2.11. Phenytoin/Fosphenytoin

Solutions

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

1. A. One way to start is to pick the average mg/kg dose for the age and then round to a reasonable daily dose. The dose range is ~4–7 mg/kg/day or 280–490 mg/day, a rather large difference. Another approach is to pick the mid-point of the desired range, in this case 15 mg/L, and estimate a dose for that concentration.

$K_m = 4.3$ mg/L

$V_{max} = 7$ mg/kg/day × 70 kg

$= 490$ mg/day

$$\frac{S \times F \times D}{\tau} = \frac{(V_{max})(Css_{avg})}{K_m + Css_{avg}}$$

$$D = \frac{(V_{max})(Css_{avg}) \times \tau}{(K_m + Css_{avg}) \times S \times F} = \frac{(490 \text{ mg/day})(15 \text{ mg/L}) \times 1 \text{ day}}{(4.3 \text{ mg/L} + 15 \text{ mg/L}) \times 0.92 \times 1}$$

= 414 mg/day

The closest easy dose is 400 mg/day. Next, solve for the predicted Css_{avg} on this dose.

$$Css_{avg} = \frac{(K_m)\left(\frac{S \times F \times D}{\tau}\right)}{V_{max} - \left(\frac{S \times F \times D}{\tau}\right)} = \frac{(4.3 \text{ mg/L})\left(\frac{0.92 \times 1 \times 400 \text{ mg}}{\text{day}}\right)}{490 \text{ mg/day} - \left(\frac{0.92 \times 1 \times 400 \text{ mg}}{\text{day}}\right)}$$

= 13.0 mg/L

Another possibility that would work is a combination of 100-mg capsules and 30-mg capsules to create a dose of **430 mg/day**.

1. (continued)

The predicted concentration on this dose is 18.0 mg/L.

$$Css_{avg} = \frac{(K_m)\left(\frac{S \times F \times D}{\tau}\right)}{V_{max} - \left(\frac{S \times F \times D}{\tau}\right)}$$

$$= \frac{(4.3\ \text{mg/L})\left(\frac{0.92 \times 1 \times 430\ \text{mg}}{\text{day}}\right)}{490\ \text{mg/day} - \left(\frac{0.92 \times 1 \times 430\ \text{mg}}{\text{day}}\right)}$$

= 18.0 mg/L

Note: A dose can be picked and then a concentration can be predicted on that dosing schedule. The difficulty then is how much to adjust the dose if it does not lead to predicted concentrations in the therapeutic range. The results above demonstrate how subtle dose changes can lead to larger and sometimes profound changes in concentration when the daily dose approaches V_{max}.

B. Assume use of 400 mg/day (200 mg every 12 hours) and a target concentration of 13.0 mg/L. The loading dose designed to reach that concentration is determined as follows:

$$D = \frac{C_{\Delta} \times V}{S \times F} = \frac{13.0\ \text{mg/L} \times 45.5\ \text{L}}{0.92 \times 1}$$

= 643 mg

This would likely be rounded to 600 or 700 mg.

If 430 mg were the maintenance dose, and the predicted concentration is 18.0 mg/L, the loading dose would be:

$$D = \frac{C_{\Delta} \times V}{S \times F} = \frac{18.0\ \text{mg/L} \times 45.5\ \text{L}}{0.92 \times 1}$$

= 890 mg

This would likely be rounded to 900 or 1000 mg, with corresponding proportional changes estimated in C_0.

2. A. For this patient we must adjust the concentration based on binding according to the equation provided.

$$C_{\text{normal binding}} = \frac{C_{\text{reported}}}{\left[(0.9)\left(\frac{\text{albumin}}{4.4}\right)\right] + 0.1}$$

$$= \frac{16\ \text{mg/L}}{\left[(0.9)\left(\frac{2.8}{4.4}\right)\right] + 0.1}$$

= 23.8 mg/L

B. The effect of change in fraction bound makes the concentration of 16 mg/L have the same predicted unbound concentration as would be expected if normal fraction unbound (10% = 0.1) was occurring and the concentration was 23.8 mg/L, which is above the normal therapeutic range of 1–2 mg/L unbound (10% of 10–20 mg/L total concentration).

3. First, determine ideal weight in case the patient is obese.

IBW_{female} = 45.5 kg + 2.3 (62 – 60) kg

= 50.1 kg

ABW/IBW = 75 kg / 50.1 kg = 1.5 (obese)

Volume of distribution equation for obese patients:

V (L) = 0.65 L/kg × [IBW + 1.33 (ABW – IBW)]

V (L) = 0.65 L/kg × [50.1 kg + 1.33 (75 kg – 50.1 kg)]

= 54.09 L

Note: The dosing weight was not calculated, but rather volume (in liters). The portion of the equation above in brackets would give the dosing weight for the loading dose.

$$D = \frac{C_0 \times V}{S \times F} = \frac{18\ \text{mg/L} \times 54.09\ \text{L}}{0.92 \times 1}$$

= 1058 mg

This would likely be rounded to 1000, 1050, or 1100 mg, with corresponding proportional changes estimated in C_0.

4. A. Determine the loading dose (in mg).

$$18\ \text{lb} \times \left(\frac{1\ \text{kg}}{2.2\ \text{lb}}\right) = 8.18\ \text{kg}$$

V = 1 L/kg × 8.18 kg = 8.18 L

The loading dose will be given as phenytoin sodium (either actually phenytoin sodium [S = 0.92] or phenytoin