Spring 2003

PHA 5128
Case Study 5 (Answers)

1. L.E., a 80 kg male patient (6'2", 52 y.o., SeCr 0.9 mg/dl) received a 30 mg methotrexate loading dose iv followed by a 30 mg/h infusion over 36 hours. At 36 h, leucovorin rescue (10 mg/m^2 q6h) was started. The following levels were monitored:

24h	12 μM
48 h	0.7 μM
60 h	0.4 μM

Make a recommendation how to continue therapy. When do you expect the methotrexate level to fall below 0.1 μM?

$$k_\alpha = \frac{\ln \frac{12}{0.7}}{12} = 0.237$$

$t_{1/2}$ = 2.9 h

t for 0.5 μM: $$t = \frac{\ln \frac{12}{0.5}}{0.237} = 13.4h \rightarrow \text{at } 49.4h$$

$$k_\beta = \frac{\ln\left(\frac{0.5}{0.4}\right)}{10.6} = 0.021h^{-1} \rightarrow t_{1/2\beta} = 33h$$

t for 0.1 μM: $$t = \frac{\ln \frac{0.5}{0.1}}{0.021} = 76.6h \rightarrow \text{at } 126 \text{ h}$$

→ continue to give leucovorin to at least 132-144 h (5.5-6 days)

2. Camille Carton is a 36 year old female with newly diagnosed atrial fibrillation with accompanying severe obesity. She is 5'7" tall and weights 338 lbs. Her cardiologist calls the pharmacy and states that he has had trouble in dosing similar patients in the past and would like some assistance in designing a loading and maintenance IV Lanoxin dosage regimen. She has no other complicating drugs or diseases (serum creatinine = 0.7 mg/dl) except that she is being continued on Quinidex Extentabs 300 mg Q8H which she has been reliably taking for 3 years. Respond to the physician's request and in addition, volunteer some helpful TDM guidelines.
   Upon receiving your recommended digoxin regimen for 5 days, you have the following serum digoxin concentrations: Start date 2/2/01 at 8 a.m., SDC = 1.3 ng/ml at 7 a.m. 2/4/01 and 1.7 ng/ml at 7 a.m., 2//7/01. Prepare a follow-up consult and include a warning as to what might be expected if quinidine were discontinued but digoxin remained at the current dosage.

   Given information:

   5'7", 36 y.o. female
   338 lbs
   SeCr = 0.7

For any calculations, IBW should be used.

IBW = 45 + 2.3 x (height above 5')
= 45 + (2.3)(7) = 61.1 kg

Creatinine clearance may now be calculated:

$$Cl_{creat}(\text{female}) = \frac{(0.852)(140 - age)\cdot \text{weight}}{(72)\cdot \text{SeCr}}$$

$$= \frac{(0.85)(140-36)(61.1)}{(72)(0.7)}$$

= 107 ml/min

Cl and Vd may be estimated using the empirical equations

Cl_{TOT} = (0.8 ml/min/kg)(IBW) + Cl_{creat} (ml/min)

= (0.8 ml/min/kg)(61.1 kg) + 107 ml/min

= 156 ml/min

Since quinidine is being co-administered, this value is multiplied by 0.5. Thus, for this patient

Cl_{TOT} = (156 ml/min)(0.5)
= 78 ml/min · 1440 min/day · 1L/1000 ml = 112 L/day

$$Vd = 3.8 L/kg \cdot IBW + 3.1 \cdot Cl_{creat}(ml/\text{min})$$

$= (3.8L/kg)(61.1kg) + (3.1)(107)$

= 564 L

= (564 L)(0.7) = 395 L if on quinidine as well

To obtain an initial concentration of 1.5 μg/mL

$$Cp_0 = \frac{D}{Vd}$$

is solved for D (or LD/loading dose) to give

$LD = Cp_0 \cdot Vd$

= (1.5 μg/L)(395 L) = 593 ~ <u>600 μg</u>

A maintenance dose to provide the same concentration is

$$MD = Cl \cdot \overline{C}pss \cdot \tau$$

= (112 L/day)(1.5 μg/L)(1 day)

= 168 μg/day

~ 175 μg/day

From measured Cp = 1.7 μg/mL, we can calculate

$$Cp_{ss} = \frac{175}{CL \cdot 1} = 1.7 \rightarrow CL = \frac{175}{1.7} = 103L/d$$

To provide an average concentration of 1.5 μg/ml,

MD = $Cl \cdot \overline{C}pss \cdot \tau$

= (103 L/day)(1.5 μg/day)(1 day)

=155 ~ <u>150 μg/day</u>

This dose is smaller since clearance had been overestimated for this patient. If quinidine were discontinued, clearance would increase (double) and maintenance dose would need to be increased to provide therapeutic concentrations.

3. Doug Durango is 37 year old male executive with uncontrolled hyperthyroidism with PAT. He as no history of previous illnesses and is not currently receiving any medications. He is 6'3 and weighs 198 Ibs. Lab: serum potassium = 4.8 mEq/L, serum creatinine = 0.7 mg/dl.

Design a loading and maintenance dosage regimen for IV or PO digoxin as you are not sure what the physician will prescribe. Three days after the patient receives your recommended regimen IV, the physician requests a serum digoxin conc. It is reported by the lab to be 0.9 ng/ml (1 hour before the next dose). The physician asks 3 questions: 1. What should be the dose IV if I want the trough to be 1.4 ng/ml at steady-state? 2. What should be the dose if we later switch to PO and keep 1.4 as the target trough for Lanoxicaps or Lanoxin tabs? 3. He plans to have surgery next week to control his hyperthyroidism. Will there need to be a change in his digoxin dosage at that time? If so what should be the recommended dosage regimen and a follow-up TDM plan?

IBW = $50 + 15 \cdot 2.3 = 84.5$

$$CL_{cr} = \frac{(140 - 37) \cdot 84.5}{72 \cdot 0.7} = 172 mL / \min$$

CL = $0.8 \cdot 84.5 + 172 = 240$ mL/min = 14.4 L/h

Hyperthyroid: $1.3 \cdot 246 = 312$ mL/min = 18.7 L/h

Vd = $3.8 \cdot 84.5 + 3.1 \cdot 172 = 854$ L Hyperthyroid: Vd = $1.3 \cdot 854 = 1110$ L

LD = $1.5 \cdot 1110 = 1.7$ mg IV or $1.7/0.7 = 2.4$ mg PO

MD = $1.5 \cdot 18.7 \cdot 24 = 673$ µg/day IV or 962 µg/day PO $\rightarrow$ 750 µg IV or 1000 µg PO

1) $$CL = \frac{750}{0.9 \cdot 24} = 34.7 L / h \rightarrow D = 34.7 \cdot 24 \cdot 1.4 = 1166 \mu g \rightarrow 1.25 \text{mg/day}$$

2) $$D = \frac{34.7 \cdot 24 \cdot 1.4}{0.7} = 1666 \rightarrow 1.75 \text{ mg/day}$$

capsules 1.25 mg/day (like iv)

3) decrease dose by 30%

4. P.M., a 55 year-old, 70 kg males, was admitted to the coronary care unit with a diagnosis of heart failure, probable myocardial infarction (MI), and premature ventricular contractions (PVCs). Calculate a bolus dose of lidocaine that should achieve an immediate response for P.M. At what rate should this dose be administration? Calculate a maintenance infusion rate that will achieve a steady-state plasma lidocaine concentration of 2 mg/L for P.M.

   P.M.'s PVCs were controlled by the bolus dose of lidocaine and an infusion of 1 mg/min was begun. Fifteen minutes later, PVCs were again noted. What might account for the reappearance of PVCs? What is an appropriate course of action at this point?

$$LD = \frac{3 \cdot 0.3 \cdot 70}{0.87} = 72mg$$ Slow i.v. push (25-50 mg/min)

$$MD = \frac{0.42 \cdot 2}{0.87} = 0.97mg/\min$$

distribution; give second and third loading dose (35 mg each)