Designing Individualized Dosage Regimens Using One Compartment Model Equations

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Introduction

- The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions.

- One compartment model equations can be used to compute initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient.

Introduction

- The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured.

- At that time, individualized dosage regimens at steady state can be designed for a patient.

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Intravenous Bolus

- If the **Vd** & **K_e** can be estimated for a patient, a loading dose and **initial** maintenance dose can be computed.

- To design these doses, estimates of pharmacokinetic constants are obtained using patient characteristics such as
  - *Weight*
  - *Age*
  - *Gender*
  - *Renal and liver function*
  - *Other disease states & conditions that are known to effect the disposition and elimination of the drug*

Intravenous Bolus

- When the actual K_e and Vd are measured for the medication, a maintenance dose to achieve any target steady-state concentrations can be designed.

- If the patient has never received the drug before, the therapeutic range can be used to choose starting concentrations.

- If the patient has taken the drug on previous occasions, safe and effective concentrations may be known.

Intravenous Bolus

- The dosage interval (τ) can be computed using the desired maximum (Css_{max}) and minimum (Css_{min}) steady state concentrations:

Css_{max} occurs (t = 0 hour after the bolus is given)

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$$

$$D = [Css_{max} V(1 - e^{-ke\tau})]/e^{-k e (0 h)}$$

$$LD = Css_{max} V$$

Intravenous Bolus

- An example, a patient that needs to be treated for complex partial seizures with intravenous phenobarbital.

- An initial dosage regimen is designed using population pharmacokinetic parameters (k_e = 0.139 d^{-1}, V = 50 L)

- To achieve Css_{max} & Css_{min} equal to 30 mg/L and 25 mg/L, respectively.

Intravenous Bolus

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$$

$$= [\ln (30 \text{ mg/L}) - \ln (25 \text{ mg/L})] / 0.139 \text{ d}^{-1} = 1.3 \text{ d}$$

round to a practical dosage interval of 1 d

$$D = Css_{max} V(1 - e^{-k_e \tau})$$

$$= (30 \text{ mg/L} \cdot 50 \text{ L})(1 - e^{(-0.139 \text{ d}^{-1})(1 \text{ d})})$$

$$= 195 \text{ mg}$$, round to a practical dose of 200 mg.

The patient would be prescribed intravenous phenobarbital 200 mg daily.

Continuous Intravenous Infusion

- An example, a patient with a ventricular arrhythmia after a myocardial infarction needing treatment with lidocaine at a Css of 3.0 mg/L (population pharmacokinetic parameters used: V = 50 L, Cl = 1.0 L/min)

LD = CssV

= (3 mg/L)(50 L) = 150 mg

k_0 = CssCl

= (3 mg/L)(1.0 L/min) = 3 mg/min

The patient would be prescribed lidocaine 150 mg intravenously followed by a 3 mg/min continuous infusion.

Intermittent Intravenous Infusion

- For intermittent intravenous infusions, the dosage interval (τ) is computed by choosing Css_{min} and Css_{max} :

$$\tau = [(\ln Css\ max - \ln Css\ min)/ke] + t'$$

t‘: is the infusion time

- The maintenance dose is calculated by

$$k_0 = Css_{max}\ k_e\ V[(1 - e^{-ke\ \tau})/(1 - e^{-ke\ t'})]$$

- Loading dose:

$$LD = k_0/(1 - e^{-ke\ t})$$

Intermittent Intravenous Infusion

- An example, a patient receiving tobramycin for the treatment of intraabdominal sepsis.

- Using pharmacokinetic parameters (V = 20 L, k_e = 0.087 h^{-1}) previously measured in the patient using serum concentrations.

- **Compute** a tobramycin dose (infused over 1 hour) that would provide Css_{max} & Css_{min} of 6 mg/L and 1 mg/L, respectively.

Intermittent Intravenous Infusion

$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$

$= [(\ln 6\ mg/L - \ln 1\ mg/L) / 0.087\ h^{-1}] + 1\ h$

$= 22\ h$, round to practical dosage interval of 24 h

$k_0 = Css_{max}\ k_e\ V[(1 - e^{-k_e \tau})/(1 - e^{-k_e t'})]$

$= [(6\ mg/L)(0.087\ h\text{-}1)(20\ L)][(1 - e^{(-0.087\ h\text{-}1)(24\ h)})/(1 - e^{(-0.087\ h\ -1)(1\ h)})]$

$= 110\ mg$

- The patient would be prescribed tobramycin 110 mg infused over 1 hour every 24 hours.

Extravascular

- The dosage regimen for extravascular doses is determined by choosing Css_{max} & Css_{min}:

$$T = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$$

T_{max} is the time that the maximum concentration occurs

$$D = [(Css_{max}\ V)/F][(1 - e^{-ke\ T})/e^{-ke Tmax}]$$

$$LD = (Css_{max}\ V)/F$$

Extravascular

- An example, a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, k e = 0.05 h-1, T max = 3 h, F = 1.0) and maintain Css_{max} & Css_{min} of 80 mg/L and 50 mg/L, respectively:

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$$

$= [(\ln 80\ mg/L - \ln 50\ mg/L) / 0.05\ h^{-1}] + 3\ h$

$= 12.4\ h$, round to practical dosage interval of 12 h

Extravascular

$$D = [(Css_{max}\ V)/F][(1 - e^{-ke\ \tau})/e^{-keTmax}]$$

$$=[(80\ mg/L \cdot 12\ L)/1.0)][(1 - e^{(-0.05\ h\text{-}1)(12\ h)})/e^{(-0.05\ h\text{-}1)(3\ h)}]$$

$$= 503\ mg,\ round\ to\ practical\ dose\ of\ 500\ mg.$$

- The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.

Average Steady-State Concentration

- If the drug is administered as a sustained-release dosage form or the half-life is long compared to the dosage interval, it is possible to use the average steady-state concentration equation to individualize doses.

- The dosage regimen is computed using the following equation:

$$D = (Css\ Cl\ \tau)/F$$

$$D = (Css\ k_e\ V\tau)/F$$

$$LD = (CssV)/F$$

Average Steady-State Concentration

- An example, a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h based on current procainamide continuous infusion; F = 0.85, τ = 12 h for sustained-release tablet) and an average steady-state procainamide concentration equal to 5 mg/L:

$$D = (C_{ss}\, Cl\, \tau)/F$$

= (5 mg/L · 24 L/h · 12 h) / 0.85 = 1694 mg, round to a practical dose of 1500 mg

- The patient would be prescribed procainamide sustained-release tablets 1500 mg orally every 12 hours.

Any Questions ?????????