2.12. Valproic Acid

Solutions

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

1. First, solve for clearance for each patient type (use Table 1.12-1). Next, solve for the daily dose to produce a concentration in the desired range (pick 65 mg/L, since it is halfway between). Next, find a reasonable dose (and interval) that is actually available and then solve for the Css_{avg} for the dose chosen. Use 0.95 for F.

   A. $\frac{105 \text{ lb}}{2.2 \text{ lb/kg}} = 47.73 \text{ kg}$

   Without height you cannot solve for IBW in this child, so you must use weight alone.

   CL = 0.018 L/hr/kg × 47.73 kg = 0.859 L/hr

   $$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{65 \text{ mg/L} \times 0.859 \times 24 \text{ hr}}{1 \times 0.95} = 1410.6 \text{ mg}$$

   The nearest dose would be **500 mg** every 8 hours, or **750 mg** every 12 hours.

   $$Css_{avg} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 0.95 \times 750 \text{ mg}}{0.859 \text{ L/hr} \times 12 \text{ hr}} = \mathbf{69.1 \text{ mg/L}}$$

   You can also just use the 24-hour dose, because it gives the same Css_{avg}.

   The easiest way to solve for the Css_{avg} is by ratio:

   $\frac{1500}{1410.6} \times 65 \text{ mg/L} =$ **69.1 mg/L**

1. (continued)

B. $\frac{205 \text{ lb}}{2.2 \text{ lb/kg}}$ = 93.18 kg

IBW = 50 + 2.3(68 – 60) = 68.4 kg

Thus, obese; use IBW for CL.

CL = 0.009 L/hr/kg × 68.4 kg = 0.616 L/hr

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{65\text{ mg/L} \times 0.616 \times 24\text{ hr}}{1 \times 0.95}$$

= 1011 mg

The nearest doses would be **500 mg** every 12 hours; **375 mg** every 8 hours (1125 mg/day) could also be used.

$$Css_{avg} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 0.95 \times 500\text{ mg}}{0.616\text{ L/hr} \times 12\text{ hr}}$$

= 64.3 mg/L

By ratio: $\frac{1000}{1011}$ × 65 mg/L = 64.3 mg/L

By ratio: $\frac{1125}{1011}$ × 65 mg/L = 72.3 mg/L

C. CL = 0.007 L/hr/kg × 60 kg = 0.420 L/hr

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{65\text{ mg/L} \times 0.420 \times 24\text{ hr}}{1 \times 0.95}$$

= 689.7 mg

The nearest dose would be **375 mg** every 12 hours or **250 mg** every 8 hours.

Both provide the same daily dose, but the every 8-hour regimen is less complicated as only one prescription is needed compared to two for every 12 hours (125 mg + 250 mg), although every 12 hours provides an easier schedule.

$$Css_{avg} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 0.95 \times 375\text{ mg}}{0.420\text{ L/hr} \times 12\text{ hr}}$$

= 70.7 mg/L

By ratio: $\frac{750}{689.7}$ × 65 mg/L = 70.7 mg/L

2. A. $$CL = \frac{S \times F \times D}{Css_{avg} \times \tau} = \frac{1 \times 0.95 \times 500\text{ mg}}{44\text{ mg/L} \times 8\text{ hr}}$$

$= \frac{1.35\text{ L/hr}}{78\text{ kg}}$ = **0.017 L/hr/kg**

This is quite a bit off from the predicted population average of 0.009 L/hr/kg. Thus, the patient's clearance appears to be considerably higher than the population average.

This might be due to the patient actually having a higher clearance but could possibly be due to a missed dose, an unaccounted for drug interaction, or a variety of other system errors.

B. The critical decision is whether to adjust the dose based on this concentration. The measured concentration is slightly below the therapeutic range and the trough concentration would be even lower. If the patient is responding well (i.e., no seizure activity), the dose may be continued as is. Because the clearance is nearly double that predicted from the population value, it would be important to investigate possible reasons for the lower than estimated concentration prior to increasing the dose.

C. If the patient is still having seizures, the dose can be adjusted as follows for a target of 75 mg/L using ratio or the formulas for Css_{avg}:

500 mg every 8 hr × $\frac{75\text{ mg/L}}{44\text{ mg/L}}$

= 852 mg every 8 hours.

An appropriate dose would be **750 mg every 8 hours**. The anticipated Css_{avg} would be:

Css_{avg} = 75 mg/L × $\frac{750\text{ mg}}{852\text{ mg}}$

Css_{avg} = **66.0 mg/L**

Alternately, the dose can be determined using:

$$D = \frac{Css_{avg} \times CL \times \tau}{S \times F} = \frac{75\text{ mg/L} \times 1.35\text{ L/hr} \times 8\text{ hr}}{1 \times 0.95}$$

= 853 mg