Appendix S1: Derivation of AUC24/MIC

According to the book 《Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations》 (the first edition edited by Rosenbaum SE and published by Wiley in 2011), in the administration mode of using intermittent infusion (see supplementary Figure 1), relationship of concentration (C) v.s. time (t) can be expressed by the following equations, assuming that the in vivo disposition of the target drug fits one-compartment model.

1. during infusion (or in ascending branch of curve)

\[ C = \frac{v}{KV_d} \cdot (1 - e^{-Kt})(0 \leq t \leq t_{inf}) \]

Obviously, C achieves the maximum (C_{max}) at t_{inf}.

2. after completion of infusion (or in descending branch of curve)

\[ C' = C_{max} \cdot e^{-Kt} \quad (0 \leq t < \infty) \]

Set \( v/(KV_d) \) as \( A \), then,

\[ C_{max} = A \cdot (1 - e^{-Kt_{inf}}) \]

Set \( A(1-e^{-Kt_{inf}}) \) as \( B \), then,

\[ C' = Be^{-Kt} \]

Note: C, concentration in ascending branch of curve; \( C' \), concentration in descending branch of curve; \( K \), elimination rate constant; \( V_d \), distribution volume; \( t \), time during or after infusion; \( t_{inf} \), infusion time; \( v \), zero-order infusion rate, calculated as each dose divided by infusion time [i.e., \( D_{van}/(24/\text{dosing interval} \times t_{inf}) \)]/

\[ C_{max}, \text{ maximum concentration; } e, \text{ natural constant.} \]

From Figure 1 (Suppl), it can be seen that in any (set as \( n^{th} \) dose), \( C_n \) achieves \( (C_{max})_n \) at \( t_{inf} \) and \( C'_n \) achieves \( (C_{min})_n \) at \( \tau \). Based on the above equations, it can be seen that in 1\(^{st} \) dose, \( (C_{max})_1 \) is equal to \( B \) and \( (C_{min})_1 \) is equal to \( Be^{-K(\tau-t_{inf})} \); and in 2\(^{nd} \) dose, \( (C_{max})_2 \) will be equal to \([ (C_{max})_1 + (C_{min})_1 ] \) due to the residual concentration of \( (C_{min})_1 \) in 1\(^{st} \) dose, and \( (C_{min})_2 \) will be equal to \( (C_{max})_2 e^{-K(\tau-t_{inf})} \).

By analogy, \( C_n \) and \( C'_n \) in \( n^{th} \) dose can be deduced, as well as \( (C_{max})_n \) and \( (C_{min})_n \). Derivation of \( C_n \), \( C'_n \), \( (C_{max})_n \) and \( (C_{min})_n \) in any \( (n^{th}) \) dose is as follows:

1. in 1\(^{st} \) dose (or 1\(^{st} \) curve)
   - \( C_1 = A(1-e^{-Kt}) \)
   - \( (C_{max})_1 = B \)
   - \( C'_1 = Be^{-Kt} \)
   - \( (C_{min})_1 = Be^{-K(\tau-t_{inf})} \)
2. in 2\(^{nd} \) dose (or 2\(^{nd} \) curve)

![Figure 1 (Suppl) C-t curve in the administration mode of using intermittent infusion. \( t_{inf} \), infusion time; \( \tau \), dosing interval; \( C_n \), concentration in ascending branch of \( n^{th} \) curve; \( (C_{max})_n \), maximum concentration of \( n^{th} \) curve; \( C'_n \), concentration in descending branch of \( n^{th} \) curve; \( \bar{C}_{ss} \), mean steady-state concentration; AUC, area under curve.](image-url)
Due to the following relationship in one-compartment model,

\[ C_2 = B e^{K(t_{w})} + A (1 - e^{-K t_w}) \]

(3) in 3rd dose (or 3rd curve)

\[ C_3 = B [e^{K (t_{w})} + e^{-2K (t_{w})}] + A (1 - e^{-K t_w}) \]

(4) in nth dose (or nth curve)

\[ C_n = B [e^{K (t_{w})} + e^{-2K (t_{w})} + e^{-3K (t_{w})} + \ldots + e^{-K (n-1) t_{w}}] + A (1 - e^{-K t_w}) \]

Then, 

\[ r e^{K (t_{w})} = [e^{K (t_{w})} + e^{-2K (t_{w})} + e^{-3K (t_{w})} + \ldots + e^{-K (n-1) t_{w}}] \]

By solving this equation, then,

\[ r = [1 - e^{-nK (t_{w})}] / [1 - e^{-K t_w}] \]

Thus,

\[ C_n = B [1 - e^{-nK (t_{w})}] / [1 - e^{-K (t_{w})}] + A (1 - e^{-K t_w}) \]

When \( n \) is close to “infinity” or reaches the steady state, \( e^{nK (t_{w})} \) is close to “0”. Then,

\[ C_n' = B [1 - e^{-K (t_{w})}] e^{-K t_w} \]

According to Figure 1 (Suppl) and the integral relationship for AUC calculation, then,

\[ \text{AUC} = \int_0^t [B e^{K(t_{w})} / (1 - e^{K(t_{w})}) + A (1 - e^{-K t_w})] dt + \int_0^{t_{w}} [B (1 - e^{-K t_w})] e^{-K t_w} dt \]

Due to the following relationship in one-compartment model,

\[ CL = KV_d \]

\[ B = A (1 - e^{K t_w}) \]

\[ A = v / (KV_d) \]

And combining the calculation rules of definite integral, then,

\[ \text{AUC} = \frac{v \cdot t_{w}}{CL} \cdot \frac{1 - e^{-CL/V_d}}{1 - e^{-CL/V_d} (t_{w})} + \frac{\left( e^{-CL/V_d (t_{w})} - 1 \right) \cdot e^{-CL/V_d (t_{w}) - 2CL/V_d (t_{w})} - e^{-CL/V_d (t_{w})}}{1 - e^{-CL/V_d (t_{w})}} \]
Due to 24/τ curves being formed within 24 h, then,

$$AUC_{24} = \frac{24}{\tau} \left[ \frac{\nu \cdot t_{\inf}}{CL} \left( 1 - e^{-CL/\nu \cdot \tau} \right) + \frac{\nu \cdot \left( e^{-CL/\nu \cdot (\tau - t_{\inf})} - 1 \right) \cdot e^{-CL/\nu \cdot (2\tau - t_{\inf})} - e^{-CL/\nu \cdot (\tau - t_{\inf})}}{V_d} \right]$$

By transformation, then,

$$AUC_{24} = \frac{24\nu}{\tau \cdot \left( e^{CL/\nu \cdot \tau} - e^{CL/\nu \cdot t_{\inf}} \right)} \left[ \frac{t_{\inf} \left( e^{CL/\nu \cdot \tau} - 1 \right) - \left( e^{CL/\nu \cdot t_{\inf}} - 1 \right)^2}{CL} \right]$$

Thus,

$$AUC_{24}/MIC = \frac{\frac{24\nu}{\tau \cdot \left( e^{CL/\nu \cdot \tau} - e^{CL/\nu \cdot t_{\inf}} \right)} \left[ \frac{t_{\inf} \left( e^{CL/\nu \cdot \tau} - 1 \right) - \left( e^{CL/\nu \cdot t_{\inf}} - 1 \right)^2}{CL} \right]}{MIC}$$