazepine acetate; ESL = eslicarbazepine (active metabolite of ESL-a); ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; H-OXC = 10-hydroxy-oxcarbazepine (active metabolite of OXC); LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PGB = pregabalin; PRM = primidone; RET = retigabine; RFN = rufinamide; STP stiripentol; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; VGB = vigabatrin; ZNS = zonisamide.

AI = autoinduction; NA = none anticipated; NCCP = not commonly co-prescribed; ↔ = No change; ↓ = a usually minor (or inconsistent) decrease in plasma level;
⇓ = a usually clinically significant decrease in plasma level; ↑ = a usually minor (or inconsistent) increase in plasma level; ⇑ = a usually clinically significant increase in plasma level.
* = free (pharmacologically active) level may increase; ** = the effect of the active metabolite H-OXC is not known; ? = unknown, an interaction could occur