

Pharmacokinetics of Antimicrobials in Animals: Lessons Learned

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Value of Animal Models

- Time course of drug concentrations at sites of infection
- Time course of antimicrobial activity at sites of infection
- Dose-response relationships
- Correlation of PK/PD parameters with efficacy
- Magnitude of PK/PD parameter required for efficacy

Pharmacokinetics in Animals

- Clearance and half-life related to body weight and heart rate
- Elimination of drugs are much faster in small rodents than in humans
- Need to give larger doses or more frequent dosing to simulate drug exposures in humans

Half-Lives in Mice and Humans

<u>Drug</u>	Half-life in Minutes	
	<u>Mice</u>	<u>Humans</u>
Penicillin G	5	30
Imipenem	8	60
Cefazolin	15	108
Gentamicin	18	150
Ciprofloxacin	32	240
Erythromycin	35	180
Minocycline	120	1080

Pharmacokinetics of Ciprofloxacin in Animals

<u>Species</u>	<u>Dose</u>	<u>Cmax</u>	<u>T1/2</u>	<u>AUC</u>
Mouse	5	1.5	0.52	1.8
Rat	5	1.2	1.2	2.2
Dog	5	1.5	3.0	4.8
Man	7	2.7	4.4	11

Ways to Reduce Clearance and Prolong Half-life

- Probenecid - reduces tubular secretion of beta-lactam antibiotics
- Renal impairment - can be induced in mice and rats by administering uranyl nitrate. Slows elimination of renally excreted drugs
- Increase protein binding of drugs eliminated primarily by glomerular filtration

Serum Protein Binding of Antimicrobials in Animals

- In vivo antimicrobial activity is dependent on the free drug concentration
- Serum protein binding of most antimicrobials is less in animals than in man
- A few antimicrobials have higher binding in animals than in man

Serum Protein Binding of Antimicrobials in Animals

<u>Drug</u>	<u>Mice</u>	<u>Human</u>
Cefonacid	78%	97%
Ceftiaxone	76%	95%
Cefditoren	87%	88%
Telithromycin	88%	60%

Efficacy of Once-Daily Dosing of Ceftriaxone against *K. pneumoniae* (MIC=0.12 mg/L) in Neutropenic Mice with Murine and Human Pharmacokinetics

	<u>Murine</u>	<u>Human</u>
Dose (mg/kg)	30	30
Peak (mg/L)	40	250
T _{1/2} (hr)	0.6	8
Binding (%)	76	95
T>MIC Total (hr)	5.6	>24
T>MIC Free (hr)	4.4	>24
Efficacy	NO	YES

Efficacy of Once-Daily Dosing of Amikacin against *K. pneumoniae* (MIC=0.5 mg/L) in Neutropenic Mice with Murine and Human Pharmacokinetics

	<u>Murine</u>	<u>Human</u>
Dose (mg/kg)	15	15
Peak (mg/L)	16	46
T _{1/2} (min)	17	104
AUC	14	128
T _{>MIC} (hr)	1.7	11.7
PAE (hr)	3.8	12.3
Efficacy	NO	YES

Non-Linear Pharmacokinetics

- The need to use larger doses in animals than in humans often results in non-linear pharmacokinetics
- Usually due to saturation of drug elimination process (e.g. renal secretion, biliary excretion, metabolism)
- Cannot accurately estimate drug concentrations from results of low doses

Pharmacokinetics of Tobramycin in Mice

<u>Dose</u>	<u>Half-Life</u>	<u>AUC</u>	<u>AUC/Dose</u>
8	15 min	6.0	0.76
32	16 min	25.5	0.80
96	18 min	100	1.04
192	24 min	281	1.46

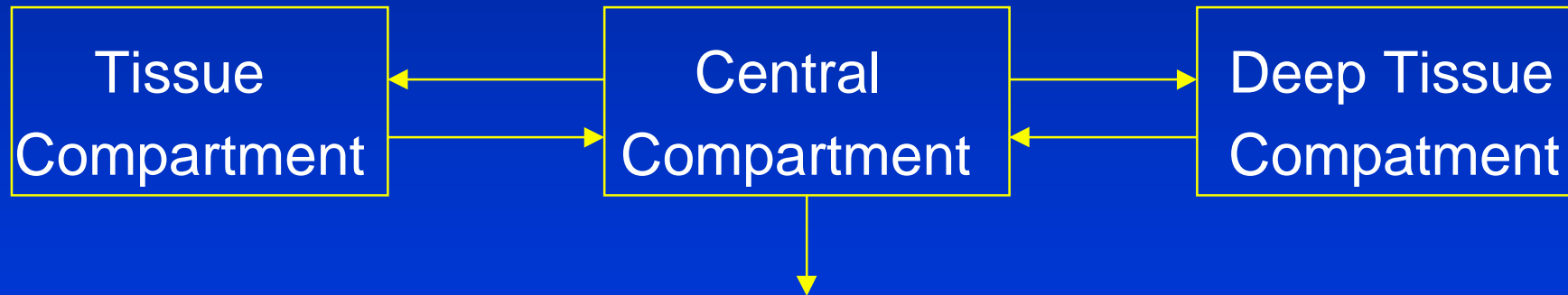
Pharmacokinetics of Ceftazidime in Mice

<u>Dose</u>	<u>Half-Life</u>	<u>AUC</u>	<u>AUC/Dose</u>
6.25	21 min	5.86	0.93
25.0	22 min	17.7	0.71
100	24 min	63.4	0.63
400	27 min	266	0.67

Pharmacokinetics of Gatifloxacin in Mice

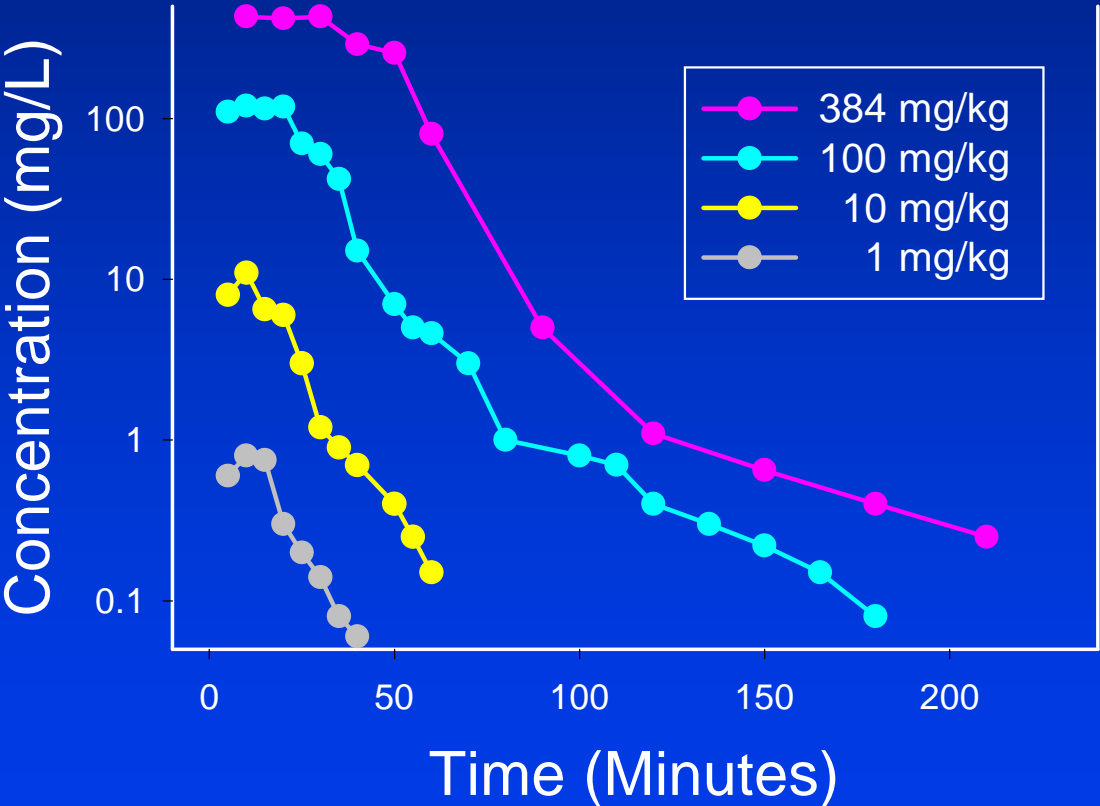
<u>Dose</u>	<u>Half-Life</u>	<u>AUC</u>	<u>AUC/Dose</u>
4.38	0.47 hr	1.76	0.40
18.8	0.59 hr	8.75	0.47
75.0	1.10 hr	56.9	0.76

Three-Compartment Model



$$C_{\text{cent}} = Ae^{-at} + Be^{-bt} + Ce^{-ct}$$

Serum Levels of Penicillin G in Mice



Pharmacokinetics of Penicillin G In Human Volunteers

	<u>Half-life (Hrs)</u>	<u>Time Above 0.01 mg/L</u>
β (beta)-phase	0.53 ± 0.09	6 hrs
γ (gamma)-phase	3.09 ± 1.28	16 hrs

Ebert, Leggett, Vogelmann, Craig J Infect Dis 158:200, 1988

Impact of Gamma-Phase on Duration of In-Vivo Postantibiotic Effect in Mice

- An in-vivo PAE of several hours with pneumococci and other streptococci if only beta-phase elimination is considered
- No in-vivo PAE if gamma-phase elimination is considered
- No PAE for beta-lactams with streptococci also observed in other animal models

Other Factors to Consider with Pharmacokinetics in Animal Models

- **Infection can significantly alter pharmacokinetics in animals. Usually get higher concentrations and larger AUCs**
- **Penetration of antimicrobials into fibrin can vary remarkably**
- **Drug concentrations in extracellular fluid of tissues related to ratio of the surface area for diffusion and the volume of fluid.**
- **Good correlation in interstitial fluids with those in serum. Lower peak levels and higher trough levels in fluid collections**

Conclusions

- Serum clearance of most antimicrobials is faster in animals than in man
- Serum protein binding is usually less in animals than in man
- The higher doses required for studies in animal models may result in non-linear kinetics
- Sensitive drug assays should be used to identify deep tissue compartments that could prolong activity against very susceptible organisms