

# Pharmacokinetics for the nephrologist: Influence of renal disease and dialysis on drug dosing

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## Disclosure:

*Consultant to:* Sigma Tau Research, Merck Research Laboratories, Glaxo Smith Kline, Schering-Plough, 3D Communications, Worldwide Clinical Trials, ARCA biopharma, Consumers Healthcare Products Association, Catabasis, Dyax, N30 Pharmaceuticals, Lundbeck A/S, Kowa Research, Novo Nordisk, McNeil

*Equity in:* Calistoga Pharmaceuticals, Catabasis

# Objectives

- Review principles of pharmacokinetics
- Discuss impact of extracorporeal therapies on pharmacokinetics
- Illustrate the influence of extracorporeal therapies on antimicrobial pharmacokinetics

# Pharmacokinetics

- Defines in quantitative terms the processes of drug absorption, distribution and elimination that determine the time course of drug action
- Mathematically, expressing
$$[ ] = f(t)$$
- Utility lies in defining drug efficacy or toxicity, or
$$\text{Action} = f([ ])$$

# Pharmacokinetics – Getting the drug into the system

Bioavailability – Fraction of the administered dose that reaches the systemic circulation

- Degree of absorption
- Pre-systemic clearance

Propranolol

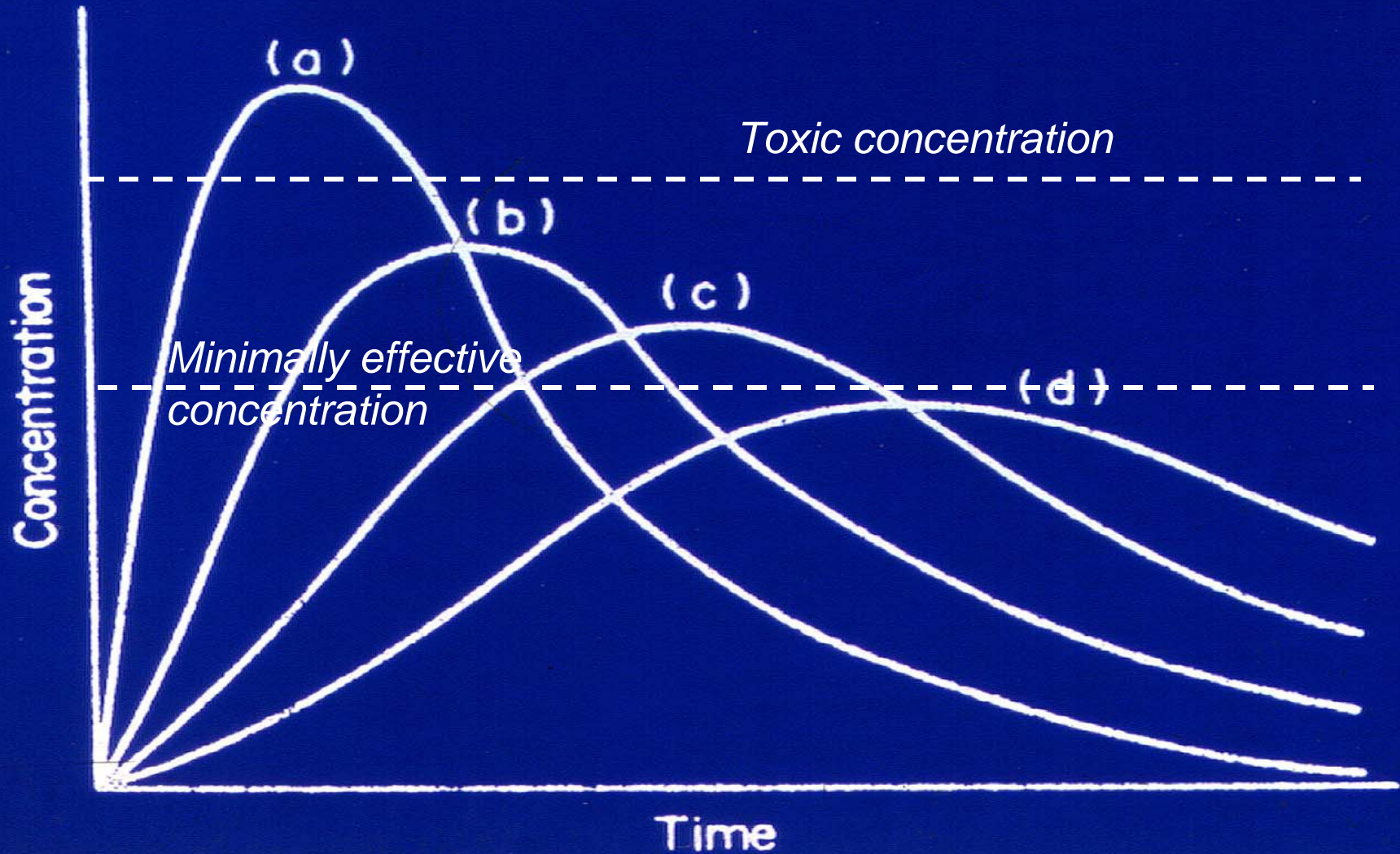
Oral dose: 40 mg

IV dose: 1-2 mg

Mathematically, systemic bioavailability expressed as  $F$ , the fraction of dose reaching systemic circulation

# Rate vs. extent of absorption

Which curve represents the highest bioavailability?



# DISTRIBUTION PHASE

## Equilibration of drug between plasma and tissue compartment(s)

- Determined by physical-chemical properties of drug
  - lipid solubility
  - protein binding
- Volume of distribution ( $V_d$ )
  - Idealized volume relating total drug in body vs. plasma drug concentration

$$V_d = \frac{\text{Amount of drug in body}}{\text{Plasma drug concentration}}$$

# LOADING DOSE AND THE VOLUME OF DISTRIBUTION

Plasma concentration = Amount of drug/(Vd)

- ❖ Indicates the distribution of drug between plasma and extra-plasma compartments
- ❖ Amount of drug in the body usually NOT known except for acute additions – loading doses

Consider patient with no drug in system, given a bolus dose...

**Amount of drug in the body = Dose given**

Thus,

$$\text{Resulting drug concentration} = \frac{\text{Dose} * F}{Vd}$$

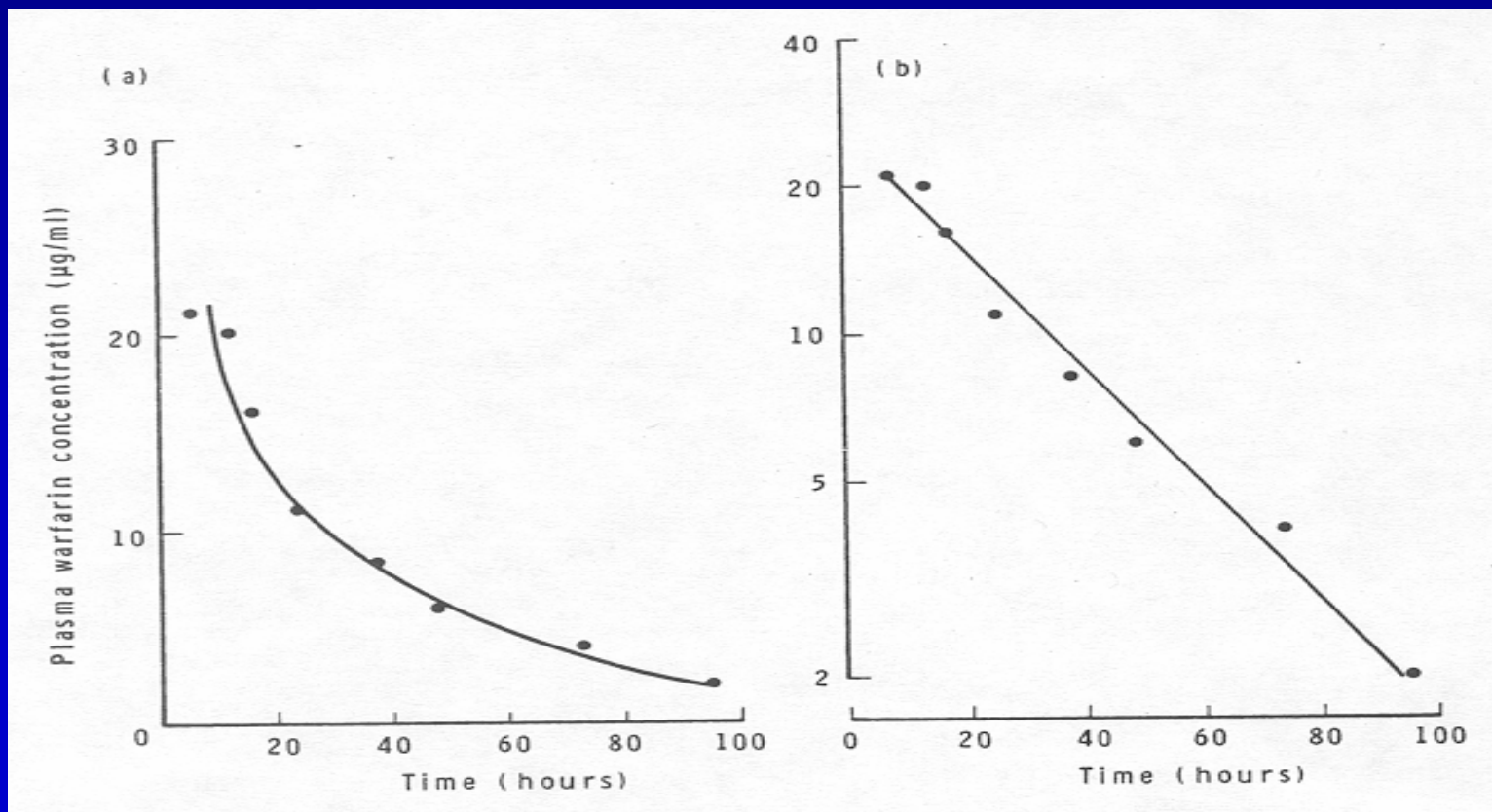
# Importance of plasma protein binding

- Only unbound, or “free” drug can:
  - Interact with target receptors, exert pharmacologic effects
  - Diffuse from plasma compartment (usually)
  - Provide substrate for metabolic enzymes
  - Be filtered by glomerulus
- Most drug assays measure “total” drug (bound + free)

# Pharmacokinetics - drug elimination

## FIRST ORDER ELIMINATION

- Constant *fraction* of drug in the body eliminated per unit time
- Exponential decay vs. time – linear log [ ] vs. time
- Most common elimination pattern clinically



# Clearance – Quantitative description of drug elimination

Clearance relates the *amount* of drug eliminated to the plasma drug concentration.

How much plasma would need to be *completely* cleared of drug to account for the amount of drug eliminated?

$$\text{Clearance} = \frac{\text{Amount of drug eliminated per time}}{\text{Plasma drug concentration}}$$

For drugs with first order kinetics, clearance is independent of concentration

# What determines the steady state concentration of a drug?

Steady state:

$$IN = OUT$$

$$IN = DOSE * F$$

DRUG OUT = Volume of plasma cleared of  
drug per unit time x [drug]  
in plasma

$$DRUG OUT = Clearance x [Drug]$$

OR

$$DOSE * F = Cl x [Drug]$$

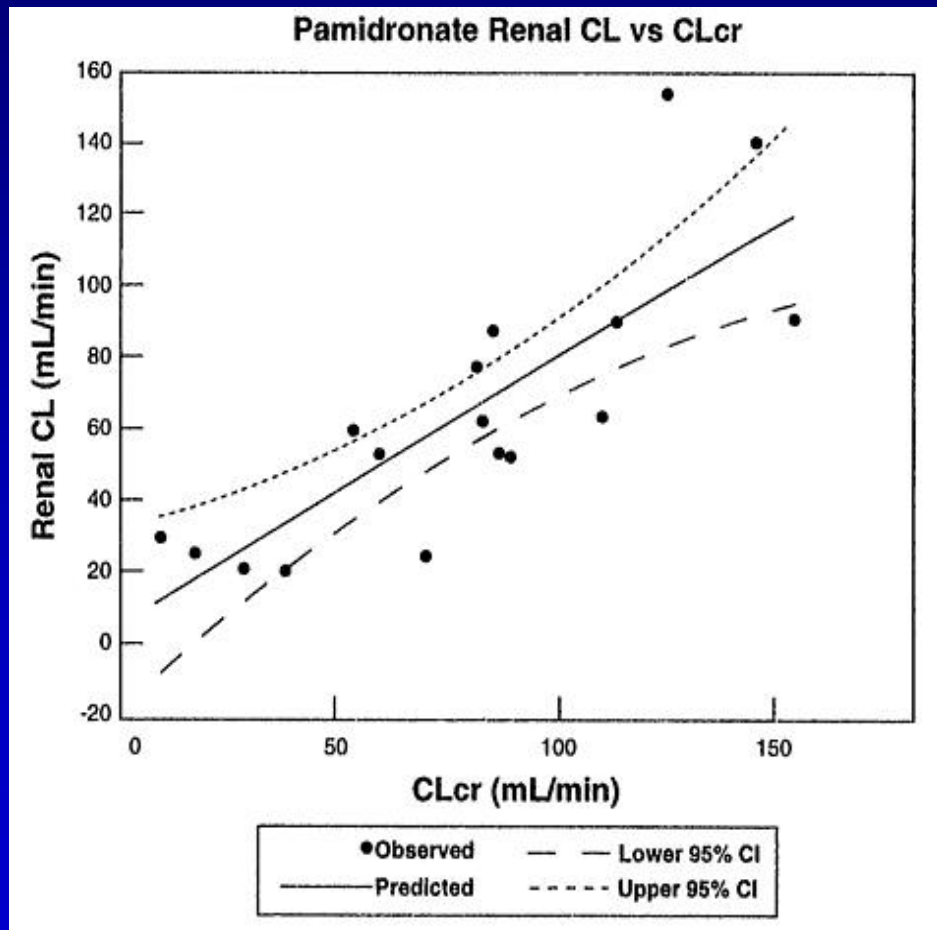
# Clearances are mechanism independent

$$\text{Dose} * F = \text{Cl} * [\text{Drug}]$$

If more than one route of elimination, than:

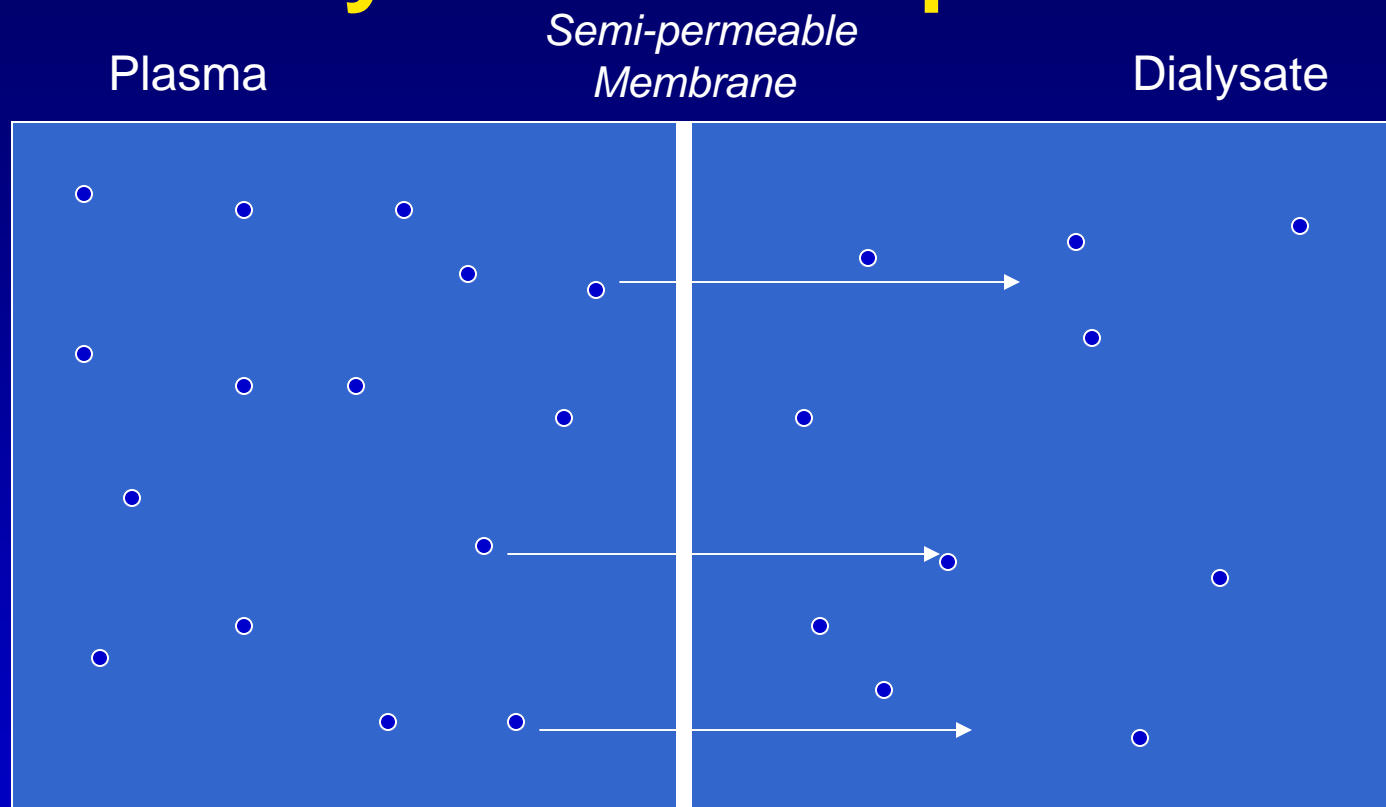
$$\text{Cl}_{\text{Total}} = \text{Cl}_{\text{Hepatic}} + \text{Cl}_{\text{Renal}} + \text{Cl}_{\text{Other}}$$

# Relationship between renal clearance and creatinine clearance



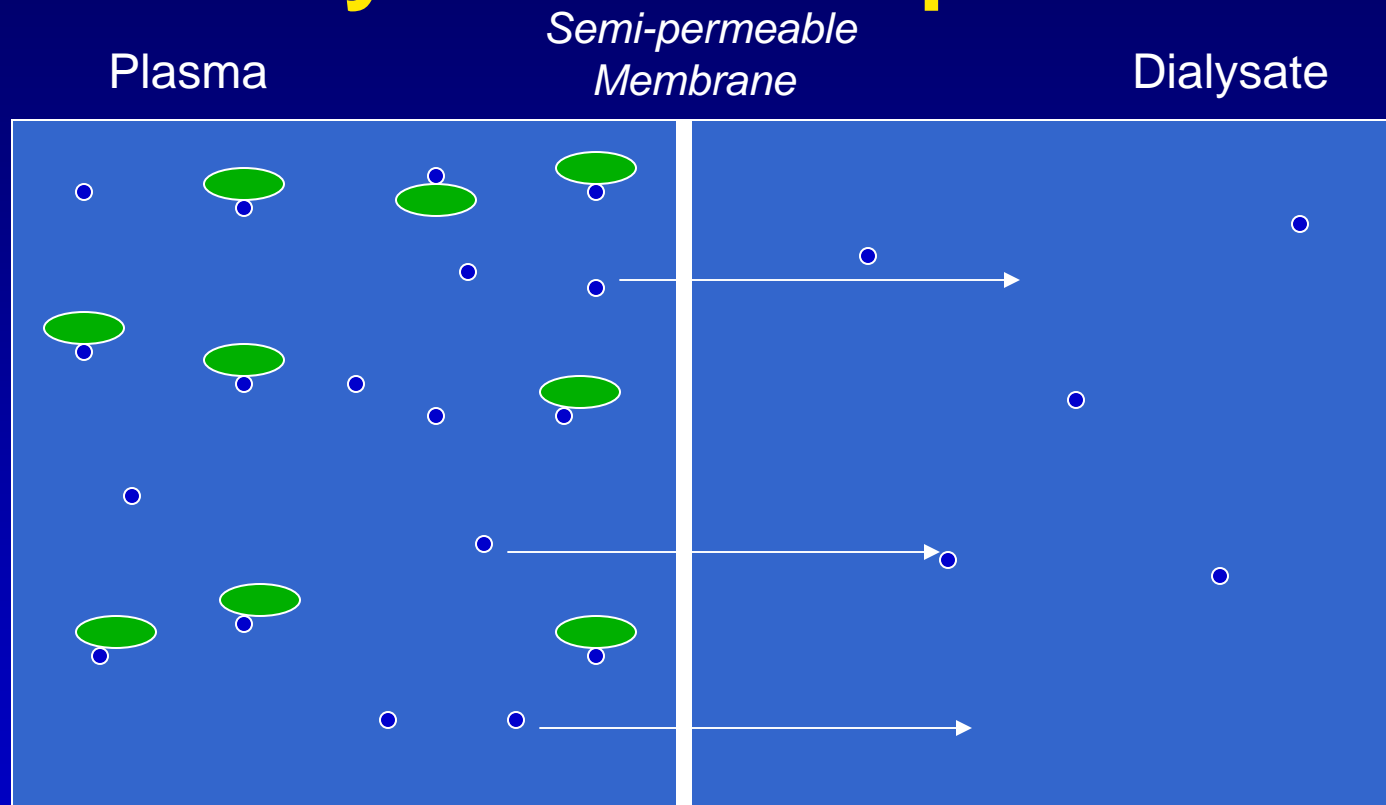
- Renal Cl often tracks CrCl making predictions easy
- What might it mean if slope of line greater than 1?
- What might it mean if slope of line less than 1?
- What if the y-axis was  $Cl_{Total}$  and y-intercept of line was 50 ml/min?

# Extracorporeal drug removal: Hemodialysis and simple diffusion



- Extraction =  $(C_{in} - C_{out}) / C_{in}$  ; if 100% removed, then  $E = 1$
- If  $E = 1$  than  $Cl_{dialysis} = \text{blood flow rate}$

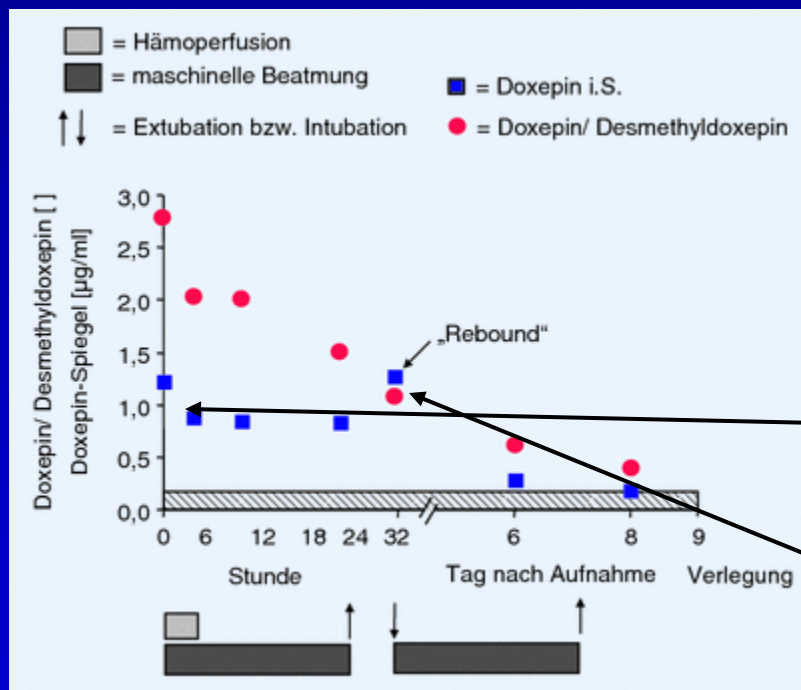
# Extracorporeal drug removal: Hemodialysis and simple diffusion



Only “free” drug can equilibrate effectively  
decreasing E and thus  $Cl_{\text{dialysis}}$

# But don't forget about Volume of Distribution!

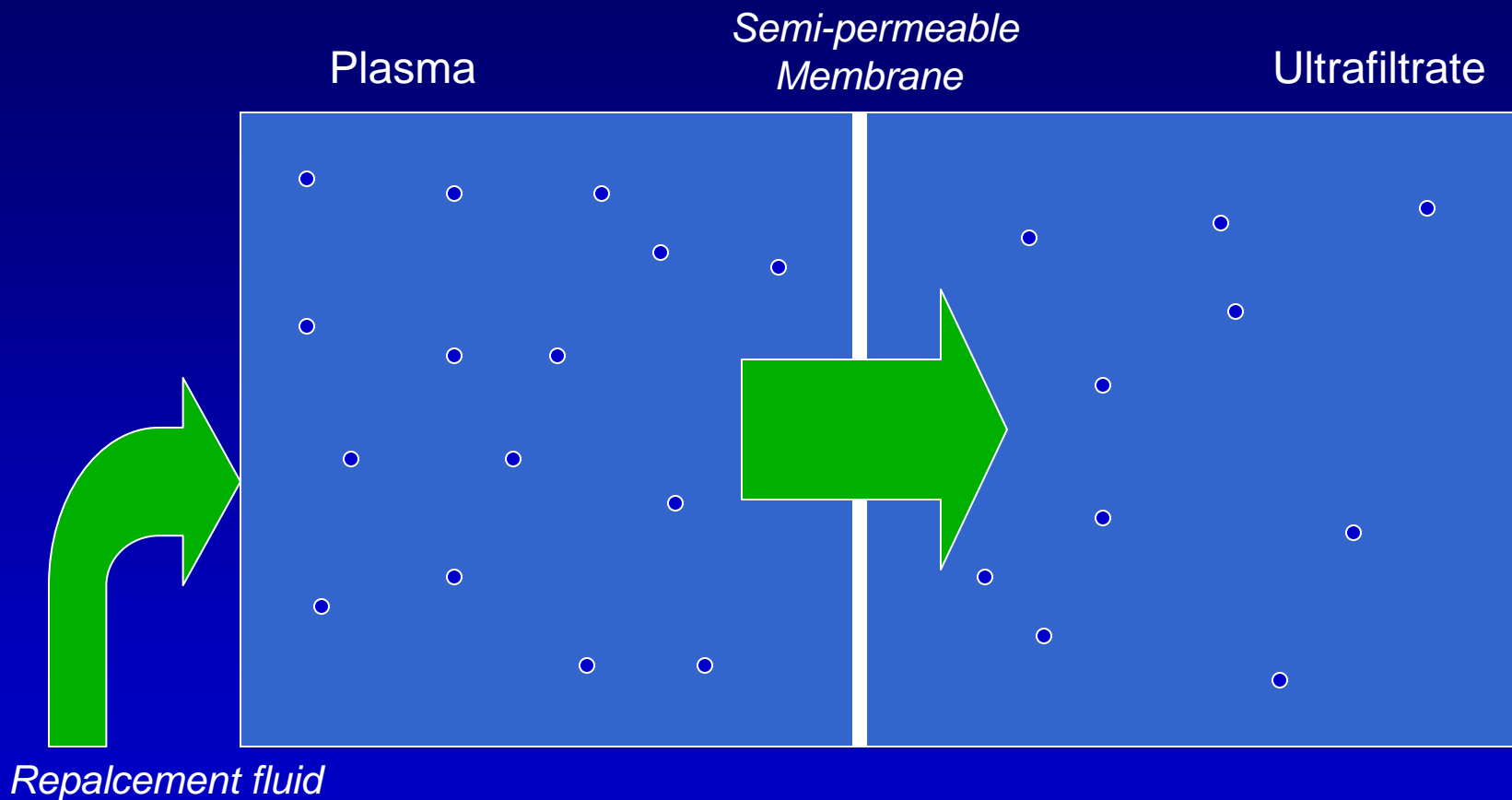
Even if  $E = 1$ , if drug is sequestered in tissue, clinical impact of extracorporeal clearance may be minimal. True for treatment of poisonings with large  $V_d$  drugs (Digoxin, TCA's)



- Doxepin OD
- $E$  for charcoal hemoperfusion approx = 1
- But  $V_d = 25 \text{ L/kg}$
- So, hemoperfusion acutely lowered plasma concentration,
- But drug in tissues then entered plasma causing rebound in [ ] and symptoms

Sakka JG et al *Anaesthesist*, 56:581, 2007

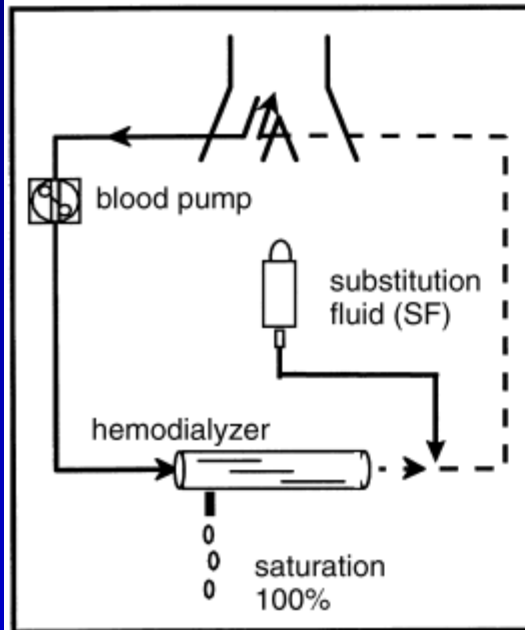
# Extracorporeal drug removal: Hemofiltration and convection



- Pressure drives fluid movement, drug follows fluid  
Sieving Coefficient ( $S_c$ ) =  $C_{UF}/C_P$

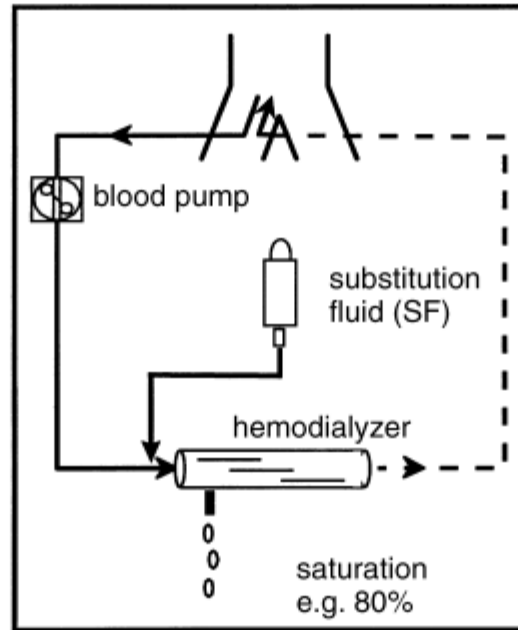
# Plumbing circuitry matters

**A Hemofiltration:  
Postdilution mode**  
Solute removal by convection



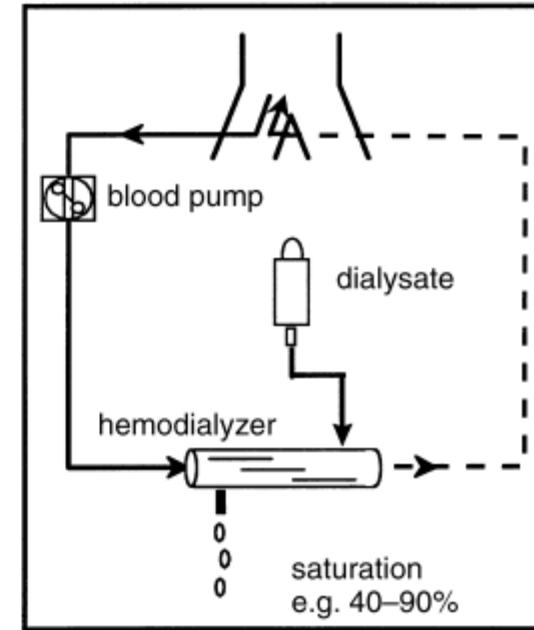
**Drug clearance**  
= ultrafiltration rate

**B Hemofiltration:  
Predilution mode**  
Solute, diluted by substitution  
fluid, removed by convection



**Drug clearance**  
= (UF rate × blood flow) /  
(blood flow + SF flow rate)

**C Hemodialysis:**  
Solute removal by  
diffusion depending  
on molecular weight



**Drug clearance** depends  
on molecular weight  
(see Fig. 2)

# Determinants of clearance by using hemofiltration

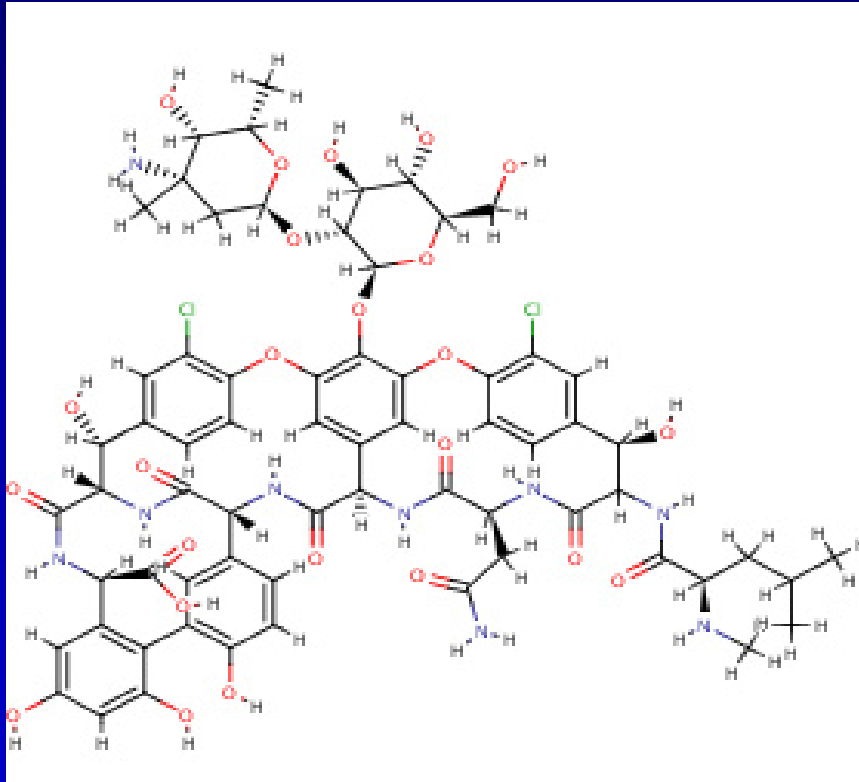
- Hemofiltration with post-dilution fluid replacement

$$Cl_{HF} = Q_{UF} * S_c$$

- Hemofiltration in predilution mode, drug diluted prior to filtration

$$Cl_{HF} = (Q_{UF} * S_c * Q_{BF}) / (Q_{BF} + Q_{RF})$$

# An example: vancomycin



Molecular weight 1486  
Hydrophilic

- 10 – 20 % Plasma protein bound
- $Cl_{sys}$  approx 7.8 L/hr (130 ml/min) in healthy adult
- $Cl_{Renal}$  approx 5.4 L/hr (90 ml/min) in healthy adult
- $Cl_{Non-renal}$  therefore approx 2.4 L/hr (40 ml/min) in healthy adult

# Predicting hemofiltration clearance for vancomycin

$$Cl_{HF} = (Q_{UF} * S_c * Q_{BF}) / (Q_{BF} + Q_{RF})$$

$S_c$  estimate at 0.8 based on protein binding

$$Q_{BF} = 200 \text{ ml/min}$$

$$Q_{UF} = 2 \text{ L/hr}$$

$$Q_{RF} = 2 \text{ L/hr}$$

$$Cl_{HF} = 1.4 \text{ L/hr}$$

(remember  $Cl_{Nonrenal} = 2.4 \text{ L/hr}$  in healthy,  $C_{SYS}$  would be predicted as 3.8 L/hr on HF)

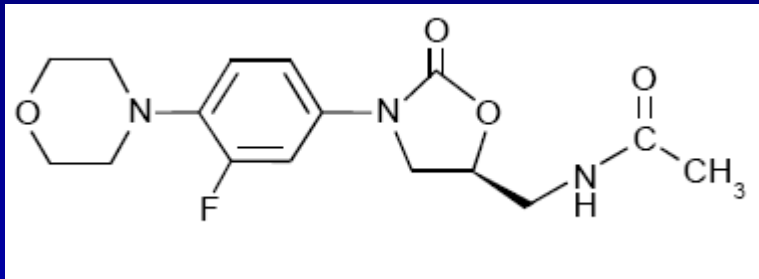
# Vancomycin clearance during CVVHDF

DeIDot ME, Lipman J and Tett SE, Br J Clin Pharmacol 58: 259, 2004

|                        | <u>Predict</u> | <u>Actual</u> |
|------------------------|----------------|---------------|
| $Cl_{\text{CVVHDF}}$   | 1.4 L/hr       | 1.8 L/hr      |
| $Cl_{\text{SYS}}$      | 3.8 L/hr       | 2.5 L/hr      |
| $Cl_{\text{Nonrenal}}$ | 2.4 L/hr       | 0.7 L/hr      |

Nonrenal clearance decreased in renal failure!

# Linezolid



MW = 337

- Protein binding 30%
- Renal and non-renal elimination

$Cl_{\text{Total}} = 120 \text{ ml/min}$

$Cl_{\text{Renal}} = 1/3$

$Cl_{\text{Nonrenal}} = 2/3$

# Linezolid and hemofiltration

- Estimate using  $S_c$  of 0.7  $Cl_{HF} = 20$  ml/min
  - vs. Healthy subjects est.  $Cl_{Renal}$  40 ml/min and  $Cl_{Nonrenal}$  80 ml/min)
- Data (Mauri LKS et al Am J Kid Dis 47:83, 2006)
  - $Cl_{HF} = 16$  ml/min
  - $Cl_{Total} = 189$  ml/min
- Thus, theory and data suggest linezolid dosing while on hemofiltration similar to that of healthy subjects

# Effect of flow rates on fluconazole hemofiltration clearance

|           | $Cl_{\text{Total}}$ | $Cl_{\text{HF}}$ | $Cl_{\text{Non-HF}}$ |
|-----------|---------------------|------------------|----------------------|
| UF 1L/hr  | 30 ml/min           | 12 ml/min        | 18 ml/min            |
| UF 2 L/hr | 37 ml/min           | 19ml/min         | 19 ml/min            |

*Bergner et al NDT 21:1019, 2006*

# Some last thoughts...

- Renal failure or severe illness may affect PK parameters other than Cl (protein binding, third spacing of fluid, etc)
- Half-life as hybrid parameter
$$t_{1/2} = (0.69) * Vd / Cl$$
- Vary amount per dose or dosing interval?
  - Does peak concentration matter, time above MIC or AUC/MIC (for efficacy or toxicity)

# Some last thoughts...

- References with specific information:
  - Pea et al. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet 46: 997, 2007
  - Trotman et al, Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy, Clin Infect Dis, 41: 1159, 2005

# SUMMARY

- Pharmacokinetics can:
  - Quantify the time course of drug concentrations/action
  - Allow prediction of factors that affect drug handling, both on population and individual patient levels
- Hemodialysis (by diffusion) and hemofiltration (by convection) can result in drug elimination
  - Factors affecting drug elimination by these modalities well understood and can be predicted
  - Understanding of the principles underlying drug elimination by these techniques and of pharmacokinetic principles allows for rational drug dosing