ANTIBIOTIC DOSE AND DOSE INTERVALS IN RRT and ECMO

Professor Jeffrey Lipman

Department of Intensive Care Medicine Royal Brisbane Hospital University of Queensland
NO CONFLICT OF INTERESTS
Important concept

Recommended dosages are obtained from healthy volunteers and possibly (ward) “sick” patients.
Antibiotic regimens are derived from non-critically ill volunteers. Their haemodynamic system is normal, as is their liver and kidney blood flow. They have not leaky capillaries nor have they drips and pipes in every orifice.
The kidney and antibiotics

Blot S et al. *Diagnostic Microbiology and Infectious Disease* 2014;79:77–84
Antibiotic related IMPORTANT pharmacokinetic parameters

- $C_{\text{max}}$: Peak Concentration
- $C_{\text{min}}$: Trough Concentration
- $t_{1/2}$: Half-life
- $V$ (or $V_D$): Volume of distribution
- AUC: Area under curve
- Cl: Clearance

Protein binding
Capillary lead and fluid administration
Volume of distribution (l/kg)

$r = 0.7; P < 0.001$

APACHE II score
we have found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations.

35mg/kg loading 35mg/kg/day
Antibiotics that stay in extravascular and extracellular space ie that don’t penetrate “solid” organs, (hydrophilic tendencies) namely

- AminoGlycosides
- Glycopeptides
- β-Lactams (to a lesser extent)
- Colistin
LOADING DOSE vs CLEARANCES

Fundamental concept

Loading dose is INDEPENDENT of clearances

EVEN IN RENAL FAILURE (without clearance) YOU MUST GIVE LOADING DOSE
LOW EXPOSURE TO ANTIBIOTICS ENABLES DEVELOPMENT OF RESISTANCE

Antibiotic resistance—What’s dosing got to do with it?

Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Critical Care Medicine August 2008;36:2433-40
Sepsis changes PK

SEPSIS

- Increased Cardiac Output
  - Increased CL
    - Low Plasma Concentrations

- Leaky Capillaries &/or altered protein binding
  - Increased Vd
    - Increased Vd
      - Extracorporeal circuits

- Normal Organ Function
  - Unchanged Vd
    - Normal Plasma Concentrations

- End Organ Dysfunction (e.g., renal or hepatic)
  - Decreased CL
    - Decreased CL
    - Altered CL and Increased Vd cf AKI
      - High Plasma Concentrations

? Plasma concentrations
(C)RRT (Continuous) Renal Replacement Therapy
CRRT Effects on Electrolytes and Water .....and Drugs.
If you know

1. Membrane Pore Size
2. Drug Size
3. Sieving Coefficient

Then it’s easy!
DRUG CLEARANCE

If you know

1. Membrane Pore Size
2. Drug Size
3. Sieving Coefficient

Then it's easy!

Or is it?
CRRT
Continuous Renal Replacement Therapy

Kidney Filter

Access (Pre-Filter) From Patient

Semi-permeable Membrane

Return (Post Filter) To Patient

Ultrafiltrate

Dialysate
Continuous Veno-Venous Hemodialysis

CVVHD

NO Replacement Fluid.

Access (Pre-Filter)

To Patient

Return (Post Filter)

Kidney Filter

Semi-permeable Membrane

Ultrafiltrate

Dialysate

FLOW

FLOW
CVVHD
Removal of urea, toxins, electrolytes & DRUGS (small molecules)
CVVHD

\[ S_d = \frac{[\text{Antibiotic}]_{\text{dialysate}}}{[\text{Antibiotic}]_{\text{plasma}}} \]
$$C_l_{CVVHD} \approx Q_d \times S_d$$
CVVH

Removal of $H_2O$, urea, toxins, electrolytes & DRUGS (small + middle molecules)
CVVH
Continuous Veno-Venous Hemofiltration

Replacement Fluid can be either Pre-Filter or Post Filter.

Access (Pre-Filter) From Patient

Semi-permeable Membrane

Return (Post Filter) To Patient

Ultrafiltrate

NO Dialysate
CVVH

\[
S_c = \frac{[\text{Antibiotic}]_{\text{ultrafiltrate}}}{[\text{Antibiotic}]_{\text{plasma}}}
\]
CVVH

\[ Cl_{CVVH(pre)} = Q_f \times Sc \times CF \]

where \( CF = \frac{Q_b}{Q_b + Q_{pre}} \)
CVVHDF
Continuous Veno-Venous Heamodialysis

Replacement Fluid can be either Pre-Filter or Post Filter.
SLEDD as an alternative

And then there is SLEDD

Slow Low Efficiency Daily Dialysis, Extended Daily Dialysis
A “Hybrid” of CRRT + IHD

Minimal antibiotic clearance data published
Antibiotic dosing during sustained low-efficiency dialysis: Special considerations in adult critically ill patients*

Kimberly N. Bogard, PharmD, BCPS; Nicole T. Peterson, PharmD, BCPS; Troy J. Plumb, MD; Michael W. Erwin, PharmD, BCPS; Patrick D. Fuller, PharmD, BCPS; Keith M. Olsen, PharmD, FCCP, FCCM

Nine original research articles plus a few case reports

Sustained low efficiency dialysis allows rational renal replacement therapy, but does it allow rational drug dosing?*

Therapeutic Options of RRT Differ

CVVH
CVVHD
CVVHDF
SCUF
SLEDD
Tables and equations

\[ F_{\text{EC}} = \frac{Cl_{\text{EC}}}{Cl_{\text{EC}} + Cl_{\text{NR}} (+ Cl_{\text{R}})} \]

- \( Cl_{\text{EC}} = \) extracorporeal clearance
- \( Cl_{\text{NR}} = \) non-renal clearance
- \( Cl_{\text{R}} = \) renal clearance

\[ Cl_{\text{HDF}} = Q_F \times S + Q_d \times S_d \]

\[ Cl_{\text{HF}} = Q_F \times S \]

\[ Cl_{\text{HD}} = Q_d \times S_d \]

\[ Cl_{\text{HDF}} = Q_F \times S + Q_d \times S_d \]

\[ S = \frac{C_{\text{uf}}}{C_p} \]

\[ Cl_{\text{HF}} = Q_F \times S(\alpha) \]

\[ S_d = \frac{C_d}{C_p} \]

\[ Cl_{\text{HD}} = Q_d \times S_d \]

\[ Fr_{\text{EC}} = \frac{Cl_{\text{EC}}}{Cl_{\text{EC}} + Cl_{\text{NR}} (+ Cl_{\text{R}})} \]

\[ D = \frac{D_{\text{anuria}}}{1 - Fr_{\text{EC}}} \]
If you know

1. Membrane Pore Size
2. Drug Size
3. Sieving Coefficient

Then it’s easy!
If you know

1. Membrane Pore Size
2. Drug Size
3. Sieving Coefficient

Then it’s easy!
HOW DO WE DOSE AT MY HOSPITAL?
Therapeutic drug monitoring of β-lactams for critically ill patients: unwarranted or essential?


Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts a,b,c,*, Marta Ulledomolins a,d, Michael S. Roberts e,f, Brett McWhinney g, Jacobus Ungerer g, David L. Paterson h,i, Jeffrey Lipman a,c

Loading dose = Desired concentration (table 2) x Vd (table 5)

Calculate CRRT clearance based on mode of CRRT, formulae in text & values in table 5

Total clearance (Cl_tot) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

- Cmax/MIC & AUCC24>MIC
- Cmax/MIC ratio

Calculate elimination rate = concentration x Cl_tot

Calculate half-life = \(0.693 \times \frac{Vd}{Cl_{tot}}\)

Maintenance infusion rate = elimination rate

Calculate time to reach target trough concentration

Repeat loading dose at calculated time

Calculate target mean concentration = target AUCC24/24

Calculate dosing interval = Dose/(Cp x Cl_{tot} / f)

Repeat loading dose at calculated dosing interval
CRRT and MEROPENEM

CRRT and PIPTAZO

CRRT and VANC

ONE WAY

Loading dose = Desired concentration (table 2) \times Vd (table 5)

Calculate CRRT clearance based on mode of CRRT, formulae in text & values in table 5

Total clearance ($C_{\text{tot}}$) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

- $C_{\text{max}}/\text{MIC}$ & $\text{AUC}_{24}/\text{MIC}$
- $C_{\text{max}}/\text{MIC}$ ratio

Calculate elimination rate = concentration \times $C_{\text{tot}}$

Calculate half-life = $0.693 \times Vd / C_{\text{tot}}$

Calculate time to reach target trough concentration

Maintenance infusion rate = elimination rate

Calculate target mean concentration = target $\text{AUC}_{24}/24$

Calculate dosing interval = Dose / ($Cp \times C_{\text{tot}} / f$)

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval

Advantages

Individualized CRRT MIC
Takes PK/PD relationships into account

Alternatively

Choose a PK article that most closely resembles the form of CRRT you use
Use their clearances – see if it seems a reasonable estimate of your clearances
Dose accordingly
How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy?

Diagnostic Microbiology and Infectious Disease
Jamal JA, Mueller BA, Choi GYS, Lipman J, Roberts JA

How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy?

Diagnostic Microbiology and Infectious Disease

TABLE 1: Pharmacokinetic parameters of different class of antibiotics in critically ill patients receiving variable types of renal replacement therapy modalities
You may prescribe Continuous RRT.... but is it continuous? How often do you come on morning ward round to here the “kidney” was off for xxx hours? How often do you do rounds to here “Oh we are changing the filter”......

Do you factor in for the “down time”?
What do you do when you want to cease RRT. We say “leave the filter off for awhile to see if pt passes urine…”
And often forget to change dose of drugs…..

**Do you factor in for the “down time”?**
Conclusions:

This matched cohort study confirms an increase in Vd and a decrease in CL for meropenem in adult patients receiving ECMO. In patients receiving meropenem on ECMO, standard dosing does not always result in optimal drug concentrations because of the significant PK changes in the setting of critical illness, ECMO and RRT. Therapeutic drug monitoring where possible is recommended until robust dosing guidelines become available.
Therapeutic Drug Monitoring (TDM) refers to analysis and subsequent interpretation of drug concentrations in biological fluids.
TDM should be used to

**maximise efficacy**

**minimise toxicity**

To personalise dosing for high probability of therapeutic success, prevent development of resistance, provide low probability of toxicity
Safe drugs
Large therapeutic range

TDM should be used to
maximise efficacy
minimize toxicity
Short communication

Analysis of 12 beta-lactam antibiotics in human plasma by HPLC with ultraviolet detection

Brett C. McWhinney, Steven C. Wallis, Tara Hillister, Jason A. Roberts, Jeffrey Lipman, Jacobus P.J. Ungerer

a Chemical Pathology, Pathology Queensland, Brisbane, Queensland, Australia
b Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Queensland, Australia
CONCLUSION

For various reasons therapeutic drug monitoring (TDM) of most antibiotics is difficult if not impossible. We have set up a TDM service for all our beta-lactam use and have (not surprisingly) shown that in more than half of our ICU patients we are dose adjusting once receiving back a drug level!
THE END!

j.lipman@uq.edu.au

www.som.uq.edu.au/btccrc
ONE WAY

Loading dose = Desired concentration (table 2) x Vd (table 5)

Calculate CRRT clearance based on mode of CRRT, formulae in text & values in table 5

Total clearance ($C_{tot}$) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

- Time above threshold concentration
- $C_{max}$: MIC & AUC$_{24}$:MIC
- $C_{max}$/MIC ratio

Calculate elimination rate = concentration x $C_{tot}$

Calculate half-life = $0.693 x Vd / C_{tot}$

Calculate target mean concentration = target AUC$_{24}$/24

Calculate target mean concentration = target AUC$_{24}$/24

Calculate time to reach target trough concentration

Calculate dosing interval = Dose/(Cp x $C_{tot}$ / f)

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval

Time above threshold concentration

Concentration

\( C_{\text{max}} \): MIC & AUC \(_{24}\)/MIC

Total clearance (\( C_{\text{tot}} \)) = calculated CRRT clearance + non-CRRT clearance

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Loading dose = Desired concentration \( \times V_d \)

Pharmacokinetic target?

\( C_{\text{max}}/\text{MIC ratio} \)

Calculate elimination rate = concentration \( \times C_{\text{tot}} \)

Calculate half-life = \( 0.693 \times V_d / C_{\text{tot}} \)

Calculate total clearance (\( C_{\text{tot}} \)) = calculated CRRT clearance + non-CRRT clearance

Calculate half-life = \( 0.693 \times V_d / C_{\text{tot}} \)

Calculate time to reach target trough concentration

Calculate maintenance infusion rate = elimination rate

Calculate target mean concentration = target AUC \(_{24}/24\)

Calculate dosing interval = Dose / (\( C_p \times C_{\text{tot}} \))

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval

Maintenance infusion rate = elimination rate
Loading dose = Desired concentration x Vd (28 l)
Desired concentration = 5 x MIC = 20 mg/l
Loading dose = 20 x 28 ≈ 500 mg
Calculate CRRT clearance based on mode of CRRT & published Sc or Sd values

\[ Cl_{CVVH} \text{ (post)} = Qf \times Sc \]

\[ = 2450 \times 0.95 = 2327 \text{ ml/h} = 39 \text{ ml/min} \]
Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance \( (\text{Cl}_{\text{tot}}) \) = calculated CRRT clearance + non-CRRT clearance
\[ = 39 + 60 \approx 100 \text{ ml/min} = 0.1 \text{ l/min} \]

Pharmacokinetic target? [Diagram]

- Time above threshold concentration
- \( C_{\text{max}}/\text{MIC} \) & \( \text{AUC}_{24}/\text{MIC} \)
- \( C_{\text{max}}/\text{MIC} \) ratio

Calculate elimination rate = concentration x \( \text{Cl}_{\text{tot}} \)

Calculate half-life = \( 0.693 \times \text{Vd} / \text{Cl}_{\text{tot}} \)

Calculate time to reach target trough concentration

Maintenance infusion rate = elimination rate

Calculate target mean concentration = target \( \text{AUC}_{24}/24 \)

Calculate dosing interval = \( \frac{\text{Dose}}{(\text{Cp} \times \text{Cl}_{\text{tot}})} \)

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval
Loading dose = Desired concentration \times V_d

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance \( (\text{Cl}_{\text{tot}}) \) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

Calculate elimination rate
\[ \text{Elimination rate} = \text{concentration} \times \text{Cl}_{\text{tot}} \]
\[ = 20 \times 0.1 = 2 \text{ mg/min} \]

Calculate half-life
\[ \text{Half-life} = 0.693 \times \frac{\text{Vd}}{\text{Cl}_{\text{tot}}} \]

Calculate time to reach target trough concentration

Repeat loading dose at calculated time

Maintenance infusion rate = elimination rate

Calculate target mean concentration
\[ \text{Target AUC}_{24/24} \]

Calculate dosing interval
\[ \text{Dose} / (\text{Cp} \times \text{Cl}_{\text{tot}}) \]

Calculate target mean concentration

Repeat loading dose at calculated dosing interval
Loading dose = Desired concentration x Vd

Calculate CRRT clearance based on mode of CRRT, formulae & published values

Total clearance ($Cl_{tot}$) = calculated CRRT clearance + non-CRRT clearance

Pharmacokinetic target?

- Time above threshold concentration
- $C_{max}/MIC$ & $AUC_{24}/MIC$
- $C_{max}/MIC$ ratio

Calculate elimination rate = concentration x $Cl_{tot}$

Calculate half-life = $0.693 \times Vd / Cl_{tot}$

Calculate target mean concentration = target $AUC_{24}/24$

Calculate dosing interval = $Dose / (Cp \times Cl_{tot})$

Calculate time to reach trough concentration

Repeat loading dose at calculated time

Repeat loading dose at calculated dosing interval

Maintenance infusion rate = elimination rate = 2 mg/min