Choosing Antiepileptics: What are the Common Pitfalls?

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Choosing antiepileptics

- Seizure type/ epilepsy syndrome
- Pharmacodynamic/ pharmacokinetic profiles
- Drug interactions
- Comorbidities
- Expected adverse effects

Narrow-Spectrum Drugs: Partial or Secondarily Generalized Tonic-Clonic Seizures

- Carbamazepine
- Gabapentin
- Lacosamide
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Tiagabine

Broad-Spectrum Drugs: Partial and Generalized Seizures

- Lamotrigine
- Levetiracetam
- Topiramate
- Valproate
- Zonisamide
- Rufinamide

AED combinations determined by isobolographic studies in animals to have favourable effects

- CBZ : GBP, LEV, TPM, VPA
- CZP : OXC
- GBP : LEV, LTG, OXC, PB, PHT, TPM, VPA
- LEV : CBZ, OXC, PB, TPM
- LTG: FBM, GBP, TPM, VPA
- PHT: GBP, PB, VPA
- TPM: CBZ , FBM,GBP, LEV, LTG, OXC, VPA
- VPA : CBZ, ESX ,GBP, LTG, PHT, TPM

Pharmaceuticals **2010, 3, 2362-2379; doi:10.3390/ph3082362**

AED combinations determined by isobolographic studies in animals to have unfavourable effects

- CBZ: LTG
- CZP: FBM
- ***LTG: CBZ, OXC***
- OXC: FBM, LTG, PHT
- PTH: OXC

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Pharmacokinetic parameters and reference ranges for the AEDs

Drug	Oral bioavailability	Serum protein binding	Time to peak conc. (hrs)	Serum half-life (hrs)	Reference range in serum (mg/L)
Carbamazepine	>70	75	4-8	10-20	4-10
Clonazepam	>95	85	1-2	20-26	0.009-0.07
Eslicarbazepine acetate	≥80	30	1-4	20-24	Not established
Ethosuximide	>90	0	2-4	30-50	40-100
Felbamate	>90	25	2-6	16-22[a]	30-60
Gabapentin	<60	0	2-3	5-9	2-20
Lacosamide	≥95	15	0.5-4	12-15	5-10
Lamotrigine	≥95	55	1-3	15-35[a,b]	3-14
Levetiracetam	≥95	0	1	6-8	12-46
Oxcarbazepine	90	40	3-6	8-15[a]	3-35
Phenobarbital	>95	50	4-12	90-110	10-25
Phenytoin	90	>95	4-12	6-24	10-20
Primidone	≥90	20	2-4	10-20	8-12
Pregabalin	≥90	0	1-2	5-7	2.8-8.3
Rufinamide	85	30	5-6	8-12[a]	Not established
Stiripentol	≥90	99	1-2	Variable	4-22
Tiagabine	≥90	96	1-2	5-9[a]	0.02-0.2
Topiramate	≥80	15	2-4	20-30	5-20
Valproic acid	>95	>90	1-4	11-17	30-100
Vigabatrin	≥60	0	1-2	5-8	0.8-36
Zonisamide	≥65	50	2-5	50-70[a]	10-40

Elimination half-life of antiepileptic drugs and time to reach steady-state

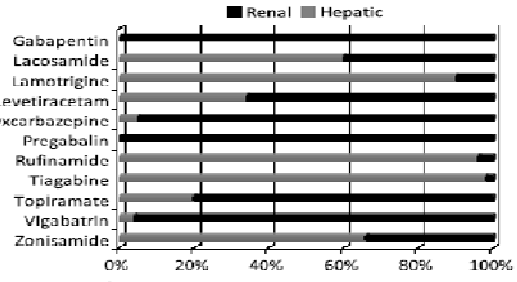
Antiepileptic	Steady State, Days	Elimination Half-life, h
Carbamazepine	2–6	Single dose: 25–65 Self-Induction: 16
Phenytoin[a]	4–24 Load dose: 48–96 h	Low doses 6–12 High dose: 12–60
Phenobarbital	10–25	90–100
Primidone	2–4	9–22
Valproic acid	2–4 Load dose: 24h	15
Ethosuximide	5–15	30–60
Clonazepam	6	10–30
Gabapentin	2	5–9
Lamotrigine	5–6	15–60
Tiagabine	1–2	5–8
Topiramate	4–6	12–30
Vigabatrin	2	5–8
Levetiracetam	5	7
Oxcarbazepine	1	1–2
Felbamate	4	14–23

[a] Pharmacokinetics are dose-dependent.

Practical aspects of pharmacokinetic monitoring

- Optimum extraction time for monitoring antiepileptic treatments that are administered orally is just before the morning dose (trough, baseline, minimum or pre-dose level)
- 2 h after loading dose
- Serum is the recommended biological matrix for quantifying antiepileptic levels.
- Caution when using collection tubes that contain gels, as these may cause adsorption phenomena.

Routes of elimination of the newer antiepileptic drugs



Neurologic Clinics 2010;28:843-52

AED dosage adjustment in renal disease and dialysis

AED	% renal excretion	Adjustment required	Removed by dialysis?
Carbamazepine	Minimal	Decrease 25% if GFR <10 ml/min	No
Ethosuximide	10–20	Decrease 25% if GFR <10 ml/min	Yes
Phenobarbital	25–30	Increase dose interval by 50–100%	Yes
Phenytoin	Minimal	No	No
Primidone	20	Increase dosing interval	Yes
Valproate	Minimal	No	No
Gabapentin	100	Clearance proportional to creatinine clearance In failure, dose after dialysis	Yes
Lamotrigine	90	Decrease dose 25–50%	Yes
Topiramate	70	Decrease dose by 50%	Yes

Clin Neuropharmacol 2003;26:38-52

Some aspects on pharmacokinetics of antiepileptic drugs in pregnancy and during lactation

	Decrease in total plasma concentration (%)	Ratio of infant/maternal plasma concentration [20]
Phenytoin	25–50[a]	0.1–0.6
Phenobarbital	25–50	0.3–0.5
Ethosuximide	[c]	0.8–1.0
Carbamazepine	<25	0.1–0.3
Valproate	25–50[b]	0.01–0.1
Oxcarbazepine MHD	>50	0.5
Vigabatrin	[c]	[c]
Lamotrigine	>50	0.4–0.8
Gabapentin	[c]	0.7–1.3
Topiramate	[c]	0.7–1.1
Tiagabine	[c]	[c]
Levetiracetam	>50	0.8–1.3
Pregabalin	[c]	[c]
Zonisamide	25–50	0.5–0.9

MHD, monohydroxy metabolite.
[a] Unbound concentration declines <25%.
[b] Unbound concentration often unchanged.
[c] Published data lacking.

Wolters Kluwer | OvidSP
Current Opinion in Neurology. 22(2):157-161, April 2009.
DOI: 10.1097/WCO.0b013e3283292b37

Cytochrome P450 polymorphism

- Of the old and new AEDs, only ***phenytoin*** and ***phenobarbital*** metabolism are subject to genetic cytochrome P450 (CYP450) polymorphism
- Both are metabolized by CYP2C9 and CYP2C19
- Fraction of phenobarbital that is eliminated by CYP2C9- or CYP2C19-dependent oxidation is significantly smaller (<25%) than for phenytoin

TDM 2008;30(2):173-80

Genotype-based dose guidance of phenytoin

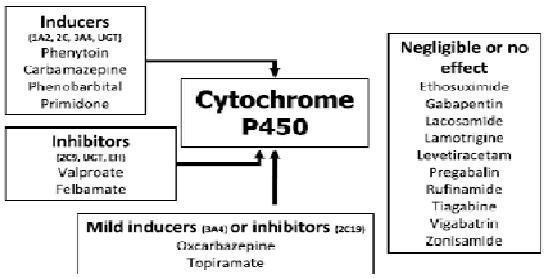
2C9	2C19	Suggested dose
***1/*1**	***1/*1**	**5.5 - 7 mg/kg/d**
*1/*1	*1/*2 or *3	5 - 7
*1/*1	*2/*2 or *3	5 – 6
*1/*3	*1/*2 or *3	3 – 4
*1/*3	*2/*2 or *3	2 – 3

Ther Drug Monit 2004;26(5):534-40

Relative drug-drug interaction potential of the antiepileptic drugs

None	Low	High
Ethosuximide Gabapentin Levetiracetam Pregabalin Vigabatrin	Lacosamide Lamotrigine Oxcarbazepine Rufinamide Topiramate Tiagabine Zonisamide	Carbamazepine Felbamate Phenytoin Phenobarbital Primidone Valproate

Effects of antiepileptic drugs on the cytochrome P450



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Antiepileptic drugs in brain-tumor related epilepsy (BTRE)

- BTRE can be considered as a “drug resistant epilepsy”
- due to over-expression of genes and proteins that mediate nonspecific resistance to treatment (multidrug resistant proteins (MDR) or P-glycoprotein (P-gp)
- P-gp is the most important transport protein in pharmaco-resistant epilepsy as it is capable of carrying a large number of AEDs, including: CBZ, FBM, GBP, LEV, LTG, OXC, PB, PHT, and TPM

Effectiveness of AED in BTRE

- 62.9% of seizure-free patients with OXC monotherapy;
- 55.6% with topiramate monotherapy;
- a responder rate from 27.4 to 100% with gabapentin, lacosamide, pregabalin, tiagabine, and zonisamide in add-on;
- 47.4–88% of seizure-free patients with levetiracetam both in mono-therapy and as add-on

Chemotherapy and drug interactions with AEDs

- Erlotinim, imatinib, cediranib, irinotecan, taxanes, vinca alkaloids, and teniposide are significantly metabolized by the CYP450 hepatic system
- Carbamazepine, phenobarbital, and phenytoin are enzyme inducer thus resulting in a decreased efficacy which clinically translates to a reduced survival of patients
- In this patient population, *new generation drugs such as gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide are preferred* because they have fewer drug interactions and cause fewer side effects

Neurol Sci
DOI: 10.1007/s10072-011-0868-3

Verapamil and diltiazem vs CBZ & PHT

- 40–400% increase in carbamazepine and phenytoin possible
- Monitor serum concentrations in 7 days
- Effect of diltiazem can be reduced
- Check blood pressure

Cyclosporin and tacrolimusvs CBZ & PHT

- Concentration of cyclosporin and tacrolimusvs reduced
- May need a 2- to 5-fold increase in dosage
- Monitor serum cyclosporin and tacrolimus or use alternative antiepileptic

Epileptic patients with comorbidities

- *Migraine*: VPA, TPM
- *Bipolar mania*: CBZ, VPA
- *Bipolar depression*: VPA, LTG
- *Anxiety/insomnia/ pain*: PGB
- *Agitation and mood problems in association with CNS neurologic abnormalities, such as head trauma or seizures*: VPA
- *Impulsive control*: CBZ
- *Essential tremor/Parkinson's disease*: ZNS

Adverse effects issues

- Sedation: PB, TPM
- Cosmetic: PHT
- Weight gain: VPA, GBP, PGB
- Weight loss: TPM, ZNS
- Reproductive function: VPA
- Behavioral: FBM, LEV
- Allergic: PHT, CBZ, PB, LTG

Drugs that reduced seizure threshold

- TCAs, bupoprion
- Clozapine and high dose low potency antipsychotics
- INH, imipenem and other analogs, penicillins
- High dose ChEIs (donepezil, rivastigmine, galantamine)
- Nicergoline and other ergot derivatives
- CNS stimulants
- Theophylline