

# Reappraisal of TDM in Pharmacogenomic Generation

Hirotoishi Echizen, MD, PhD  
Meiji Pharmaceutical University  
Japan

## Scope of the lecture:

To review the exposure-response relationship of drugs for TDM and reappraise the concept of therapeutic drug concentrations.

## Learning objectives:

1. To review approaches for incorporating pharmacodynamic information into TDM.
2. To reappraise the concept of therapeutic drug concentrations in TDM.

## Extended abstract:

Therapeutic drug monitoring (TDM) has been firmly established as one of the clinical disciplines that are useful for guiding doses of drugs toward better therapeutic outcomes. TDM is particularly useful in patients whose pharmacokinetics of drugs are deviated from average patients due to renal or hepatic dysfunction or polymorphisms of drug metabolizing enzymes or transporters. Plasma (or serum) therapeutic or toxic concentrations have been proposed for many drugs based mainly on uncontrolled clinical observations of patients whose plasma drug concentrations were monitored and interpreted in the light of concomitantly observed pharmacological effects. Since the concept of therapeutic plasma concentrations is simple and easy to understand to prescribers to titrate drugs with narrow therapeutic range, TDM has prevailed in routine clinical practice. Advances in the understanding of physiological pharmacokinetic (PK) models and developments of tools for modeling and simulation enabled forecasting drug exposure to organs possible. Adopting appropriate pharmacodynamic (PD) models, we can also estimate the time-course of pharmacological effects of drugs. Consequently, numbers of drugs to which TDM was implemented have increased substantially.

In contrast to remarkable advances in the understanding of PK-PD relationship of many drugs, it appears that only few attempts have been made for sophisticating the concept of therapeutic plasma concentrations. Therapeutic concentrations of many drugs have been proposed based on the analysis of the exposure-response relationships on uncontrolled clinical observations in small number of patients. Nevertheless, previous studies revealed that surrogate biomarkers of drug efficacy do not necessarily be tightly linked to their ultimate outcomes. For instance, it was revealed in the CAST that doses of antiarrhythmic drugs associated with suppression of arrhythmias did not warrant improvement of survival but rather deteriorated clinical outcome as compared placebo in patients with a previous history of myocardial infarction. These findings revealed that plasma concentrations of

antiarrhythmic drugs associated with immediate antiarrhythmic effects would not be relevant therapeutic concentrations. While higher serum concentrations of digoxin within therapeutic range (1.2 to 2.0 ng/mL) were associated with better inotropic effects on left ventricular than lower concentrations, the latter (0.5 to 0.8 ng/mL) was shown to be associated with better survival in patients with heart failure. Subsequently, therapeutic concentrations of digoxin have been reappraised. In this context, therapeutic plasma concentrations should be established in the light of the relationships between exposure and clinical events that are associated more closely to ultimate therapeutic outcomes.

Since the introduction of the concept of evidence based medicine (EBM) in 1990s, any recommendations to decision-making process in clinical practice are required to be presented with probabilistic descriptions (e.g., hazard ratio, number needed to treat and others). In the era of EBM naïve concept of traditional therapeutic plasma concentrations of TDM appears less attractive than other recommendations or even obsolete to practitioners. In this context, we are request to reappraise traditional therapeutic plasma concentrations of drugs with controlled clinical studies or cohort studies with a large number of patients with which plasma concentrations of drugs and other clinical variables are analyzed comprehensively. Particularly, recent advances in pharmacogenomic research have shed light on the genetic variants of receptors or enzymes involved in the signal transduction of PD. Many genetic variants of functional proteins have been discovered to be associated with a large interindividual variability of PD in many drugs. Some of them have already been incorporated in the dose individualization formulas. Collectively, plasma drug concentrations should be assessed their contributions to ultimate clinical responses along with genetic and/or non-genetic PD variables. For instance, different therapeutic plasma concentrations may be proposed for patients having different PD variables. Eventually, plasma drug concentrations may be incorporated into one of the variables of formulas forecasting individualized doses of drugs to patients having variable clinical backgrounds.