2.6. Carbamazepine

Solutions

To view a video demonstrating solutions to carbamazepine problems, go to https://www.youtube.com/user/murphyassessment.

1. A. The formula below calculates the dose for Css_{avg} based on 24-hour dosing. The dose determined can then be divided as needed for an appropriate interval.

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{7\ mg/L \times CL \times 24\ hr}{1 \times 1}$$

A bioavailability of 1 must be used because all clearance determinations were done as CL/F.

From Table 1.6-1:

$CL_{chronic}$ = 0.05 to 0.10 L/hr/kg.

The midpoint of this range is:

0.075 L/hr/kg × 80 kg = 6 L/hr.

The clearance range would be:

0.05 L/hr/kg × 80 kg = 4 L/hr to 0.1 L/hr/kg × 80 kg = 8 L/hr.

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{7\ mg/L \times 6\ L/hr \times 24\ hr}{1 \times 1}$$

= **1008 mg every 24 hr** (on middle of range CL)

The range of possible doses using range of clearance:

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{7\ mg/L \times 4\ L/hr \times 24\ hr}{1 \times 1}$$

= **672 mg every 24 hr**

1. (continued)

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{7\ mg/L \times 8\ L/hr \times 24\ hr}{1 \times 1}$$

= 1344 mg every 24 hr

The dose would then be divided into an appropriate interval, such as every 8 hours.

B. Therapy is generally initiated approximately according to the following schedule:

Week 1: ¼ to ⅓ of the predicted maintenance dose (200–300 mg/day in divided doses).

Week 2: ⅓ to ½ of the predicted maintenance dose (300–400 mg/day in divided doses).

Week 3: Full maintenance dose.

If the full maintenance dose is started right away, the concentrations will initially exceed the final steady state concentrations, and concentration-related side effects may be noted. These concentrations could be roughly estimated using the initial clearance. It is important to remember that clearance will be *higher* and concentrations *lower* after autoinduction.

2. A. CL/F (L/hr) = [(0.0134 × 80 kg) + 3.58]

= 4.652 L/hr

This compares to the range above of 4–8 L/hr (midpoint = 6 L/hr).

B. The clearance adjustment factor for phenytoin is 1.42. Thus, the clearance under the impact of the drug–drug interaction would be:

CL_{DDI} = 4.652 L/hr × 1.42 = **6.606 L/hr**

C. As the carbamazepine clearance adjustment factor for the phenytoin interaction is 1.42, when the interaction is removed the carbamazepine concentration would be expected to increase due to the reduction in clearance.

$Css_{(previous\ with\ interaction)}$ = 6 mg/L

$$= \frac{S \times F \times D}{1.42 \times CL \times \tau}$$

S, F, D, and interval are unchanged with the removal of the interaction. Only the CL and Css_{avg} will change. Thus,

Css_{new} = $Css_{previous}$ × clearance factor

= 6 mg/L × 1.42 = **8.5 mg/L**

3. For a suspension or tablet dose for the adult, it would likely be divided into 200 mg every 6 hours. An adult could take either controlled-release tablets or sustained-release capsules, then the dose could be 400 mg every 12 hours or 300 mg every 8 hours.

$$Css_{avg} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 1 \times 200\ mg}{6\ L/hr \times 6\ hr}$$

= 5.56 mg/L

$$Css_{avg} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 1 \times 300\ mg}{6\ L/hr \times 8\ hr}$$

= 6.25 mg/L

Ratio could also be used (using the 24-hour dose for this example):

$$7\ mg/L \times \frac{800\ mg/day}{1008\ mg/day} = 5.56\ mg/L$$

$$7\ mg/L \times \frac{900\ mg/day}{1008\ mg/day} = 6.25\ mg/L$$

4. No, discontinuation is not required, but the patient's blood counts should be monitored more closely.

5. For all drug–drug interactions, the impact depends on how long the therapies will be used together, whether the interaction is inducing or inhibiting when metabolism is affected (inducing interactions take longer to fully manifest, while inhibiting interactions can occur fairly quickly), and where in the therapeutic range concentrations lie before the interacting drug is added.

Phenytoin: Decreases carbamazepine concentrations. Carbamazepine leads to increases in phenytoin concentrations. Side effects also increase on polytherapy with these two agents.