Case Study IV
PHA 5128
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Case 1:

A.M. is a 40 years old 75 kg man, suffering from epilepsy. He receives a 300 mg/day dose of phenytoin, however his seizures a not totally under control. His plasma levels are measured twice a year and were both times recorded as 7.2 mg/l. Calculate a maintenance dose to achieve plasma levels of 15mg/l.

Answer:

What is to consider:

- Capacity limited metabolism

Metabolism is normally proportional to plasma concentration and clearance, the volume cleared per time can be viewed as a fixed proportionality constant that makes the administration rate equal to the steady state plasma concentration.

Ra= Cl * Cssave
@ steady state rate in equals rate out.

But in this case the clearance of phenytoin decreases as Cssave of phenytoin increases. Therefore, if the maintenance dose is increased, the levels raise disproportionally.

The mechanism is best described by the Michaelis-Menten model:

$V=(Vm*S)/(Km+S)$

Vm= maximum metabolic capacity
Km = substrate concentration where V=1/2 Vm

When we substitute V by the daily administration rate and S (substrate concentration) with the Cssave we get the following formula:

$S*F* (Dose/tau)= (Vm*Cssave)/(Km+Cssave)$

To solve this question we have to assume a value either for Vm or Km. Lets assume Km= 4mg/l.

And solve for Vm:

$Vm = [S*F*(Dose/tau) *(Km+Cssave)] / Cssave$

S=0.92 for phenytoin , F=1

Vm=429.3 mg/day

Using this Vm we can calculate his new dose.

S*F* (Dose/tau)= (Vm*Cssave)/(Km+Cssave)

Solving for dose:

Dose= (Vm*Cssave*tau)/[(Km+Cssave)*S*F]

Assuming Km=4mg/l

Dose = 368 mg pheytoin/day

Note: an increase from 300mg/day to 368 mg/day leads to almost 100% increase in steady state concentration.

Case 2:

G.B. a 50 year old 85 kg male patient has received 350 mg of phenytoin sodium over the past 3 weeks (21 days). His levels were measured and returned to be 15 mg/l. Are those levels likely to represent the steady state levels?

Answer:

If we could assume first order kinetics than the answer would be yes. But in this case we have capacity limited metabolism and the time to reach steady state is longer than assumed using first order pharmacokinetics.

To answer this question, we use the empiric equation

$$90\%\ t = [115+(35)*C]*C\ /(S*F*Dose/day)$$

this equation is only valid for adults and should be normalized to a dose for a 70 kg patient.

Note: for this equation a Km value of 2mg/l is assumed. That means that it takes longer to reach steady state and the time to reach steady state would be overestimated in patients with higher Km values.

Normalizing the dose:

350 / 85 *(70) = 288.2 mg for a 70 kg patient

substituting in the formula above:

$90\%t = [115+35*15)*15\ /\ (\ 0.92*1*288.2) = 36$ days

His steady state might not be achieved, since the time to reach SS would be after 36 days and he is only on day 21. But he could be at steady state if his Km was greater than 2mg/l or he received a loading dose.

Case3:

M.M a 10 year old 30 kg male receives 250 mg valproic acid every 12 hours for his absence seizures. But his seizures are only partially controlled. He reports no adverse effects at this dosing, and his renal and hepatic function are normal. What is his expected trough concentration?

Answer:

Due to fluctuations peak and trough level measurement would be desirable. But, due to uncertainty at which time the peak occurs, trough levels are usually measured.

At steady state Ra = Re (rate of administration = rate of elimination)
Hence in order to calculate his trough levels we need to know his rate of elimination by calculating ke.

Calculate the ke through the population parameters of CL and VD

CL=13ml/kg/h * 30 kg = 390 ml/h or 0.390 l/h
Vd = 0.14*l/kg * 30 = 4.2 l

Using this we can calculate his ke:

Ke = Cl/Vd = 0.0928
and
t1/2 = ln2 / ke = 7.5 h

assuming ss has been achieved and S and F = 1

$Cssmin= [(S*F*Dose / Vd) / (1-e^{-ke*tau})] * e^{-ke*tau}$

= 29.12 mg/l

Case 4:

G.G the II a 25 year old 72 kg male has developed serious seizures after watching a Japanese cartoon. Phenobarbital treatment is initiated to control his seizures. Calculate an oral loading dose to provide a plasma concentration of 20 m/l. Calculate and oral maintenance dose to achieve the same plasma levels. Recommend a dosing interval.

Answer:

LD= (V*C)/ (S*F)

S and F = 1 (use S=1 since a correction for the salt factor is seldom made and the therapeutic range is broad)

Vd = 0.7 L / kg * 72 kg = 50.4 L

LD = 50.4 * 20 = 1008 mg or 1 g

Clearance is the major determinant of the maintenance dose, hence it must be estimated form the population parameters.
Cl= 4 mg/kg/h or 0.1 l /day * 72 = 7.2 l / day

MD = CL * Cssave * tau / (S*F)
= 7.2 * 20 * day /(S*F) = 144 mg / day

since phenobarbial has a long t1/2 once daily dosing is sufficient, dose should be taken prior to bedtime to minimize sedation side effects.

T1/2 = 0.693 * VD / Cl = 5 days