적정약물요법을 위한 약동학/약력학적 개념

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Dosing Methods

1) trial and error method
2) nomogram or algorithm: based on the population pharmacokinetics
   ex) Sarubbi-Hull nomogram, Hurst algorithm for aminoglycosides
3) Feedback method: dose adjustment with parameters estimated from prior measured concentration data(TDM)
   - simple dose adjustment : Dose = Cpss,des x Cl(Dose,old/Cpss,meas)
   - nonlinear least square regression method
   - Bayesian method

Interpretation of plasma drug concentration:

1) is within therapeutic range
2) if supra- or sub-therapeutic level, is there any reason ?
3) if beyond the therapeutic range, is need feedback dose adjustment ?

"Target Concentration Strategy"

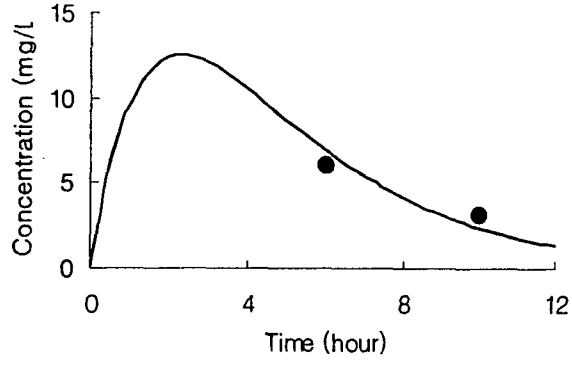
- the measured concentration in therapeutic range : target concentration
- the measured concentrations in toxic or subtherapeutic range
  ⇒ dose adjustment with using pharmacokinetic principles to be in therapeutic range

Therapeutic Range:

- term derived from clinical pharmacology
- probability concept from plasma drug concentration-response relationship
- hypothetical range above which toxic effect become manifest and below which a therapeutic effect is absent
- usually for total drug concentration

Nonlinear least square regression:

· fitting of pharmacokinetic model to the concentration data with maximum likelihood principle



$$OBJ = \sum_{i=1}^{n} \frac{(Ci - \hat{C}i)^2}{\sigma i^2}$$

· estimation of pharmacokinetic parameters: from the patient' s concentration data only

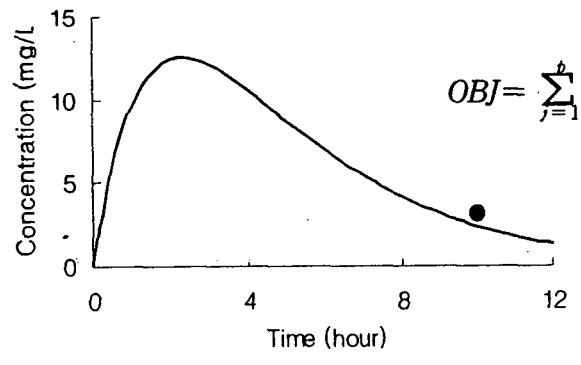
· minimum number of concentration data: depends on the number of parameters in the pharmacokinetic model - e.g.) aminoglycoside - one compartment (Vd, Cl): 2 samples

※ modified least square method: fixing one or more parameter values

Bayesian method

· Bayes theorem and maximum likelihood estimation

$$prob(p \mid c) = \frac{prob(p) \times prob(c \mid p)}{prob(c)}$$



$$OBJ = \sum_{j=1}^{p} \frac{(Pj - \hat{P}j)^2}{\sigma pj^2} + \sum_{i=1}^{n} \frac{(Ci - \hat{C}i)^2}{\sigma i^2}$$

· can reduce number of sampling point

· require population pharmacokinetic parameters estimated previously

· need software to estimate the pharmacokinetic parameters (pharmacokinetic analysis) of each patient:PKs, USC package, etc.

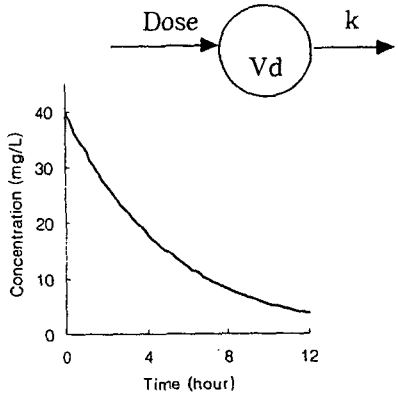
Pharmacokinetic Analysis:

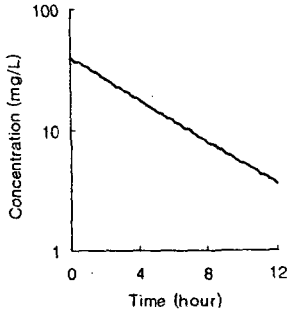
- Compartmental Analysis
  - · need pharmacokinetic model and sophisticated calculation
  - · point prediction, need minimum samples
    - → good for TMD dose adjustment
- Noncompartmental Analysis
  - · not required model or sophisticated calculation
  - · need many data points → not useful clinically, only for research

Pharmacokinetic Compartment Models:

1. One Compartment Model

1) Single IV bolus dose



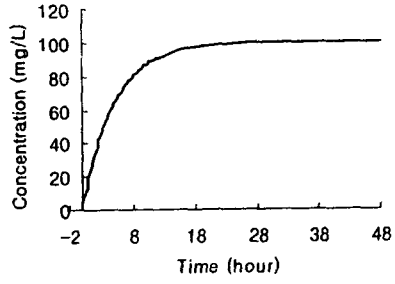


$$Cp = Dose/Vd(e^{-k*t})$$
$$= Cp_0e^{-k*t}$$

$$lnCp = ln(Dose/Vd) - 2.303k*t$$
$$lnCp = lnCp_0 - 2.303k*t$$

$$t_{1/2} = ln(Cp_0 / 1/2 \times Cp_0)/k$$
$$= ln2/k = 0.693/k$$

2) Single IV Continuous Infusion



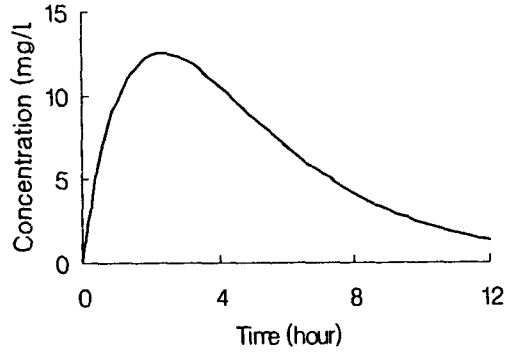
$Cp = R_0/Cl\ (1-e^{-k*t})$

$= Cpss\ (1-e^{-k*t})$

Time at one half-life:
reach to 50% of Cpss

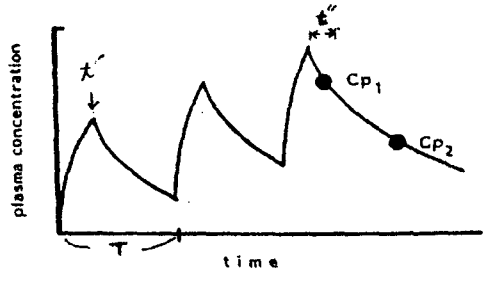
- Time to reach steady-state: determined by half-life

3) Single Oral (extravascular) dose



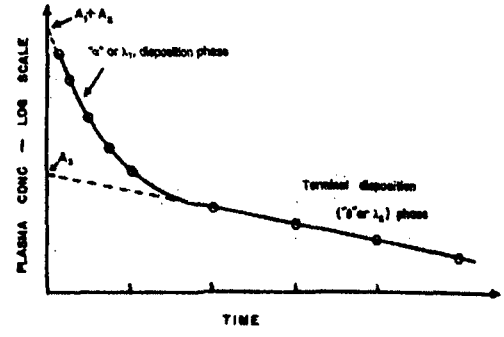
$$Cp = \frac{F \cdot Dose \cdot ka}{Vd(ka-k)} \times (e^{-k*t} - e^{-ka*t})$$

4) Multiple intermittent IV infusion



$$Cpn = \frac{R(1-e^{-k*t'})(1-e^{-nk*T})}{Cl(1-e^{-k*T})} \times e^{-k*t''}$$

2. two compartment model



Drugs which action site are in central compartment (rapid kinetic equilibrium with intravascular space):
lidocaine, procainamide, NAPA, thiopental

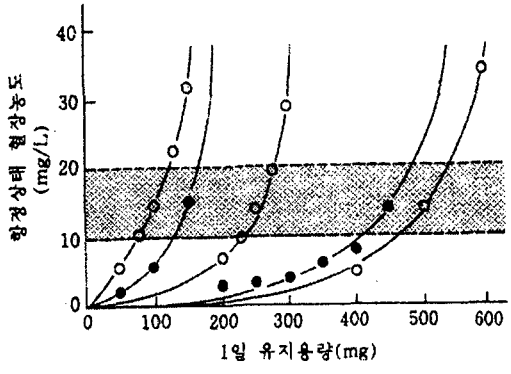
- plasma concentration at distribution phase: related to the effect
  cf) slow tissue distribution: e.g. digoxin
- sampling after completion of distribution

3. Nonlinear Pharmacokinetics

- e.g. phenytoin, salicylate, ethanol

· therapeutic range: above the Km value

· nonproportional higher increase of plasma concentration after small change of therapeutic dose

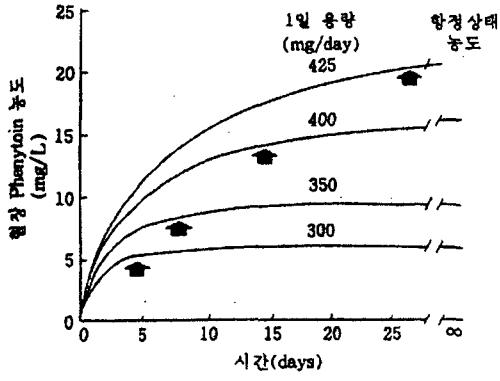


Phenytoin 유지용량과 항정상태 혈장농도 (Cpss) 의 관계

at steady-state,

$$F \cdot (Dose/T) = \frac{Vmax \cdot Cpss,ave}{Km + Cpss,ave}$$

Phenytoin 유지용량 (daily dose) 증가에 따른 항정상태 도달 시간의 연장 및 항정 상태 혈장농도 (Cpss)



· half-life : change according to the plasma concentration

$T_{1/2} = 0.693Vd \times K_m/V_{max} + Cp_{ss,ave}$

Simulation (Prediction) of Plasma Drug Concentrations:

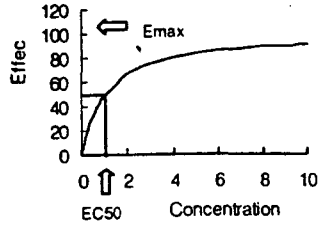
· Main PK parameters determining plasma drug concentrations:
- Concentration following initial or loading dose: Vd
  cf) immediately after rapid IV infusion: Vc
- steady-state concentration: clearance, bioavailability
- time course of drug concentration: half-life

· Prediction of new steady-state concentration: can be estimated by pre-determined PK parameters obtained from prior concentration of TDM with appropriate PK model

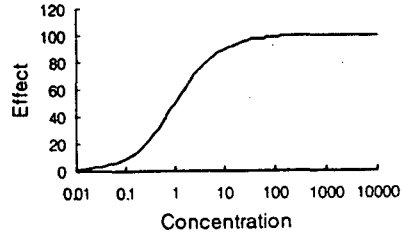
Pharmacokinetic / Pharmacodynamics Analysis

Concentration-Response relationship

1) Emax model



$$E = \frac{Emax \cdot Conc}{EC50 + Conc}$$



Log transformation
: frequently used

Terminology

E: drug effect

Conc: concentration at the receptor (plasma ?)

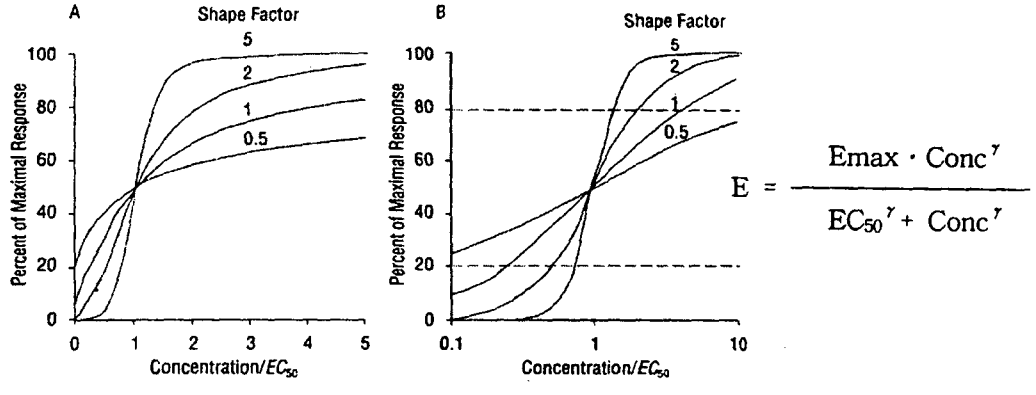
Emax: maximum drug effect (maximum change in effect produced by the drug) used to measure the efficacy (intrinsic activity) of a drug

EC_{50}: the effect concentration of drug that causes 50% of the maximum response used to measure the potency of a drug

Low EC_{50} means high potency

2) Sigmoid Emax model

: steep concentration response



$$E = \frac{Emax \cdot Conc^{\gamma}}{EC_{50}{}^{\gamma} + Conc^{\gamma}}$$

γ: Hill's coefficient, determine the steepness of the curve (generally $1<\gamma<3$)

$\gamma>3$: all or none response

- Interindividual difference: EC_{50} and γ (also in Emax)
- different EC_{50} within individuals : different operation condition by alfentanil (upper abdominal surgery >lower abdominal surgery > breast surgery)
- Time course of tolerance: minutes to weeks, by depletion of endogenous transmitter or receptor, or homeostatic mechanism (e.g. blood lowering effect of nifedipine after prompt increase or slow continuous increase of concentration)

3) linear model

$E = \alpha \cdot Conc + E_0$

- concentration data bolow EC_{50} value of the drug

The onset, duration, and intensity of a drug

1. drugs that distribute rapidly to the action site

- relate to the drug disposition
- assumption: i) drug acts recersibly and directly at the site of action to produce a response
  ii) metabolites are not involved in response (inactive metabolite or very low concentration)
  iii) no tolerance, no affect on its own pharmacokinetics

1) onset of action: time to reach threshold concentration(minimum effective con)
   - determined by release rate of drug from its dosage form, route of administration, distribution to target site, etc
   - increasing dose, subjects with low EC_{50}: shortened onset time
2) duration of action: duration of maintaining threshold concentration (MEC)
   - determined by dose and rate of drug removal from action site

   A) single bolus dose
      - duration: proportional to log dose
        $t_d \propto \log(Dose/Am)$, Am: minimum amount needed in the body
        doubling of dose: increase duration by one half-life of the drug
        ($t_d = t_d + t_{1/2}$)

   B) multiple bolus dose
      - intensity and duration: increase after second dose
      - no further increase of effect after third or subsequent doses

2. drugs that distribute slowly to the action site

- consider two compartment distribution
- determined by speed of equilibration of drug at site of action and size of dose

A) Single bolus dose
   : the situation in which site of action is in a rapidly equilibrating, well perfused tissue
   - peak effect: immediately after IV dose, effect is directly related to plasma concentration
   - duration of effect: increase disproportionally with log dose at small doses, proportional increase with log dose when the effect wears off in the terminal phase (e.g. d-tubocurarine)

B) multiple dosing
   a) site of action is in a rapidly equilibrating, well perfused tissue
      - duration of effect: progressively longer until the amount eliminated from body equals the dose administered ($\because$ rise of drug in slow equilibrating tissue after repeated dose $\rightarrow$ diminish the

tendency to distribute out from blood and other rapidly equilibrating tissue)

- intensity of effect: no further increase beyond the second dose

b) site of action is in a slowly equilibrating

- delayed onset of effect, delayed wear off of effect after discontinuation of dose due to slow equilibration

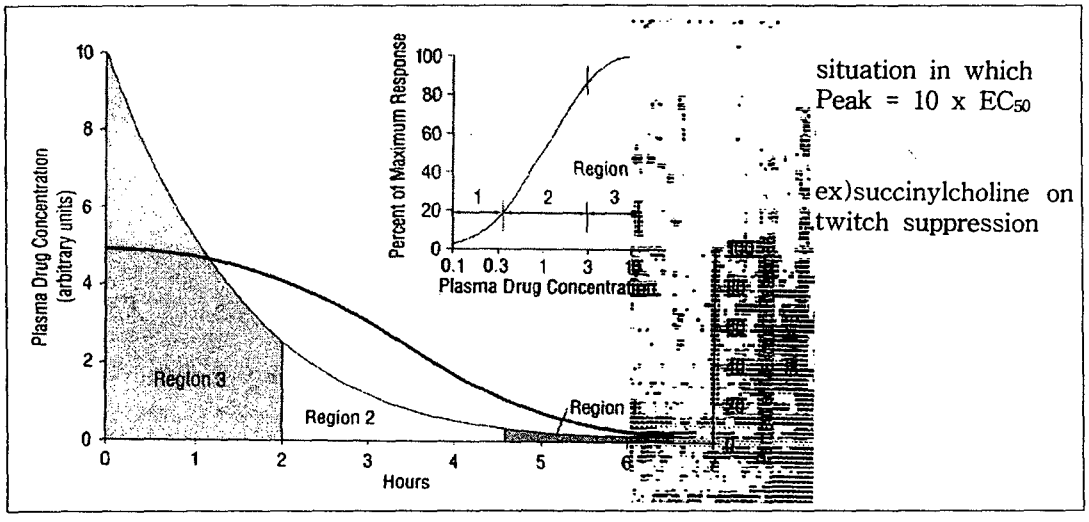
cf) methotorexate: delayed wear off of effect due to tight binding of drug at action site

Time course of intensity of effect

1. drugs that distribute rapidly to the action site

assumption: constant concentration-response relationship at all times one compartmental distribution and first order elimination

1) IV bolus dose



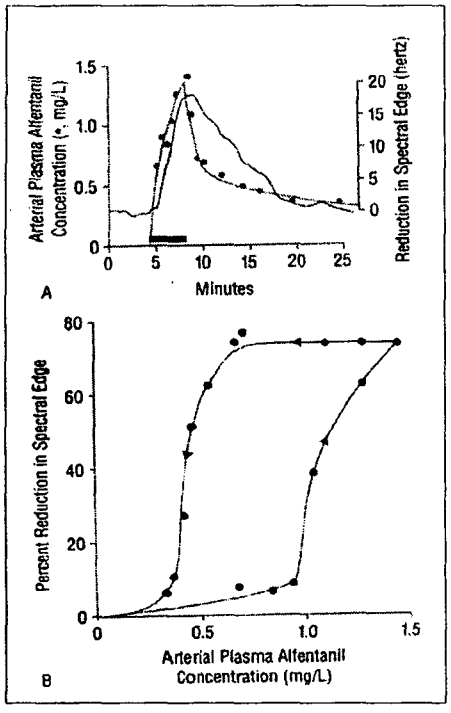
※ situation in which peak concentration is around EC50: proportional decrease of effect

2) Other mode of administration

- much more complex than IV bolus, no general answer
- same dose of furosemide, but greater natriuretic effect of 8mg bolus and 8-hour infusion of 4mg/h than the effect of 40mg bolus dose

2. drugs that distribute slowly to the action site

- time lag between effect and plasma concentration
- **hysteresis** (mean: late) in concentration-response relationship



Counterclockwise hysteresis:

i) delayed distribution to action site
ii) formation of active metabolite
iii) increased sensitivity (up-regulation of receptor)
iv) indirect measure of true effect
v) can observe response only when concentration of endogenous compound falls below to critical value

Clockwise hysteresis (proteresis)

1) development of tolerance
ii) formation of inhibitory metabolite
iii) effect site equilibrates with arterial blood drug concentrations faster than does the concentration at sampling site (forearm venous blood)

* Pharmacokinetic /pharmacodynamic simutaneous modeling

: - understand the concentration-response relationship that accounts for the delay or equilibration between plasma concentration and action site (effect site)

- advantage: can use nonsteady-state data to understand pharmacodynamics

References

1. Rowland M and Tozer TN. Clinical Pharmacokinetics: Concepts and Applications. 3rd ed., Williams & Wilkins, Baltimore, 1995
2. Evans WE, Schentag JJ, Jusko WJ. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. 3rd ed., Applied Therapeutics, Inc. Vancouver, 1992