Vancomycin Therapeutic Drug Monitoring and Nephrotoxicity
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Objectives:
• Review what’s changed with vancomycin and the environment that we consider it’s use.
  (A New Mind Set, still in evolution) – Just the Bottom Line Please!
  ❏ PK/PD and Efficacy Data
  ❏ PK/PD and Sensitivity and Resistance Data
  ❏ PK/PD and Toxicity Data
• Review the principles of Vancomycin Therapeutic Drug Monitoring in November 2008. (A moving target)

Just the Bottom Line
PK/PD and Efficacy
PK/PD: Susceptibility and Resistance Issues
PK/PD and Toxicity
PK/PD and Efficacy – Bottom Line November 2008

IDSA has recommended troughs between 15-20mg/L for meningitis based on knowledge of vancomycin PKs, poor outcome when target troughs of <10mg/L used (BIII) (Tunkel A, et al. Clinical Infectious Diseases 2004;39:1267-84.)

IDSA/ATS hospital acquired pneumonia, ventilator associated pneumonia, and healthcare associated pneumonia, recommend trough concentrations of 15-20mg/L for the treatment of MRSA pneumonia based on vancomycin susceptibility, pharmacokinetic and pharmacodynamic properties and clinical experience with failure rates of 40% or greater when traditional vancomycin dosing of 1g every 12 hours was used. (American Thoracic Society, Infectious Diseases Society of America. Am J Respir Crit Care Med 2005;171:388-416.)

PK/PD and Efficacy – Bottom Line November 2008

Vancomycin has concentration-independent killing (i.e. presumably time dependent killing where AUC/MIC ratio may be the best PK/PD predictor of activity) (Moise-Broder PA et al. Clin Pharmacokinet 2004;43(13):925-42) - but adopting this into clinical practice would dramatically change daily doses and monitoring – too early to adopt – further data needed

Troughs >15mg/L (4-5 times MIC) associated with better initial response (Hidayat LK et al. Arch Intern Med 2006;166:2138-44.)

Was a trend to higher resolution of fever after 72h vancomycin among patients with trough > 15mg/L (87.5% vs 69.7%, p = 0.055) (Jeffres MN et al. CHEST 2006;130:947-55.)

However, there is a low likelihood of attaining vancomycin trough concentrations between 15 – 20mg/L with 15mg/kg q12h dosing. Need to explore other dosing options. (Drusano G et al. IDSA annual meeting (abstract 447), Oct 2007)

No data that convinces ME to abandon the rationale that higher troughs (15 – 20mg/L) MAY improve clinical outcome in difficult infections as of November 2008.

“Absence of evidence is not evidence of absence.”
Carl Sagan
US astronomer, writer and scientist
(1934 - 1996)

PK/PD and Efficacy – Bottom Line November 2008
**PK/PD Susceptibility and Resistance Issues: Trough >10mg/L**

- Klepser et al. suggested trough >10mg/L associated with more rapid bacterial eradication than lower [trough]. (Klepser ME et al. Abstract in Program and abstracts of the ACCP Annual Winter Meeting; 1994 Feb.)
- Majority of cases of GISA or VISA in pts receiving PD or HD who had prolonged, and repeated courses of vancomycin, with serum concentrations consistently <10mg/L (Rybak MJ. CID 2006;42:S35-9)
- MRSA recovered from killing assays where vancomycin concentrations were 16mg/L did not show changes in vancomycin heteroresistance compared to parent strain. (Sakoulas G, et al. CID 2006;42(suppl1):S40-60.)
- Failure to achieve a 99.9% bactericidal endpoint after 24h of incubation with vancomycin at 16mg/L is not uncommon in isolates of MRSA. (Sakoulas G, et al. J Clin Microbiol 2004;42(6):2398-402 – statement in discussion of their unpublished observations.)

**PK/PD: Susceptibility and Resistance Issues Bottom Line November 2008**

- MIC in “S” does not necessarily mean successful outcome.
- Within the current range of “S” for MRSA, outcome may differ for MIC < 1.5mg/L vs >1.5-2mg/L. (Lodise TP et al. AAC 2008;3315-20) Due to not meeting PK/PD target (e.g. AUC/MIC)?? (Mohr JF, Murray BE. CID 2007;44:1036-42.)
- Data to support correlation of higher troughs with more rapid bacterial eradication (Klepser et al.) and decreased risk of selecting more resistant strains of MRSA (i.e. hVISA, VISA) (Charles PG et al. Clin Infect Dis 2004;38:448-51; Sakoulas G, et al. CID 2006;42(suppl1):S40-60.)

Some evidence exists to lend support for aiming for troughs btwn 15-20mg/L to avoid selecting for more resistant strains of MRSA in patients on prolonged vancomycin (>14 days) and to increase the probability of attaining AUC/MIC targets with MRSA having MIC < 2mg/L.

**Toxicity and Vancomycin Concentrations:**


- Pure preparations of vancomycin used today show no evidence of ototoxicity (animal models / humans)
- Nephrotoxic potential of ≤ 5% in the absence of concomitant nephrotoxins
PK/PD and Toxicity Issues Bottom Line November 2008

- Assess risk vs benefit in each patient – e.g. Mortality >40% vs reversible nephrotoxicity 15-20% with troughs >20mg/L (comparable to that seen with concomitant nephrotoxins) vs data that support increased odds ratio for mortality in patients with AKI.
- Recent Retrospective or “Prospective” cohort design studies may be hypothesis generating, but do not provide any conclusive evidence of increased risk of nephrotoxicity with troughs >15mg/L and <20mg/L, since each study had a number of design flaws and potential confounders. (Hidayat LK et al. Arch Intern Med 2006;166:2138-44.; Jeffres MN et al. 46th ICAAC 2006: abstract #K-789.; Lee-Buch SC, Overholser BR, Munoz-Price LS, 46th ICAAC 2006:abstract L-1298; Nguyen M, Wong J, Lee C et al. 47th ICAAC 2006:abstract K-1096)
- However, there is reasonable data to exercise caution when targeting troughs to be between 15 - 20mg/L, to ensure that troughs do not go above 20mg/L. Since there is some evidence that higher troughs, particularly in patients on concomitant nephrotoxins and / or receiving prolonged therapy of >2 weeks, may be at higher risk of nephrotoxicity when the trough is >20mg/L. (Nguyen M, Wong J, Lee C et al. 47th ICAAC 2006:abstract K-1096; Hidayat LK et al. Arch Intern Med 2006;166:2138-44.)
- There is reasonable data to maintain total daily doses <4g/day, to reduce risk of nephrotoxicity, whenever possible. Using q8h dosing or q6h dosing may allow target trough attainment, while preventing use of large daily vancomycin doses of >4g/day. (Lodise T et al. AAC April 2008;52(4):1330-36.)

Vancomycin and Nephrotoxicity:

- Risk with monotherapy <5%
- Risk may increase to >15% if any of the following apply:
  – Duration of therapy >14 days
  – Dose per day exceeds 4g
  – Trough vancomycin levels are maintained above 20mg/L
  – Use of concomitant nephrotoxins (AMGs, AmphoB, Cisplatin, Diuretics, NSAIDS)

Vancomycin Therapeutic Drug Monitoring
Pharmacokinetic / Pharmacodynamic Measures:

- Peak/MIC or Cmax/MIC
- AUC/MIC
- MIC
- T>MIC

Pertinent Vancomycin Pharmacokinetics:

- Strictly, to completely describe the PK of vancomycin, a 2 or 3 compartment model is required.
- Has an average distribution period of 30 minutes to 1 hour.
- If vancomycin levels for TDM are obtained after the distribution phase is completed, a one compartment model can be used for dosing calculations.

- Distribution issues: poor distribution to CNS (0-20% uninflamed meninges up to 50% with inflamed meninges, ~30% in patients on adjunctive dexamethasone in meningitis), Bone (15%), heart valves, lung tissue or epithelial lining fluid (20-50%)
- Average of ~50% protein binding
- Elimination t½ with normal renal function ~6h.
- Average volume of distribution ~0.6L/kg
- Factors that affect the overall activity include: tissue-distribution, inoculum size and protein binding.
Pharmacokinetic Principles:

- The fraction / proportion / percentage of the total amount of drug removed per unit of time remains constant (elimination rate constant (ke)), as long as drug clearance (metabolism and elimination) and volume of distribution doesn’t change.
- Half-life remains constant, as long as drug clearance (metabolism and elimination) and volume of distribution doesn’t change.
- The peak and trough concentration will be directly proportional to the dose administered.
- Increasing the dose, keep interval constant: proportionally increases both the peak and the trough concentrations, but get wider fluctuations between the peak and trough concentration.
- Decreasing the interval, keep dose constant: also increases both the peak and trough, but the difference between the peak and trough concentrations is smaller – smaller fluctuations between the peak and trough concentration...
  but, can’t estimate the change as a given proportion, since the relationship is an exponential and will be affected by the patient’s half-life.

Steady State

- Rate of drug going in = Rate of drug going out
- Equilibrium is reached, and no further accumulation occurs, so that the maximum and minimum concentrations remain constant with each subsequent dose.

<table>
<thead>
<tr>
<th>Duration of Drug Administration (half-lives)</th>
<th>Steady-State Concentration Reached (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>87.5</td>
</tr>
<tr>
<td>4</td>
<td>93.75</td>
</tr>
<tr>
<td>5</td>
<td>96.875</td>
</tr>
<tr>
<td>6</td>
<td>98.4735</td>
</tr>
<tr>
<td>7</td>
<td>99.25</td>
</tr>
</tbody>
</table>
Loading Dose General Principles:

- \( V_d \) is a proportionality constant that relates the amount of drug in the body to the serum concentration. (amount in body = \( C \times V_d \))
- \( V_d \) is used to calculate the loading dose (LD) of a drug that will immediately achieve a desiredCss. (LD = \( \text{Css} \times V_d \))
- A loading dose is useful for drugs that will be administered by intermittent administration that have a long half-life, since it takes 3-5 half-lives to reach steady state. (LD = \( \text{Css,peak} \times V_d \))
- A loading dose may also be used for drugs administered by continuous infusion, if an immediate drug effect is desired, and 3-5 half-lives is too long to wait to reach the therapeutic range. So a loading dose is administered along with initiation of the infusion so that the therapeutic range is maintained from the onset (LD = \( \text{Css,desired} \times V_d \))

Vancomycin Serum Levels at Sunnybrook 2008
Trough Levels:
- Elevated trough levels >20mg/L may be associated with an increased risk of nephrotoxicity. Therefore, the desirable range for trough levels in all patients is < 20mg/L.
- Optimal efficacy in certain clinical situations may require maintenance of adequate trough levels during therapy. Accordingly, a target trough level of 15-20mg/L is recommended in selected patients as follows:

Vancomycin Serum Levels at Sunnybrook 2008 Target trough level of 15-20 mg/L is recommended in:
- Patients with endocarditis, meningitis, or MRSA pneumonia (... and osteomyelitis) (where vancomycin penetration to the site of infection may be poor)
- Patients with a poor clinical response to therapy that is deemed to be appropriate
- Patients in whom the pathogen has an unusually high MIC
- Patients receiving a prolonged course of vancomycin therapy (> 14 days)
- Patients with renal insufficiency
- Patients with increased vancomycin clearance (e.g., burn patients, IV drug users)
- Consult Pharmacy for assistance with vancomycin dosing and serum level monitoring
Vancomycin Serum Levels at Sunnybrook 2008

Peak (2-hr post-infusion) Levels:

- There is no evidence of any association between toxicity and elevated peak (2-hour post-infusion) levels. Accordingly, the acceptable range for peak levels (2-hour post-infusion) is 20-80 mg/L.
- The clinical importance of peak (2-hour post-infusion) levels remains controversial. However, the peak (2-hour post-infusion) level may be useful in determining individualized patient pharmacokinetics. This data may be used to guide dosing in an effort to ensure that trough levels are maintained in the targeted range of 15-20 mg/L in selected patients (see above).

- Usual dosage: 1 g IV Q12H
  Note: a higher dosage may be appropriate in some situations in which maintenance of higher trough vancomycin levels (15-20 mg/L) may be desirable

Renal Insufficiency:

- Usual initial dose is 1g IV administered at an interval based on calculated creatinine clearance (see table). Consult Pharmacy to ensure optimal dosing.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Empiric Initial Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>12</td>
</tr>
<tr>
<td>40-49</td>
<td>24</td>
</tr>
<tr>
<td>30-45</td>
<td>36</td>
</tr>
<tr>
<td>20-35</td>
<td>48</td>
</tr>
<tr>
<td>15-25</td>
<td>72</td>
</tr>
<tr>
<td>&lt;15 or PD</td>
<td>Consult Pharmacist</td>
</tr>
</tbody>
</table>

Hemodialysis: Usual post-HD dose is 500mg. Give 1g post-HD if a trough level of 15-20 mg/L is desired.

Attaining Troughs of 15-20 mg/L

- Use of our currently recommended initial dosage of 1 g IV Q12H will not provide sufficient drug to attain the desired serum levels in patients weighing > 75 kg.
- For patients >75kg, initiate vancomycin dosing based on 15 mg/kg IV per dose administered at a dosing interval based on renal function in the situations cited above.
- In order to streamline dispensing and to minimize wastage of prepared minibags, the table indicates that doses should be rounded off to the nearest 0.25 g.
Alternative dosing strategies, such as 1-1.25g q8h may be beneficial.

<table>
<thead>
<tr>
<th>Body Weight Range (kg)</th>
<th>Dose (g)</th>
<th>Range of Doses based on 15 mg/kg actual body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 75</td>
<td>1</td>
<td>≤ 1.15 g</td>
</tr>
<tr>
<td>76-90</td>
<td>1.25</td>
<td>1.15-1.35 g</td>
</tr>
<tr>
<td>91-105</td>
<td>1.5</td>
<td>1.36-1.57 g</td>
</tr>
<tr>
<td>106-125</td>
<td>1.75</td>
<td>1.58-1.87 g</td>
</tr>
<tr>
<td>126-140</td>
<td>2</td>
<td>1.88-2.10 g</td>
</tr>
<tr>
<td>&gt; 141</td>
<td>Consult ID and/or Pharmacy</td>
<td>Alternative dosing strategies, such as 1-1.25g q8h may be beneficial</td>
</tr>
</tbody>
</table>

Vancomycin Dose Recommendations for HAP, VAP or HCAP and attainment of vancomycin trough concentrations of 15-20mg/L: Cognitive Dissonance.

Drusano G et al. IDSA annual meeting (abstract 447), Oct 2007

- Examined likelihood of attaining trough 15-20mg/L with 15mg/kg q12h vancomycin dosing.
- Used PK data from 21 patients treated with vancomycin who had measured CrCl and modeled data to simulate 9,999 trough vancomycin concentrations for patients with CrCl of 100, 80, 60 and 40 mL/min.
- Probability of attaining target trough concentrations for patients with CrCl of 100, 80, 60 and 40 mL/min was 7.4%, 10.6%, 14%, and 15.7%, respectively, with q12h dosing.
- In patients with CrCl 40mL/min, 7% had trough concentrations > 40mg/L.
- Concluded: Need to explore other doses and schedules and drug monitoring is necessary to achieve effective and non-toxic drug exposure with vancomycin.

Obtaining Vancomycin Levels (off 3rd dose, assumed steady state)
**Interpreting Levels:**

\( t_{1/2} = \text{time required to reduce concentration by one-half} \)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Cmax, observed</th>
<th>Cmin, observed</th>
<th>End of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1300h )</td>
<td>30 mg/L</td>
<td>17 mg/L</td>
<td>( 1100h )</td>
</tr>
<tr>
<td>( 9h = t_{1/2} )</td>
<td>( 2200h )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Interpreting Levels:**

\( t_{1/2} = \text{time required to reduce concentration by one-half} \)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Cmax, observed</th>
<th>Cmin, observed</th>
<th>End of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1300h )</td>
<td>28 mg/L</td>
<td>8 mg/L</td>
<td>( 1100h )</td>
</tr>
<tr>
<td>( 9h = 2 t_{1/2} )</td>
<td>( 2200h )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Obtaining Vancomycin Levels**

(Not at steady state)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Cmax, observed</th>
<th>Crandom, observed</th>
<th>( \Delta T )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1300h )</td>
<td>30 mg/L</td>
<td>25 mg/L</td>
<td>24h</td>
</tr>
<tr>
<td>( 1300h ) the next day</td>
<td>Tmax, observed</td>
<td>Tmax, observed</td>
<td>Trandom, observed</td>
</tr>
</tbody>
</table>
The fraction / proportion / percentage of the total amount of drug removed per unit of time remains constant (elimination rate constant (ke)).

Started out with 30mg/L and dropped to 25mg/L in 24h. Therefore, 5mg/L drop in 24h, i.e 5mg/L of 30mg/L = 0.17. Therefore, 0.17 removed in 24h, or 0.17/24 per hour = 0.007/hour. Half-life = 0.693/0.007^th = 99 hours

\[
k = -\frac{1}{\Delta T}
\]

\[
\Delta T = \frac{0.693}{k}
\]

\[
t_{1/2} = 99 \text{ hours}
\]

...dosing interval = q4days

\[
k = -\frac{\ln C_{\text{obs.min}} - \ln C_{\text{obs.max}}}{\Delta T}
\]

\[
t_{1/2} = \frac{0.693}{k}
\]

...dosing interval = q4days

### Trough-Only Monitoring


- Recognizing that the relationship between dosing interval adjustments and predicting the steady state Cmax or Cmin is an exponential one, one can use the following relationship as an approximation of Cmax and Cmin. **Caution, overestimates the frequency or dose needed, since calculations are based on proportions, rather than taking into account the exponential relationship.**

\[
\frac{Dose_{\text{new}}}{\tau_{\text{new}}} = \frac{Dose_{\text{old}}}{\tau_{\text{old}}} \cdot \frac{C_{\text{min,ss new}}}{C_{\text{min,ss old}}}
\]

Therefore, 
\[
Dose_{\text{new}}/\tau_{\text{new}} = Dose_{\text{old}}/\tau_{\text{old}} \cdot C_{\text{min,ss new}}/C_{\text{min,ss old}}
\]

**Goal: Maintain total daily vancomycin dose < 4g / day**

<table>
<thead>
<tr>
<th>Trough &lt;10mg/L</th>
<th>Trough 10-13mg/L</th>
<th>Trough 13-20mg/L</th>
<th>Trough &gt;20mg/L and &lt; 40mg/L</th>
<th>Trough &gt;40mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>- If dose given, order Peak, determine patient’s PK based on the results of the peak and previously available trough. - While awaiting results of peak level, either ↑ dose, ↓ dosing interval or do a combination of both. - When results are available, modify dose based on levels.</td>
<td>- Increase dose by 50% - Keep same dosing interval - Round off to nearest 250mg</td>
<td>- Keep same dose and interval</td>
<td>- Decrease dose by 25 to 50% - OR decrease dose by proportion - Round off to nearest 250mg</td>
<td>- Hold Vanco - Order 2 random levels separated by at least 24 hours and determine patient’s PK.</td>
</tr>
</tbody>
</table>

Prepared by: Sandra Walker, Pharm.D Clinical Coordinator, ID Department of Pharmacy Sunnybrook HSC
...and what about continuous infusion of vancomycin?


- With CI serum drug concentration increases until equilibrium established btwn. drug dosage rate and the rate of drug elimination (i.e. rate of drug administration = rate of drug elimination).
- When serum drug concentrations reach a constant value, steady state is achieved.

- CIV to obtain plateau concentrations of 20 – 25mg/L and IIV to obtain trough concentrations of 10 – 15mg/L were comparable in clinical efficacy and safety
- Power to detect a difference in clinical outcome was only 23% to detect a 15% difference in treatment failures between groups.
- Targeted concentrations were acquired faster with fewer samples, less variability in the daily infused dose, and reduced cost with CIV
- AUC24h and daily dose comparable in tx groups
- Cost of 10 days of CIV was 23% lower than 10 day of IIV, both because less vancomycin was infused and because fewer samples were required to monitor the treatment.

Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy

Paul R. Ingram1,2, David C. Lys1, Paul A. Tambrakal1,3, Wei P. Goh1, Vincent H. Tan4

1Department of Medicine, National University Hospital Singapore. 2Trust Earned Scholarship, National University of Singapore. 3Department of Pharmacy, Duke National Medical Group, Singapore. 4Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore.


Table 1. Logistic regression analysis of nephrotoxicity associated with continuous vancomycin infusion.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis odds (95% CI)</th>
<th>P-value</th>
<th>Multivariate analysis odds (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.577 (1.029 - 6.388)</td>
<td>0.040</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.333 (0.190 - 0.580)</td>
<td>0.874</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.998 (0.939 - 1.060)</td>
<td>0.889</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dL)</td>
<td>0.4800 (0.1711 - 1.3487)</td>
<td>0.280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.321 (1.135 - 9.572)</td>
<td>0.032</td>
<td>3.307 (1.133 - 9.404)</td>
<td>0.031</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.631 (0.106 - 3.741)</td>
<td>0.633</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>3.415 (0.606 - 18.998)</td>
<td>0.160</td>
<td>4.554 (0.596 - 42.360)</td>
<td>0.163</td>
</tr>
<tr>
<td>Vancocin concentrations</td>
<td>0.479 (1.027 - 2.153)</td>
<td>0.099</td>
<td>21.256 (2.487 - 182.675)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Systolic and diastolic blood pressure in mmHg.

Vancocin concentrations = mg/mL

Note: only variables with P < 0.10 in univariate analysis are shown.

IAC indicated concentration calculated in accordance with IAC.

Other Data:

- 500mg LD followed by 2g iv q24h by continuous infusion for Css, avg of 15mg/L (James JJ. AAC 1996 – PK study)
- 1g followed by 2g iv q24h aiming for Css, avg of 15mg/L (Pea F. Clin Pharmacokinet 2008 – clinical experience and opinion)
- 2g iv q24h aiming for Css, avg of 20mg/L (Rello J. Crit Care Med 2005 – retrospective, small sample size for CI of 16 pts, mortality 25%)

Continuous Infusion Vancomycin
Bottom Line November 2008:

- Makes sense WRT PK/PD characteristics of vancomycin
- Limited data to date indicate comparable efficacy, and safety
- However, limited by small sample size
- May be a choice in patients in whom target trough levels have been difficult to achieve with traditional intermittent dosing. … i.e. patients with a short vancomycin half-life that require more frequent administration with intermittent infusion
Dosing for Continuous Infusion of Vancomycin:

- 500mg – 1000mg iv Loading dose followed by initiation of a continuous infusion of 2g iv q24h.
- Target Css,avg of 15-20mg/L
- LD = Css,desired * V
- Continuous infusion rate:
  \( (k_o) = \frac{ Css,desired }{ kV}; \) gives rate as mg per hour