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Principles of antiepileptic drug treatment of epilepsy

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Abstract
For the successful treatment of epilepsy, accurate diagnosis of epilepsy and epileptic seizures, and proper selection of antiepileptic drugs (AED) according to the classification of epileptic syndromes are fundamentally important. Efficacy of AED treatment, however, depends not only on its pharmacological action but also on its efficient use, namely a rationally thinking tailor-made treatment considering the characteristics of each patients, i.e. individual differences in pharmacokinetics, factors influencing AED concentrations, AED interactions, and comprehensively their life style and psychosocial factors.

Key words antiepileptic drugs, drug interaction, drug-induced seizure deterioration, induced microseizures, pharmacokinetics, serum concentration (level), treatment of epilepsy.

INTRODUCTION
The prognosis of epilepsy has improved; the remission rate of childhood epilepsy has gradually improved up to 80%. Recent progress in epilepsy treatment has resulted from the development of International Classification of epileptic seizures and epilepsy/epileptic syndromes, not possible without advances in diagnostic procedures such as neuroimagings, electroencephalography (EEG) and magnetoencephalography (MEG), from the elucidation of pathogenic mechanism of epilepsy, and from the development of new antiepileptic drugs (AED), clarification of their mode of action, and advances in clinical pharmacology on pharmacokinetics and dynamics. These have enabled the rational treatment of epilepsy.

PRINCIPLES OF ANTIETEPILEPTIC DRUG TREATMENT OF EPILEPSY
Drug treatment of epilepsy consists of (i) confirming diagnosis of epilepsy; (ii) accurate classification of epileptic seizures and epilepsy/syndromes; (iii) proper AED selection according to the classification; (iv) initiation of AED, principally monotherapy from a small dose with gradual increase; (v) AED adjustment to the minimal effective dose (optimal maintenance dose) of the fewest number of AEDs as possible, monitoring AED responses in seizure frequency and epileptic discharges, and adverse effects; (vi) long-term regular AED intake; and (vii) trial of AED discontinuation in those with suppression of clinical seizures and epileptic discharges for a sufficient period. Highly variable AED and its dose useful for patients even with the same kind of epilepsy, highlights the importance of a tailor-made treatment for each individual with epilepsy.

CONFIRMING THE DIAGNOSIS OF EPILEPSY
The first step of diagnosis is the analysis of clinical seizure symptomatology. EEG plays an important role in the diagnosis and classification of epilepsy and epileptic seizures, particularly in childhood epilepsy because of the high detection rate of epileptic discharges; 870/1016 patients (85.6%) in the first EEG examination in our experience and 233/308 patients (75.6%) by Yoshinaga et al. which improved to 88.7% by the second and 92.3% by the third examination.1 Investigations on ictal events are of great importance. Direct neurophysiological seizure manifestation (i.e. excessive neuronal discharges) is detected by ictal EEG and MEG. Ictal SPECT, PET, functional MRI or cerebral blood flow provide useful supporting evidence, and serum prolactin level may be a clue for differentiating pseudo-seizures.

PRACTICALITIES OF ANTIETEPILEPTIC DRUG TREATMENT
Purpose
AED treatment is usually initiated when the recurrence risk of seizures exceeds risks associated with
treatment. Investigations on the prognosis of epilepsy have raised the controversial discussion as to whether or not the age-dependently self-limited epileptic syndromes such as benign childhood epilepsy should be treated. Benignity, however, is an important consideration when subtle cognitive impairment accompanying epileptic discharges has been reported.2

Antiepileptic drug selection

With increasing understanding of pathogenesis of epilepsy and acting mechanisms of AED, ‘rationally thinking treatment’ instead of blind ‘trial and error’ has been realized; rational AED selection corresponding to the accurate classification of epileptic seizures and syndromes and mode of AED action. The most effective AED should be selected for target epileptic seizures or syndromes. Carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), primidone (PRM), and zonisamide (ZNS) are drugs of choice for partial epilepsy, ethosuximide (ESM), valproate (VPA), benzodiazepines (BZP) for generalized epilepsy, and BZP, VPA and ZNS for both partial and generalized epilepsies.

Practical antiepileptic drug use

Broad application of concentration measurement and clarification of pharmacokinetics has made an epoch in AED treatment and demonstrated the demerits of polypharmacy and promoted monotherapy. Intractable epilepsy, however, often needs a strategy for rational polypharmacy. Although epilepsy needs long-term medication, there is no AED without side-effects. Moreover, there is a risk of new adverse effects. To promote the risk–benefit paradigm, medication should be adjusted to the best efficacy-to-toxicity ratio, considering both efficacy and safety in a ‘not dose-oriented but concentration-oriented’ manner.

PHARMACOKINETICS OF ANTIEPILEPTIC DRUGS

Concentration measurement enabled elucidation of drug pharmacokinetics.3 Steady-state concentration versus AED dose is not always linear. Non-linear kinetics with increasing level–dose ratio mainly by the saturated clearance (i.e. saturation or Michaelis-Menten kinetics), is observed in PHT and that with decreasing level–dose ratio in CBZ and VPA. Monitoring serum level and kinetics has made AED adjustment efficient and safe.

Drug interaction has also been clarified and disclosed the demerits of polypharmacy and promoted the merits of monopharmacy. There exists, however, cases that achieve poor seizure control under monopharmacy and need a strategy for rational polypharmacy considering the mode of action and kinetics of AEDs.

Pharmacokinetic parameters support the efficient use of AED. Elimination half-life (T1/2) indicates the dosing frequency or administration interval of AED, and the time to reach the steady-state level/maximal mean level which tells the appropriate time for the evaluation of AED efficacy. To adjust the time to peak concentration (Tmax) to the time of highest seizure frequency may produce maximal efficacy. Protein binding rates suggest the free fraction of AED; 20–28% in CBZ, 45–55% in PB, 7–15% in PHT, and 5–16% in VPA. Only free AED is transferred into the brain to exert AED action and also into maternal milk. Therapeutic range should be considered as the safely administrable range, but not the necessary range. Seizures could be successfully controlled under the therapeutic level in not so rare cases.

Mean AED serum concentration gradually elevates to the steady-state level by 5-6-fold T1/2 as the same course of continuous i.v. administration of that dose. It is desirable to take AED with shorter interval than T1/2 to get sufficient serum level in a relatively low dose. To obtain rapid efficacy, the initial loading doubled dose quickly makes the steady-state level.

FACTORS INFLUENCING SERUM DRUG CONCENTRATIONS

Age

Reflecting the speeds of metabolism and clearance, age factors influence AED half-life and concentration. Half-life is usually shortest in infancy and early childhood and prolongs toward newborn and further for premature, and the other way toward school children, adults, and into older age. Accordingly, AED dosage per kg is greater in children than it is in adults.

Genetics

Interindividual variability in serum level is large even in the same dose. This is often the result of the genetic differences for drug metabolizing enzymes or transporters. Recently, genetic polymorphism has been clarifying in cytochrome P450 enzymes in the liver,5 proving the formerly known concept of slow and fast metabolizers.
Variation in pharmacokinetics

Variation in pharmacokinetics may occur at various sites of bioavailability, metabolism, elimination, protein binding and drug interactions.

Dissolution/absorption is influenced by differences in drug formula, grain size, existence of capsule, kind of excipient, way of administration, food content, time relation between meal and AED, and digestive tract disorders. It is better to monitor serum levels before and after the change in formula.\(^5\)

AED absorption is partly influenced by gastric emptying rate (GER), which differs from food and its content; prolonged GER, in carbohydrate-rich food than in protein/fat-rich foods, makes drug absorption gradual, usually resulting in prolonged \(T_{\text{max}}\) and lowered \(C_{\text{max}}\). Fat-soluble drugs, such as PHT, are well absorbed showing elevated \(C_{\text{max}}\) and area under curve (AUC) when taken after meals, but a water-soluble drug like VPA makes a higher concentration if taken before meals because food inhibits its absorption. Thus, PHT is recommended to be taken after meals, and VPA before meals. Small amounts of alcohol accelerates GER, but lowers the drug level by enzyme induction.

Drug interactions

Combined drugs mutually alter the antiepileptic and/or neurotoxic effects and serum concentrations. Complex pharmacokinetic interactions occur at various sites of absorption/dissolution, of metabolism, such as enzyme induction or inhibition, of protein binding, and of excretion partly influenced by urinary pH.\(^6\)

PB, PHT, CBZ and PRM are enzyme inducers. CBZ also induces its own metabolism (autoinduction). PHT markedly accelerates the conversion of PRM to PB. AED of a high protein binding rate such as PHT, VPA, BZP, and CBZ compete at the binding site and increase the free fraction which is proportional to its CSF or brain concentrations and exerts AED efficacy or toxic effect, but is usually eliminated rapidly. VPA is not an enzyme inducer, but inhibits the biotransformation of PB, ESM, lamotrigine, and CBZ-epoxide. A combination of VPA and PHT inhibits the serum increase of both drugs. PB level is elevated by its suppressed excretion caused by urinary acidification of VPA. Drug interaction occurs not only with other AED but with drugs that are not AED, such as antibiotics and antipyretics. Pharmacodynamic interactions are more difficult to quantify.

Specific conditions

Menstrual cycle, pregnancy, and various disease conditions, particularly with hepatic or renal dysfunction and decreased serum protein, often influence drug kinetics.

Pregnancy lowers serum AED level due to complex factors such as increased bodyweight, distribution volume and metabolism. Dose adjustment for it may risk intoxication after delivery. The use of folate to avoid teratogenicity has become common. Folate may decrease serum levels of PB and PHT, in addition to its own lowering effect of seizure threshold observed in animal experiments. Monitoring of serum AED level and careful seizure observation are important with those who are pregnant.

Severely handicapped patients may experience different pharmacokinetics which have been verified by the long-lasting gradual increase in serum PHT level after changing its powder form to granules.

Altered drug property

To compensate for the short half-life of VPA, its slow-release form (VPA-R) has been widely used, with prolonged \(T_{\text{max}}\) by the gradual dissolution keeping the same AUC. As some granule type VPA-R may dissolve faster in a high humidity, they should be carefully stored so as to maintain their sustained release properties.\(^7\) Twice-a-day administration of VPA-R minimizes serum level variations with lowered \(C_{\text{max}}\) and elevated \(C_{\text{min}}\), but once-a-day VPA-R enlarges serum variation with lowered \(C_{\text{max}}\) and \(C_{\text{min}}\), compared with twice-a-day VPA. Efficacy, however, is not always higher in VPA-R than in VPA even at its twice-a-day administration.

Antiepileptic drug-induced seizure deterioration

AED do not always improve but can sometimes worsen seizure control or can induce new types of seizures.\(^8\) Although its mechanism is not fully elucidated, suspected patterns are (i) paradoxical intoxication by PHT, CBZ, vigabatrin (VGB), tiagabine, VPA; (ii) narrow spectrum (relatively specific drug effect); worsening of generalized convulsions by ESM, ACTH, CBZ, VGB, trimethadione; of absence, myoclonic, or atonic seizures by CBZ, VGB, PB, PHT, gabapentin; of tonic seizures, induced microseizures by BZPs, PB, ZNS; of epileptic negative myoclonus by PB, CBZ, VGB; (iii) impaired alertness (hypnotic-sedative effect) by BZPs, PB; (iv) drug combination; induction of absence status by combined CZP and VPA; and (v) metabolic derangement: PHT encephalopathy. VPA encephalopathy. This may be caused by (i) incorrect classification of epileptic seizures or syndromes; (ii) improper AED selection; or (iii) excessive dosing or drug combination. Care should be taken to not overlook other factors than negative AED effects.
Comprehensive management

Even in childhood epilepsy with generally favorable prognosis, 10–30% are intractable cases, among which 50–60% are truly refractory cases resistant to all available conservative treatment. About 40% of seemingly intractable cases might be insufficiently or improperly treated.

Sufficient AED treatment is not expected without the cooperation of patients and/or their guardians in reporting changes in clinical features and incidence of seizures, compliance in taking medicine, and avoiding other seizure-activating factors in daily life, such as insufficient sleep, mental/physical strains, smoking or drinking. In epilepsy, which needs long-term medication, comprehensive treatment that considers quality of life, such as adaptation to community or school, employment, marriage or pregnancy, is important under the mutual reliance and cooperation among patients, guardians and physicians.

REFERENCES


