

Pharmacokinetics (PK) and Pharmacodynamics (PD) of Old and New Antiepileptic Drugs (AEDs)

Professor Meir Bialer
School of Pharmacy, Faculty of Medicine
The Hebrew University of Jerusalem
Jerusalem 91120
Israel

The old antiepileptic drugs (AEDs) phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA) have the following pharmacokinetic (PK) shortcomings: bioavailability and bioequivalence problems (PHT, CBZ), saturable or non-linear PK (PHT), time-dependent PK (CBZ), short half-life (CBZ, VPA) and elimination by metabolism which is susceptible to enzyme induction and inhibition. In addition, PB, PHT and VPA are enzyme inducers and VPA is an enzyme inhibitor. Thus, all the four established AEDs are involved in drug interactions due to enzyme induction and inhibition.

In the last decade the following thirteen new antiepileptic drugs (AEDs) were introduced: felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide (1-4). Another new AED eslicarbazepine acetate (ESL) is expected to be approved shortly by EMEA (1-3). These new AEDs (with the exception of felbamate) offer appreciable advantages in terms of their favorable pharmacokinetics (PK), improved tolerability and lower potential for drug interactions (1-5). In addition, the availability of old and new AEDs with various activity spectra and different tolerability profiles enable clinicians to better tailor drug choice to the characteristics of individual patients (5). However, in spite of the large therapeutic arsenal of old and new AEDs about 30% of epileptic patients are still not seizure-free and thus, there is a substantial need to develop new AEDs. In this respect the new AEDs thus far developed, are not completely effective, since seizure-free status is achieved in no more than 15-20% of previously refractory patients.

Most AEDs exhibit linear (concentration-independent) PK within their clinically-relevant doses, namely their plasma concentrations increase or decrease proportionally to dose. Thus, the drug's major PK parameters: clearance (CL), apparent volume of distribution (V) and half-life ($t_{1/2}$) are not affected by the dose, rate or extent of absorption and mode of administration (6, 7). Since absorption is dependent on the drug and the drug product (formulation), changes in route of administration or in the parenteral (extravascular) formulation only affect the extent and rate of absorption. In contrast, the three major PK parameters (CL, V & $t_{1/2}$) are intrinsic properties of the AED or the active entity which do not change

between single and multiple dosing and remain constant regardless of the route of administration, as long as the drug PK is linear.

The PK of the new AEDs differs from one drug to another. Three new AEDs, gabapentin, pregabalin and vigabartin are only eliminated unchanged in the urine and two AEDs, levetiracetam and topiramate are mainly eliminated in the urine (fraction excreted unchanged in the urine =65%). Topiramate, a drug which is mainly excreted unchanged in the urine, has not been reported in drug interactions due to enzyme inhibition, but is involved in pharmacokinetic drug interactions due to enzyme induction during polytherapy with the inducing AEDs phenobarbital, phenytoin and carbamazepine. These old AEDs also induce the (CYP-mediated) metabolism of tiagabine and zonisamide (7).

Enzyme inducers or inhibitors do not usually affect the renal clearance of drugs and consequently, the above three AEDs have not been involved in drug interactions. Consequently, gabapentin, pregabalin, vigabartin and levetiracetam have little or no interaction potential while topiramate's total clearance is induced and its fraction metabolized is increased by concomitant therapy with PB, PHT and CBZ. The elimination of the remaining new AEDs felbamate, lamotrigine, oxcarbazepine, tiagabine and zonisamide is by (P450-mediated and glucuronidation) metabolism. Consequently, these new AEDs are subjected to drug interactions due to enzyme induction (by PB, PHT, CBZ and other enzyme inducers) and enzyme inhibition (by VPA) (7). Lamotrigine and topiramate have a relatively long half-life of 20-30 hours and thus can be given twice daily with minimal fluctuations in their blood levels.

Unlike all other AEDs whose parent compound is the active entity, oxcarbazepine (OXC) and eslicarbazepine acetate (ESL) act as prodrugs to OXC monohydroxy derivative (MHD or licarzepine). MHD is the active entity following OXC and ESL treatment and its formation is mediated by cytosol arylketo reductase (OXC) or esterase (ESL). However the biotransformation of ESL is more stereospecific than that of OXC and therefore the ratio of (S)-MHD-to-(R)-MHD is 19 (ESL) and 4 (OXC) (3). MHD has been involved to a lesser extent than carbamazepine in drug interactions, but has been reported to alter OC plasma levels.

Except for vigabartin and tiagabine that act by single mechanism of action of GABA transaminase and GABA reuptake inhibition, respectively, all other AEDs work by a multiple mechanism of action (8, 9). The mechanisms of action of AEDs are: a) Inhibition of voltage gated sodium channels (e.g. PHT, CBZ, carisbamate, ESL lamotrigine, OXC, topiramate); b) Inhibition of T-type calcium channel (VPA ethosuximide); c) Binding to the $\alpha_2\delta$, auxiliary subunits of voltage-gated calcium channels (e.g. gabapentin, pregabalin); c) Modulation of the GABA system (e.g. barbiturates, benzodiazepines); d) Carbonic anhydrase inhibition (e.g. topiramate, zonisamide); e) Binding to SV2A, a membrane glycoprotein

present in the synaptic vesicles of neurons (e.g. levetiracetam, brivaracetam); and e) Activation of the Kv7, potassium channel that mediates the M-current which in turn acts as a brake on repetitive firing of neurons (e.g. retigabine) (9).

Compared to the old AEDs, the new AEDs offer certain PK advantages in terms of linear and less variable PK, complete oral absorption (except gabapentin) and lower interaction potential. Some new AEDs possess new mechanisms of action, but it remains to be seen to what extent these new mechanisms of action contribute to their efficacy to treat refractory (therapy-resistant) patients with epilepsy.

References

1. Bialer M, Johannessen SJ, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: A summary of the Eighth Eilat Conference (EILAT VIII). *Epilepsy Res.* 73, 1-52 (2007).
2. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Ninth Eilat Conference (EILAT IX). *Epilepsy Res.* 83, 1-43 (2009).
3. Bialer M. New antiepileptic drugs (AEDs) in clinical development which are second generation to existing AEDs. *Expert Opin. Invest. Drug*, 15, 637-647 (2006).
4. Rogawski MA. Diverse mechanisms of antiepileptic drugs in development. *Epilepsy Res.* 69, 273-284 (2006).
5. Perucca E, French J, Bialer M. Developing novel antiepileptic drugs (AEDs): Challenges, incentives and recent advances. *Lancet Neurol.* 6, 793-804 (2007).
6. Bialer M, Cloyd JC. General principles: Formulations and routes of administration. In: *Antiepileptic Drugs*, Fourth Edition, R.H. Levy, R.H. Mattson, B.S. Meldrum (Eds), Raven Press, New York, U.S.A., pp. 161-178 (1995).
7. Bialer M. The pharmacokinetics and interactions of new antiepileptic drugs (AEDs) : An overview. *Ther. Drug Monit.* 27:722-726 (2005).

8. Smith M, Wilcox KS, White HS. Discovery of antiepileptic drugs. *Neurotherapeutics* 4, 12-17 (2007).
9. Rogawski MA, Bazil CW. New molecular targets for antiepileptic drugs: $\alpha 2\delta$, SBV2A, and $K_v/KCNQ/M$ potassium channels. *Curr. Neuro..Neurosci. Rep.* 8, 345-352 (2008).