Peaks and Troughs of Aminoglycosides

There are two different sets of 'peaks' and 'troughs' that are used to characterize aminoglycoside pharmacokinetics:

- The 'true' peaks and troughs:
  C_{max} at the end of the infusion
  C_{min} at the end of the dosing interval

- The 'clinical' peaks and troughs:
  C_{max}* measured 30 minutes after the end of the infusion
  C_{min}* measured 30 minutes before the end of the infusion

Example:

A patient with a CL of 6.3 L/h, Vd of 18 L, k of 0.35 h^{-1} is dosed with 150 mg gentamicin q8h in a 30-minute-infusion. Calculate the expected peaks and troughs:

$$C_{\max} = \frac{150}{6.3 \cdot 0.5} \cdot \frac{\left(1 - e^{-0.35 \cdot 0.5}\right)}{\left(1 - e^{-0.35 \cdot 8}\right)} = 8.1 mg / L$$

$$C^{*}_{\max} = 8.1 \cdot e^{-0.35 \cdot 0.5} = 6.8 mg / L$$

$$C^{*}_{\min} = 8.1 \cdot e^{-0.35 \cdot 7} = 0.7 mg / L$$

$$C_{\min} = 8.1 \cdot e^{-0.35 \cdot 7.5} = 0.6 mg / L$$

Clinically recommended target concentrations for peaks and troughs are conventionally usually **based on the 'clinical' peaks** and troughs so that a direct comparison with the measured concentrations is possible without any calculations. Since 'true' peaks are always higher than 'clinical' peaks, it follows that if the 'clinical' peak is higher than the recommended target peak, the 'true' peak will also be above the recommended target peak. Also, since 'true' troughs are always lower than the 'clinical' troughs, it follows that if the 'clinical' trough is below the recommended target trough, the 'true' trough will also be below the recommended target trough.
However, some texts and software programs (e.g. Capcil) use the 'true' peaks and troughs as the target concentrations for peaks and trough.

Calculation of optimum dosing interval

It makes a small difference for the calculation of optimum dosing intervals and doses which target concentrations are used. Let's assume the target concentrations for our patient are 10 mg/L (peak) and 1 mg/L (trough):

- Calculation of the optimum dosing interval based on 'clinical' peaks and trough as target concentrations, i.e. C_{max}^{*}=10mg/L and C_{min}^{*}=1mg/L. There are two ways to calculate the optimum dosing interval for this case.

  (a) We can use the relationship

  $$t = \frac{\ln\left(\frac{C_{\max}}{C_{\min}}\right)}{k} + T$$

  In this equation we have to use the 'true' peaks and troughs:

  $$C_{\max} = \frac{C^{*}_{\max}}{e^{-k \cdot t^{*}_{\max}}} = \frac{10}{e^{-0.35 \cdot 0.5}} = 11.9 mg/L$$

  $$C_{\min} = C^{*}_{\min} \cdot e^{-k \cdot t^{*}_{\min}} = 1 \cdot e^{-0.35 \cdot 0.5} = 0.84 mg/L$$

  $$t = \frac{\ln\left(\frac{C_{\max}}{C_{\min}}\right)}{k} + T = \frac{\ln\left(\frac{11.9}{0.84}\right)}{0.35} + 0.5 = 8.1h$$

  In this equation, t_{max}^{*} is the time between 'true' and 'clinical' peak (0.5 h) and t_{min}^{*} is the time between 'true' and 'clinical' trough (0.5 h).

  (b) Alternatively, we can use the following relationship to obtain the same result:

  $$t = \frac{\ln\left(\frac{C^{*}_{\max}}{C^{*}_{\min}}\right)}{k} + T + t^{*}_{\max} + t^{*}_{\min} = \frac{\ln\left(\frac{C^{*}_{\max}}{C^{*}_{\min}}\right)}{k} + 1.5 = \frac{\ln\left(\frac{10}{1}\right)}{0.35} + 1.5 = 8.1h$$

- Calculation of the optimum dosing interval based on 'true' peaks and trough as target concentrations, i.e. C_{max}=10mg/L and C_{min}=1mg/L.

$$t = \frac{\ln\left(\frac{C_{\max}}{C_{\min}}\right)}{k} + T = \frac{\ln\left(\frac{10}{1}\right)}{0.35} + 0.5 = 7.1h$$

Hence, this recommendation is **one hour shorter** than the one based on 'clinical' peaks and troughs. Since we have to round off the result to 8, 12 or 24h anyway, both approaches usually come to the same recommendation. In our example, the recommendation would be 8 hours.

Calculation of the optimum dose

The optimum dose can now be calculated using the equation

$$D = C_{\max(desired)} \cdot k \cdot Vd \cdot T \cdot \frac{\left(1 - e^{-k \cdot t}\right)}{\left(1 - e^{-k \cdot T}\right)} = 11.9 \cdot 0.35 \cdot 18 \cdot 0.5 \cdot \frac{\left(1 - e^{-0.35 \cdot 8}\right)}{\left(1 - e^{-0.35 \cdot 0.5}\right)} = 219mg$$

In this equation, $C_{max(desired)}$ should be **the 'true' peak** concentration.

Calculation of the volume of distribution

The individual volume of distribution can be calculated

$$Vd = \frac{D}{k \cdot T} \cdot \frac{\left(1 - e^{-k \cdot T}\right)}{\left(C_{\max} - C_{\min} \cdot e^{-k \cdot T}\right)}$$

In this equation, Cmax and Cmin should be **the 'true' peak and trough** concentrations.