**The relationship of vancomycin 24-hour AUC and trough concentration**

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**Purpose.** Prior to the 2020 release of a joint consensus guideline on monitoring of vancomycin therapy for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections, clinicians had escalated vancomycin doses for 2 decades while targeting trough concentrations of 15 to 20 μg/mL, leading to an increased frequency of nephrotoxicity. For MRSA infections, the 2020 guideline recommends adjusting doses to achieve a 24-hour area under the concentration-time curve (AUC) of 400 to 600 μg · h/mL; however, monitoring of trough concentrations has been entrenched for 3 decades. Calculating dose regimens based on AUC will require obtaining an increased number of vancomycin serum concentrations and, possibly, advanced software. The aim of this investigation was to determine the relationship between AUC and trough concentration and the influence of dosing regimen on goal achievement.

**Methods.** The relationship between trough concentration and AUC was explored through derivation of an equation based on a 1-compartment model and simulations.

**Results.** 24-hour AUC is related to dosing interval divided by half-life in a nonlinear fashion. The target trough concentration can be individualized to achieve a desired AUC range, and limiting use of large doses (>15-20 mg/kg) can protect against excessive 24-hour AUC with trough-only monitoring.

**Conclusion.** After initially determining pharmacokinetic parameters, subsequent monitoring of AUC can be accomplished using trough concentrations only. Trough concentration may be used as a surrogate for AUC, although the acceptable target trough concentration will vary depending on dosing interval and elimination rate constant. This work included development of an AUC-trough equation to establish a patient-specific target for steady-state trough concentration.

**Keywords:** AUC, dosing, monitoring, pharmacokinetics, trough, vancomycin

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Vancomycin efficacy, specifically for *Staphylococcus aureus* infections, is optimized by achieving a ratio of daily 24-hour area under the concentration-time curve to minimum inhibitory concentration (24-hour AUC/MIC) of at least 400.[1,2] Guidelines published in 2020 recommend targeting a 24-hour AUC between 400 and 600 μg · h/mL.[3] Prior to the recent change, recommendations were to target trough concentrations of 10 to 20 μg/mL, and for serious infections involving methicillin-resistant *S. aureus* such as pneumonia, osteomyelitis, bacteremia, and endocarditis, the recommended trough concentration was 15 to 20 μg/mL. Dosing strategies to achieve these trough concentrations can be associated with excessively high vancomycin peak concentrations and/or 24-hour AUC. Two recent papers demonstrated that controlling dose to achieve a 24-hour AUC target rather than a trough concentration of 15 to 20 μg/mL results in improved safety in terms of a reduced incidence of nephrotoxicity.[4,5] Determining a 24-hour AUC requires obtaining 2 concentrations within a dosing interval and use of first-order pharmacokinetic equations, or Bayesian approaches. Herein we describe the use of trough concentration as a surrogate for 24-hour AUC and justify that trough concentrations remain useful to guide vancomycin dosing. Limiting the dose in favor of shortening the dosing interval is an effective way to ensure achievement of the target 24-hour AUC without a high risk of excessive exposure (AUC >600 μg · h/mL).[6]

There are multiple approaches to evaluate 2 serum concentrations and arrive at the elimination rate constant ($k_e$) and, in some cases, volume of distribution ($V$). AUC for the dosing interval can also be determined using several approaches.[7,8] Furthermore, 24-hour AUC is calculated by the following equation:

$$AUC(0-\tau)ss \times \frac{24}{\tau},$$

where *SS* denotes steady state and τ denotes the dosing interval. The accuracy of parameters including AUC depends on the data available. Population-based estimates for $k_e$ and *V* are the least accurate for characterizing pharmacokinetics in an individual. Adding 1 or 2 measured concentrations leads to sequential gains in accuracy, and adding more measured drug contractions leads to diminishing increases in accuracy.

To accommodate the a 24-hour AUC target, trough-only monitoring requires 1 serum vancomycin concentration coupled with some type of guessing to determine pharmacokinetic parameters (*V* and $k_e$) or exposure (24-hour AUC). Bayesian pharmacokinetic methods can standardize this guessing, but to optimize their performance, robust population estimates of the parameters and employment of predictive covariates are needed. An alternative approach is to collect 2 serum samples rather than 1, which will increase costs of monitoring. We have observed that a major contributor to an excessive 24-hour AUC is the use of relatively long dosing intervals in patients with a short vancomycin half-life (ie, $\tau/t_{½}$ greater than about 1.5). Accepting that aggressive trough concentration targets result in increased 24-hour AUC and increased nephrotoxicity, overdosing of vancomycin was an iatrogenic problem created by escalating vancomycin doses to achieve aggressive targets without consideration of dosing interval and total exposure (a 24-hour AUC). The purpose of this work is to explore the relationship between a 24-hour AUC and trough concentrations.

**Methods**

The following equation was derived to relate the trough concentration (abbreviated as $C_{min}$ here, in Table 1, and in the eAppendix) at steady state to the 24-hour AUC (details on the derivation are provided in the eAppendix):

$$AUC \qquad \frac{(1 - e^{-k\tau})}{(1 \qquad )} \qquad \frac{}{}$$

The equation involves converting the more complicated infusion model to an intravenous bolus equivalent as shown in Figure 1. A 1-compartment model is ideal for vancomycin therapeutic drug monitoring because a sufficient number of serum samples is generally not available to allow parameter estimation for a 2-compartment model. Although Bayesian software has been employed, prior probability distributions for parameters are typically derived from a selected population or relatively small diverse population without informative covariates. Too often, a 2-compartment model is so overparameterized that covariates are hard to identify.

Simulations were preformed using SAS version 9.4 (SAS Institute, Cary, NC) based on a 1-compartment model. Simulations were performed at steady state using the superposition principal and the equation below:

$$C(t) \qquad \frac{(1 - e^{-k \times T})}{\times (1 - e^{-k \times \tau})} \quad {}^{-k*(\tau+t)} \qquad \frac{ko/T \times (1 - e^{-k \times t*})}{}$$

The left-hand term considers the concentration remaining from the previous dose, and the right term is for the index dose. Parameters of $k_e$ were varied (0.058 to 0.28 $h^{-1}$). After confirming that $V$ does not affect the relationship between AUC and trough, $V$ was fixed at 63 L. The range of $k_e$ corresponds to a half-life ranging from 2.5 to 12 hours. The dosing

interval was set at 6, 8, or 12 hours, with doses ranging from 1,000 to 1,500 mg infused over 2 hours. For each case, the a 24-hour AUC associated with a fixed trough concentration of 15 μg/mL was determined. The simulations were used to test the derived equation and explore the relationship between AUC and trough concentration.

**Results**

The top panel of Figure 2 shows the relation between a 24-hour AUC and $t_{½}$ when the trough concentration is fixed at 15 μg/mL and a 2-hour infusion time is used. Note that there are separate curves for 12-, 8-, and 6-hour dosing intervals, and excessive 24-hour AUC (>600 μg/mL) occurs when $t_{½}$ is short relative to the dosing interval. The bottom panel shows the relationship between a 24-hour AUC and $\tau/t_{½}$. The curves become very similar for the 3 different dosing intervals when a 24-hour AUC is plotted versus $\tau/t_{½}$ rather than $t_{½}$. The 24-hour AUC starts to exceed 600 μg · h/mL when $\tau/t_{½}$ approaches 1.5. If the time of infusion ($T$) is changed to a value proportional to the dosing interval (eg, for a 12-hour interval, $T$ = 2 h; for an 8-hour interval, $T$ = 1.33 h; and for a 6-hour interval, $T$ = 1 h), all 3 curves become superimposed (dashed curve). Figure 3 shows the boundaries for a target $C_{min}$ ranging from 8 to 20 μg/mL. Excessive exposure (a 24-hour AUC >600 μg · h/mL) is noted when $\tau/t_{½}$ exceeds 1.5 for a target $C_{min}$ of 15 μg/mL and is expected for a target $C_{min}$ of 20 μg/mL.

A 1-compartment model is defined by 2 parameters: CL and $V$. Across doses, CL is directly related to AUC and the difference in $C_{max}$ and $C_{min}$ is mostly determined by dose and $V$. If trough concentration is used as a surrogate for AUC, one has to be careful with large doses given infrequently, as a low trough concentration can be associated with excessive a

24-hour AUC. Two examples are provided to show how trough target can be individualized to achieve a 24-hour AUC target.

**Example 1:** A 30-year-old male with an estimated $CL_{CR}$ of 110 mL/min is admitted following a motor vehicle accident. He weighs 80 kg and has a BMI of 24.5. He is given a 2,000-mg loading dose over 2 hours. The elimination rate constant and half-life can be estimated as follows $k_e = 0.00083 \times (CL_{cr}) + 0.0044$; $t_{½} = 835/(CL_{cr} + 5.30)$.[10] The $k_e$ value is a population estimate and may not be accurate. Any estimate made using this $k_e$ would need to be revised after measured concentrations become available. The patient's estimated $t_{½}$ would be 7.24 hours. From equation 11 in the eAppendix, the $C_{min,ss}$ range for an 8-hour dosing interval would be 11.6 to 17.5 µg/mL. With a 12-hour dosing interval, the $C_{min,ss}$ range would be 9.3 to 14 µg/mL to achieve the target 24-hour AUC.

**Example 2:** A 40-year-old man develops osteomyelitis after fracturing his tibia and undergoing open reduction and internal fixation. He is taken to the operating room for debridement and hardware removal. Cultures grow methicillin-resistant *S. aureus* (MRSA), and the plan is to treat the man with vancomycin for 6 weeks as an outpatient. He has been receiving 1,000 mg of vancomycin every 8 hours as an inpatient, but dosing was changed to 1,500 mg every 12 h ours for home therapy. The hospital uses Bayesian software and adjusted the dose to achieve an AUC of 400-600 µg/mL. The $k_e$ was determined to be 0.12 $h^{-1}$ and the dose was infused at a rate of 1,000 mg/h. From equation 1 in the eAppendix, the $C_{min}$ target would be 8.2 to 12.2 µg/mL to achieve the target 24-hour AUC. Instructions for monitoring trough concentrations are included in the discharge note.

**Discussion**

This work evolved from many years of observations in a changing environment. The first intervention was to change most pediatric patients to every-6-hour dosing for vancomycin. There were cases involving children with normal renal function in which 8- to 12-hour dosing was being used, and their trough concentration was always low relative to the newly implemented target range of 10 to 15 µg/mL. As trough targets increased to 10-15 µg/mL to 20 µg/mL, the most common dosage for adults was 1,000 mg every 6, 8, 12, or 24 hours, depending on renal function and trough level. Over time, the use of 1,250-mg, 1,500-mg, and occasionally 1,750-mg doses increased along with use of a fixed 12-hour dosing interval. During this time, the trough target was 15 to 20 µg/mL for serious staphylococcal infections. The total daily dose and corresponding 24-hour AUC increased for many patients. The purpose of the simulations was to either demonstrate the value of preferentially changing the dosing interval or accepting a lower trough target than specified in the 2009 guidelines. The 24-hour AUC has been a consideration throughout this time period, including before the 2020 guidelines were published. The last step involved a mathematical solution relating AUC to trough concentration. The solution was very easy for intravenous bolus dosing but required repurposing of a pharmacokinetic relationship between infusion and bolus dosing for the intravenous infusion equation.

Children exhibit a vancomycin half-life as short as 2.2 to 3.0 hours.[11] In adults less than 40 years of age, the mean vancomycin half-life is 5.1 hours.[12,13] Younger adults, along with patients who have augmented renal function or are obese, can have a relatively short $t_{½}$ and this places them at risk for achieving excessive exposure (as measured by 24-hour AUC) when aiming for trough concentrations of 15 to 20 µg/mL or even 10 to 20 µg/mL. The critical role of dosing interval in determining the relationship between trough concentration

and 24-hour AUC must be considered before monitoring trough concentrations. If the selected dosing regimen is every 12 hours versus every 6 hours but the same target trough concentration is targeted, the daily dose requirement and 24-hour AUC will be higher for the every-12-hour regimen. Either the trough target will need to be lowered with use of a 12-hour dosing regimen or use of the same trough concentration will be associated with higher 24-hour AUC and risk of toxicity.

The goal of this paper is to describe how trough-only monitoring can contribute to the current practice of AUC-based dosing in a cost-effective and efficient manner. Table 1 provides a possible approach to using the AUC-trough equation with trough monitoring. AUC-based dosing can and should be employed, and there are many ways to accomplish it. There are many hospitals and outpatient infusion groups that have not made the financial and staffing changes required in order to implement the new 2020 guidelines. If trough monitoring is used, limiting the dose to 15 mg/kg and adjusting the dosing interval will provide some protection against excessive exposure. The 2020 guidelines suggest measuring serum concentrations and determining a 24-hour AUC early after vancomycin initiation; however, there is a stewardship goal of discontinuing vancomycin within 48 hours if not indicated. Serum concentration monitoring may be delayed until after the third or fourth dose, but this requires use of population parameters for initial dosing. Once serum concentrations are available, a patient's individual $k_e$ and 24-hour AUC can be estimated. The dose regimen can then be adjusted to attain the target AUC. For future monitoring, a trough only can be determined and evaluated based on a patient-specific range. Pharmacists who are continuing to use trough monitoring should have a good understanding of how AUC and trough are related. One criticism of more frequent dosing is related to less convenience and greater administration costs. However, adjusting the dosing

interval will allow use of more standard dose sizes. The dosing interval can be planned for convenience but implemented using individualized trough targets. For example, if the estimated $t_{½}$ is 5.5 hours and vancomycin dosing is 1 g every 12 hours, use of the AUC-trough equation would show that a trough concentration of 7.8 to 11.8 µg/mL would correlate with a 24-hour AUC of 400 to 600 µg/mL.

**Conclusion**

This work provides a conceptual framework for relating 24-hour AUC to trough concentration. After the dosing regimen is adjusted to achieve the target AUC, the AUC-trough equation developed can be used to define a target tough concentration range that can be used for subsequent trough-only monitoring.

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**Key Points**

- Consistent with 2020 guidelines for vancomycin dosing and monitoring, vancomycin dosing should achieve a 24-hour AUC between 400 and 600 mg · h/L.
- Once individual pharmacokinetic parameters are determined, the AUC-trough equation can be used to designate a patient-specific target range for subsequent trough-only monitoring.
- Preferentially selecting shorter dosing intervals rather than increased doses will reduce the likelihood of excessive exposure in terms of an AUC of >600 mg · h/L.

Figure 1. Visual representation of method of transforming an infusion dose to an intravenous bolus dose equivalent to determine pharmacokinetic parameters.

Figure 2. Top panel shows the relationship between 24-hour vancomycin area under the concentration-time curve (AUC) and vancomycin half-life for 3 typical dosage intervals, assuming a fixed trough concentration of 15 μg/mL and infusion time of 2 hours. The bottom panel shows the relationship between 24-hour vancomycin AUC and the ratio of dosing interval (Tau) to half-life for 3 typical dosing intervals. If the examples shown were resimulated using an infusion time of one-sixth the dosing interval (Tau × 0.167) rather than a fixed 2-hour infusion time, the curves for all 3 dosing intervals are superimposed (as delineated by dashed lines).

Figure 3. Relationship between 24-hour vancomycin area under the curve (AUC) and ratio of dosing interval to half-life for 5 different trough concentration ($C_{min}$) values (expressed as μg/mL). The infusion time was set at one-sixth of the dosing interval. Assuming the dose is adjusted to provide a target trough concentration of 12 mg/L, administration of a dose every half-life or every 2.25 half-lives would correlate with 24-hour AUC values of 400 and 600 mg · h/L, respectively. In contrast, targeting a trough concentration of 18 mg/L would require dosing more frequently than each half-life to avoid a 24-hour AUC of >600 mg · h/L. The figure shows that trough concentrations used in the past were sometimes unrealistically incompatible with achieving the currently recommended AUC range.

**Table 1.** Suggested Approach to Vancomycin Dosing and Monitoring Using AUC-Trough Equation

| **Sequence of Events** | **Comments** |
|---|---|
| 1. Provide an initial loading dose of vancomycin 20-35 mg/kg based on total body weight. | Evidence supporting use of total body weight is limited and could lead to high initial doses. The guidelines suggest a maximum dose of 3,000 mg, and many institutions use lower maximum dose (eg 2,000 mg or 2,500 mg). |
| 2. Provide a maintenance dose for vancomycin Using a population equation relating vancomycin CL to creatinine clearance. For example:<br><br>$CL_{van}$ (L/h) = A × $CL_{cr}$ (mL/min) + B<br>Target 24-h AUC = 400-600 mg · h/L<br>Daily dose = $CL_{van}$ × AUC (use 450 or 500 for AUC) | Dosing regimen can be flexible and tailored for the local situation. For example, a daily dose of 3,000 mg can be given as 1 g every 8 h or 1.5 g every 12 h. If the physicians are set on achieving a specific trough range, then every 8 h may be appropriate. If convenience is the primary objective (eg, OPAT), every 12 h may be best. |
| 3. Plan serum concentration monitoring.<br>Plan to obtain 2 serum concentrations during 1 dosing interval to calculate PK parameters and AUC. Monitoring can be after the first dose or at either steady or nonsteady state, depending on the analysis used. | First-dose monitoring: Patient is less physiologically stable, may be dehydrated, may be unsure of creatinine stability, or vancomycin may be discontinued after 1-3 doses. Non–steady-state monitoring requires more advanced PK analysis. Steady state is achieved after at least 3.3 × $t_{½}$ (estimated) and after patient is on a stable dosing regimen. If any dose is substantially off scheduled time, calculation of time to steady state would begin anew. |
| 4. Perform PK analysis. There are many approaches to PK analysis. Assuming a one-compartment model and using first-order equations is very practical. Bayesian PK modeling may be used; however, the priors must be derived from a representative patient population. | It is helpful to have a table of actual doses received, including relative times and doses, and simulated concentrations based on population estimated parameters. Examine measured concentrations vs predicted concentrations. Perform analysis with determination of $k_e$ and CL or AUC. Calculate new daily dose to provide AUC in target range (eg, 400-600 mg · h/L) as follows: daily dose = target AUC × individual CL. It is helpful to update PK parameters to individualized estimates and repeat visual examination. |
| 5. Select dosing regimen. Start with determining the daily dose to achieve AUC values of 400 and 600 mg · h/L, respectively. Then consider a dose regimen that would be most appropriate for the local situation. One could also avoid planning a dose near the boundaries and use an AUC value of 450-550 mg · h/L for planning. | A table to help with selecting doses could be useful.<br><br>*Example:*<br>Daily dose = 2,400 mg to provide AUC of 468 mg · h/L; CL = 5.13 L/h; $V$ = 50 L<br>Minimum dose = 400 × 5.13 ÷ No. doses per day<br>Maximum dose = 600 x 5.13 ÷ No. doses per day<br><br>**Dosing interval Min dose Max dose** |

| | | |
|---|---|---|
| Every 8 h | 684 mg | 1,026 mg |
| Every 12 h | 1,026 mg | 1,539 mg |
| Every 24 h | 2,052 mg | 3,078 mg |

Suggest either 750 mg every 8 h or 1,250 mg every 12 h

6. Plan future monitoring. Monitor serum creatinine daily to twice weekly depending on the setting. Although uncommon, there can be a substantial change in vancomycin PK without change in SCr; recommend monitoring of vancomycin trough once weekly.

Use AUC targets (400 and 600 mg · h/L) along with AUC-trough equation and measured $k_e$, dosing interval, and time of infusion to create a patient-specific target trough concentration range.

*For parameters shown above:*

| **Dosing interval** | **$C_{min}$ (400)** | **$C_{min}$ (600)** |
|---|---|---|
| Every 8 h | 11.2 µg/mL | 16.7 µg/mL |
| Every 12 h | 9.02 µg/mL | 13.5 µg/mL |

If the measured trough concentration falls outside the customized range, then full patient assessment and clinical judgement should be exercised. Intervention may range from repeat serum concentrations (1 or 2) to dose adjustment to changing therapy.

Abbreviations: AUC, area under time-concentration curve; $C_{min}$, trough concentration; $CL_{cr}$, creatinine clearance; $CL_{van}$, vancomycin clearance; $k_e$, elimination rate constant; OPAT, outpatient parenteral antimicrobial therapy; Scr, serum creatinine concentration.

Figure 1

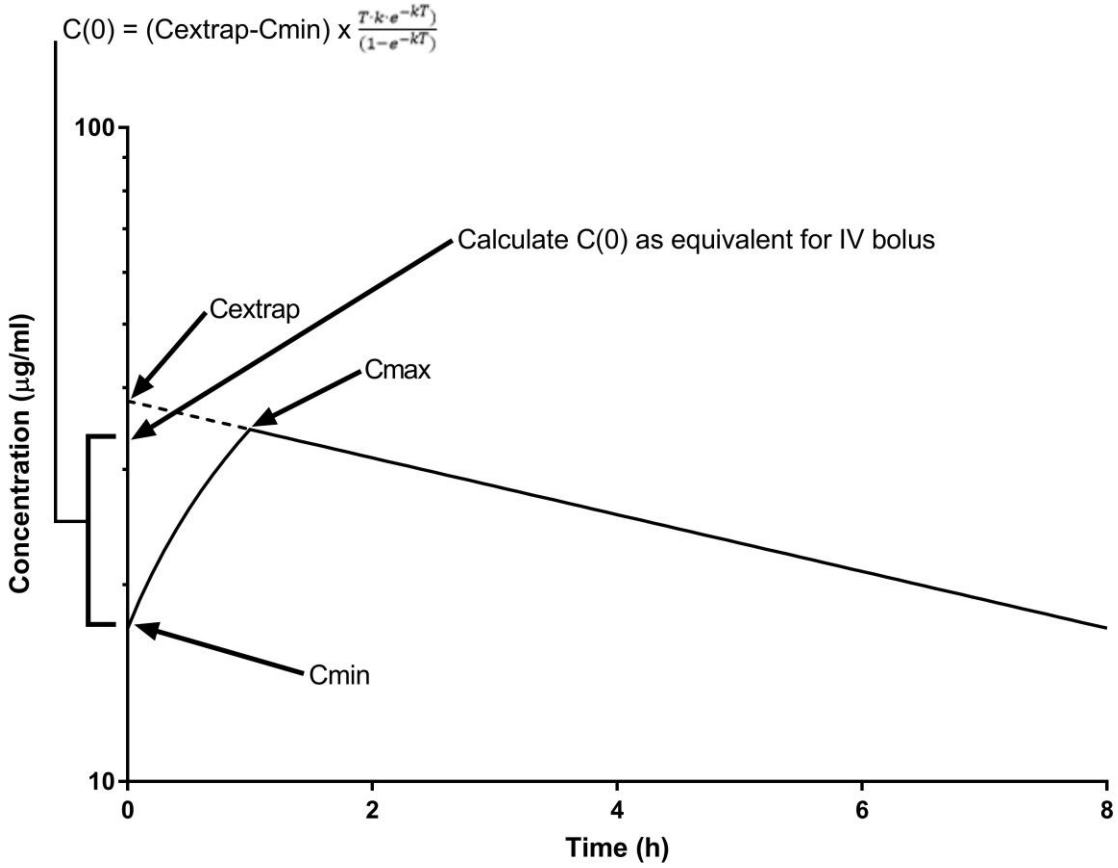

C(0) = (Cextrap-Cmin) x $\frac{T \cdot k \cdot e^{-kT}}{(1-e^{-kT})}$
100
10
Concentration (μg/ml)
Calculate C(0) as equivalent for IV bolus
Cextrap
Cmax
Cmin
0
2
4
6
8
Time (h)

Figure 2a

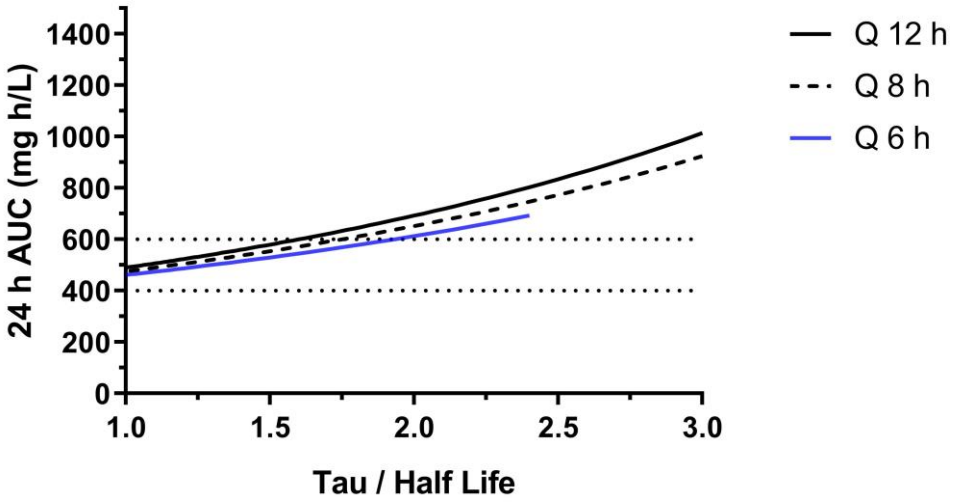

24 h AUC (mg h/L)
1400
1200
1000
800
600
400
200
0
1.0
1.5
2.0
2.5
3.0
Tau / Half Life
Q 12 h
Q 8 h
Q 6 h

Figure 2b

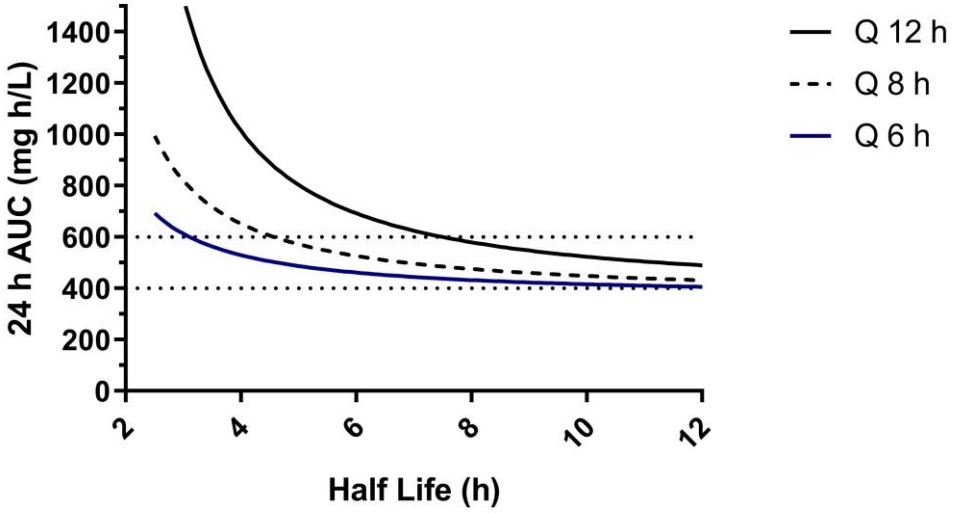
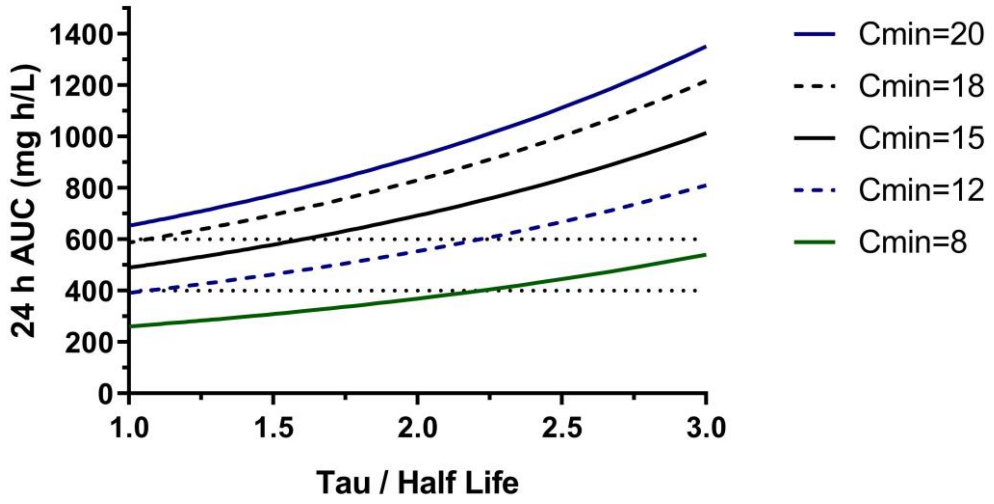

24 h AUC (mg h/L)
1400
1200
1000
800
600
400
200
0
2
4
6
8
10
12
Half Life (h)
Q 12 h
Q 8 h
Q 6 h

Figure 3


24 h AUC (mg h/L)
1400
1200
1000
800
600
400
200
0
1.0
1.5
2.0
2.5
3.0
Tau / Half Life
Cmin=20
Cmin=18
Cmin=15
Cmin=12
Cmin=8