

**Materials and Methods:** This study sought a suitable physiological parameter related to daily phenytoin dose ( $D$ ) providing a steady-state serum concentration ( $C_t$ ) and analyzed the influences of coadministered antiepileptic drugs on  $C_t$  quantitatively to adjust phenytoin dosing. Data was derived from a total of 368 epileptic patients treated with multiple oral administrations of phenytoin (PHT). Phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA), zonisamide (ZNS), clonazepam, and ethosuximide were co-administered. For the administration of PHT alone, four types of parameters, *i.e.*, total body weight, total body water volume, body surface area, and extracellular water volume ( $V_{ECW}$ ) were examined. Then, a Michaelis-Menten kinetic model was postulated including  $V_{ECW}$ , which was assumed to detect the effect of the coadministered drug quantitatively.

**Results:** Adopting  $V_{ECW}$  as a transforming factor, the level/dose ( $L/D$ ) ratio ( $C_t/(D/V_{ECW})$ ) was independent of the patient's age and gender in relation to  $C_t$  and expressed as  $C_t/(D/V_{ECW}) = 0.0245 \times C_t + 0.076$ . Analysis clarified that ratios were estimated as 0.90, 0.91, 0.89, and 0.84 for PB, CBZ, VPA, and ZNS, respectively, to maintain the same  $C_t$  level of PHT. Influences were not detected as the number ( $\geq 2$ ) of coadministered drugs increased, regardless of factor type.

**Discussion:** PHT clearance changes in an age-dependent manner, and is usually poorly correlated with weight-based dosages.  $V_{ECW}$  is more closely correlated with age-dependent changes in physiological parameters such as clearance.  $V_{ECW}$  was considered to remove the influence of age on clearance, and estimated ratios could be used for all age groups.

**Conclusions:** In the case of the addition or removal of concomitant treatment with antiepileptic drugs in the same patient, the daily PHT dose was calculated using the value of each ratio or its reciprocal. The present results will be helpful in determining PHT dosing.