TDM for new generation anti-epileptic drugs

Ikuko Yano, Ph.D.
Department of Pharmacy, Kobe University Hospital
JAPAN

Scope of the lecture:
Pharmacokinetics of new generation anti-epileptic drugs (AEDs) will be introduced and together with the factors that can cause large differences in dose requirements between and within individuals. In addition, the rationale and clinical issues related to the TDM will be discussed. Finally, our pharmacokinetic and pharmacodynamic analyses using the TDM data will be introduced.

Learning objectives:
1. Pharmacokinetics of newer AEDs
2. Reference range *versus* therapeutic individual concentration
3. TDM in Japan

Extended abstract:
Backgrounds and introduction

The majority of epilepsy patients have good control over their seizures with the use of anti-epileptic drugs (AEDs), however, approximately 30% of patients exhibit drug-resistant epilepsy, which is defined as "a failure of adequate trials of two tolerated, appropriately chosen and used anticonvulsant drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom" according to the International League Against Epilepsy (ILAE). Seventeen new generation AEDs have been licensed for clinical use during the last 20 years, and have brought more treatment options and increased ease of use.

Since seizures occur at irregular intervals, AEDs therapy is generally experiential and prophylactic. Therapeutic drug concentration monitoring (TDM) was initiated for old AEDs in the late sixties, and their large pharmacokinetic variability also promotes TDM to the effective therapeutic strategy for individual patients to produce the seizure suppression by AEDs and to minimize their adverse effects. On one hand, routine TDM for most of newer AEDs is not supported by several studies, since the relation between their serum concentration and response is highly variable from one patient to another.

In my talk, pharmacokinetics of new generation AEDs will be summarized, and the rationale and clinical issues related to the TDM will be discussed. Some our experiences of TDM of newer AEDs will be introduced.

Pharmacokinetics of newer AEDs

Since almost all the first-generation AEDs, such as carbamazepine, phenobarbital, phenytoin, and valproate, are extensively metabolized by the liver and are highly protein bound, drug-drug interactions among AEDs are important issues for the combination therapy. A part of new generation AEDs, such as gabapentin, topiramate, levetiracetam, felbamate, and vigabatrin are eliminated mainly or partly by renal excretion in unchanged form, and drug-drug interactions are less important compared with older AEDs. Since lamotrigine metabolism is accelerated by enzyme-inducing AEDs and inhibited by valproate, a large interindividual variation in the dose-concentration relationship is shown. Oxcarbazepine is a prodrug for the monohydroxy-derivative (MHD), and its pharmacokinetics is much less variable than carbamazepine.

Necessity of TDM

An updated overview on TDM of newer AEDs has recently published by Jacob and Nair. The need for TDM of newer AEDs are divided into "frequent" (stiripentol; zonisamide; tiagabine; lamotrigine), "intermediate to frequent" (rufinamide), "intermediate" (eslicarbazepine acetate; vigabatrin; pregabalin; levetiracetam; topiramate; felbamate), and "uncommon" (lacosamide; gabapentin). In another review by Schmidt and Schachter, they list the target plasma concentration of felbamate, lamotrigine, and oxcarbazepine in addition to the old AEDs of carbamazepine, phenobarbital, phenytoin, primidone, and valproate.

A complicated drug-drug interaction of lamotrigine indicates that its effective use may be facilitated by application of TDM. In addition, several studies have demonstrated pronounced alterations in the pharmacokinetics of lamotrigine as well as levetiracetam and the active metabolite MHD of oxcarbamazepine during pregnancy. Since much less is known about the pharmacokinetics of other newer AEDs during pregnancy, more data are needed.

Reference range versus individual therapeutic concentration

According to the best practice TDM guidelines for AEDs by ILAE in 2008, the "reference concentration range" means as a serum concentration range, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur. On the other hand, the "individual therapeutic concentration" is associated with the best possible response and should be selected on the basis of symptoms and associated risks in a given person. Since the reference concentration range may not always be "therapeutic", "effective", or "target", clinical judgment should not be based solely on serum concentrations, and some individuals will derive optimal benefit at concentrations outside the reference range. The concept of the "individual therapeutic concentration" is that it does not rely on the fixed therapeutic ranges, and can be applied to any AED, for some of which reference ranges have not yet been clearly defined.

TDM in Japan

Best practice TDM guidelines for AEDs by ILAE in 2008 shows the reference range of newer generation AEDs. By reference to this guidelines, the TDM guidelines for AEDs by the Japanese Society of Therapeutic Drug Monitoring indicates the reference range of four newer AEDs as follows: gabapentin 2 - 20 mg/L; topiramate 5 - 20 mg/L; lamotrigine 2.5 - 15 mg/L; levetiracetam 12 - 46 mg/L.

Serum concentrations of these four AEDs have been routinely measured by using ultra-performance liquid chromatography with tandem mass spectrometry in Kyoto University Hospital. Routinely monitored concentration data were retrospectively compared with their reference values. In addition, some our researches on population pharmacokinetics and pharmacogenomics for individualized therapy of AEDs will be introduced.

Conclusion

Although the importance of TDM varies among newer AEDs, TDM can help to know an individual therapeutic concentration, at which each patient exhibits the best response. With this concept, TDM may provide important information for the individualized dosage of newer AEDs in patients with unexpected treatment outcomes or in situations associated with pharmacokinetic alterations.

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