Slide 1

Pharmacokinetics During Hemodialysis & Hemodiafiltration Application to Amikacin Dosing

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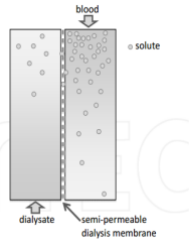
Slide 2

Dialysis

- The kidneys eliminate solutes (such as drugs) from the blood into the urine
- Hemodialysis is the most widely used form of renal replacement therapy
- Hemodialysis is based on the diffusive transport of solutes across a semipermeable membrane



Dialysis is the artificial kidney.
Conventional hemodialysis is the most widely used therapy for renal replacement therapy and is based on the concept of diffusion.

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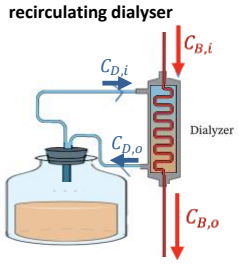
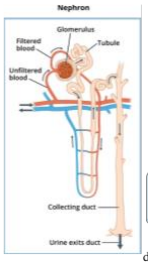
Evolution of Dialysers

Older dialyser

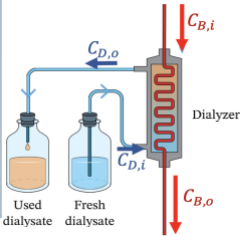
Concurrent flow recirculating dialyser





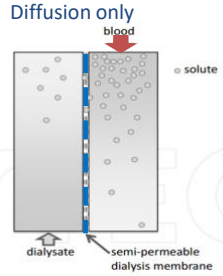
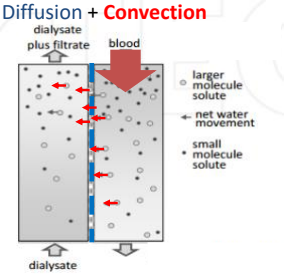
Modern dialyser

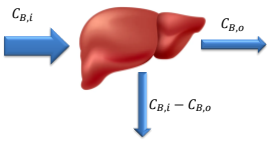
Countercurrent flow single pass dialyser

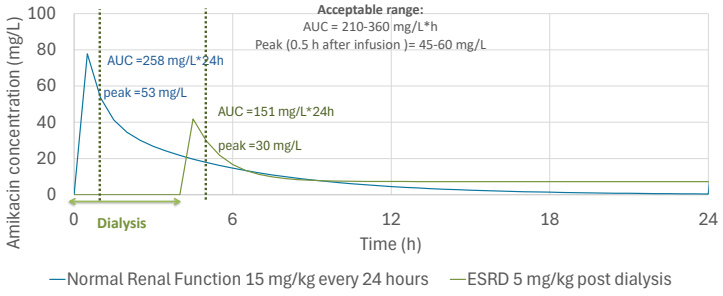


The older dialysers were concurrent flow were the blood and dialysate enter the dialyser in the same direction, and recirculating were the dialysate leaving the dialyser enter a tank and recirculated back to the dialyser.

The modern dialysers are countercurrent flow, blood and dialysate enter the dialysers in opposite directions and single pass, meaning the used dialysate is discarded and replaces with fresh dialysate.

Slide 4	**Michaels Equation** • In 1966, Michaels published a paper on concurrent and countercurrent **recirculating** but not **single-pass** dialysers • Michaels equation predict dialyser CL for any given combination of dialyser surface are A and diffusion constant K_o, blood and dialysate flow rates Q_B and Q_D – $CL_{B,i} = Q_B \times \frac{1-exp^{\frac{K_o A}{Q_B}\left(1-\frac{Q_B}{Q_D}\right)}}{\frac{Q_B}{Q_D}-exp^{\frac{K_o A}{Q_B}\left(1-\frac{Q_B}{Q_D}\right)}}$ *Countercurrent recirculating dialyser blood CL* • In his paper Michaels showed these equations but not the derivations: – $Elimination\ rate = Q_B \times (C_{B,i} - C_{B,o}) = Q_D \times (C_{D,o} - C_{D,i})$ *Mass conservation equation* – $CL_{B,i} = \frac{Elimination\ rate}{Conc}$ *Clearance* – $R_e = K_o \times A \times \overline{\Delta C_M}$ *Intrinsic clearance* – $\overline{\Delta C_M} = \frac{(C_{B,i}-C_{D,o})-(C_{B,o}-C_{D,i})}{\ln\left(\frac{C_{B,i}-C_{D,o}}{C_{B,o}-C_{D,i}}\right)}$ *Average solute conc difference* **Does Michaels equation apply to single-pass dialysers?** proved Michaels AS. Performance criteria for hemodialyzers Trans Am Soc Artif Intern Organs. 1966;12:387-92.	The equations used by Michaels to develop his eponymous equation are complex. Michaels did not provide any proof for this equation and did not claim it would work for single pass dialysers. My PhD thesis contains a proof of the ME for both re-circulating dialysers and extends the proof for single pass dialysers.
Slide 5	**Dialysis Types** *Extra feature* Hemodialysis (**HD**) Diffusion only  Up to 500 Da Hemodiafiltration (**HDF**) Diffusion + **Convection**  Up to 30000 Da Principles and Practices of Haemodiafiltration http://dx.doi.org/10.5772/59470	Conventional haemodialysis: A solute, shown dissolved in blood, moves across the semi-permeable dialysis membrane by diffusion, into the dialysate, with blood and dialysate flowing in opposite directions (countercurrent). The rate of diffusion is dependent on the initial concentration in the blood, the blood flow rate, the permeability of the membrane for the solute, and the dialysate flow rate. Hemofiltration (convection). Movement of water across the more water-permeable membrane 'drags' solute across, and leads to production of a filtrate which contains the solute. Solute transfer removal is largely dependent osmotic pressure but is limited by hemoconcentration and so 'pure' haemofiltration is not practical without replacement of fluid. Hemodiafiltration (HDF). HDF combines dialysis and filtration across a semi-permeable membrane but uses much larger volumes of dialysate. Extra ultrapure water can be added either pre-dilution or post-dilution to replace the filtrate. Small solutes are removed largely by diffusion whereas larger solutes (middle molecules) are removed by convection. Water removal (ultrafiltration) is regulated by varying the volume of replacement fluid.

Slide 6	**Convection Clearance** $Convection\ flow\ rate = \frac{Convection\ volume}{Dialysis\ duration}$ $Convection\ fraction = f_{conv} = \frac{Convection\ flow\ rate}{Q_{Pu}}$ $Maximum\ Plasma\ unbound\ Convection\ CL\ (without\ diffusion) = f_{conv} \times Q_{Pu}$ $Plasma\ unbound\ Convection\ CL\ (with\ diffusion) = f_{conv} \times Q_{Pu} \times \frac{Q_{Pu} - CL_{Pu,diff}}{Q_{Pu}}$ $CL_{Pu,conv} = f_{conv} \times (Q_{Pu} - CL_{Pu,diff})$ $\boldsymbol{Blood\ Convection\ CL = CL_{B,conv} = f_{conv} \times (Q_{Pu} - CL_{Pu,diff}) \times \frac{(1 - HCT + HCT \times f_{up} \times K_P)}{f_{up}}}$ Q_{Pu}=plasma unbound water flow; $CL_{Pu,diff}$=plasma unbound diffusion CL, HCT=hematocrit; f_{up}=fraction drug unbound in plasma; K_P=plasma/blood conc	Convection is the flow of water with solutes through a semi-permeable membrane driven by the transmembrane pressure gradient, excluding plasma proteins and protein-bound solutes. Hence, QPu*fconv is the maximum possible convection clearance of an unbound drug. Converting unbound plasma convection clearance to blood convection clearance requires knowledge of the HCT, fup and Kp.
Slide 7	**HDF Total Blood Dialysis Clearance** **Diffusion** $CL_{B,diff} = Q_B \times \frac{1 - exp^{\frac{K_o A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)}}{\frac{Q_B}{Q_D} - exp^{\frac{K_o A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)}}$ **Convection** $CL_{Pu,conv} = f_{conv} \times (Q_{Pu} - CL_{Pu,diff})$ $\boldsymbol{CL_{B,tot} = Q_B \times \frac{1 - exp^{\frac{K_o A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)}}{\frac{Q_B}{Q_D} - exp^{\frac{K_o A}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)}} + CL_{Pu,conv} \times \frac{(1 - HCT + HCT \times f_{up} \times K_P)}{f_{up}}}$	The total blood dialysis clearance of HDF is the sum of blood diffusion clearance and blood convection clearance
Slide 8	**Dialysis Efficiency** ~~"...dialysis efficiency refers to solute clearance at a given Q_d and Q_b."~~ Membranes 2021, 11(10), 767 Efficiency is the ratio of output to input $Dialysis\ Efficiency = \frac{Q_D \times C_{D,o}}{Q_B \times C_{B,i}}$ Efficiency equation $C_{D,o} = (C_{B,i} - C_{B,o}) \times \frac{Q_B}{Q_D}$ Mass conservation equation  $DE = \frac{Q_D \times (C_{B,i} - C_{B,o}) \times \frac{Q_B}{Q_D}}{Q_B \times C_{B,i}}$ Substituting $C_{D,o}$ in the DE equation and simplifying $\boldsymbol{ER = \frac{CL_{B,i}}{Q_B} = \frac{(C_{B,i} - C_{B,o})}{C_{B,i}}}$ $\boldsymbol{DE = \frac{(C_{B,i} - C_{B,o})}{C_{B,i}}}$ $\boldsymbol{Extraction\ Ratio = Dialysis\ Efficiency = \frac{CL_{B,i}}{Q_B}}$	Dilysis efficiency is equivalent to Extraction ratio, and can be calculated by dividing the blood clearance with blood flow.

Slide 9	**Aminoglycoside PK during Dialysis**	
Slide 10	**Aminoglycosides in end-stage renal disease** • Empiric treatment for gram negative infections • Dosing recommendations: Single reduced (⅓ - ½) dose at the end of dialysis • Achieves lower peak concentrations but higher trough concentrations compared to patients with normal renal function	
Slide 11	**Amikacin PK profile Normal renal function vs ESRD** 	A simulation of amikacin given once daily (15mg/kg) to a patient with normal renal function, versus a 5 mg/kg post dialysis to a patient with end stage renal disease. In the simulated patient with ESRD, the AUC and the peak (measured half an hour after the end of infusion) are not with the acceptable range.

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Aims and Methods

- Aims:
  - How much does amikacin CL differ between HD and HDF?
  - Can the normal renal function concentration vs time profile be emulated in dialysis patients?
  - Should current dosing recommendations be changed for HDF?
- Methods:
  - Single center prospective study in adult chronic dialysis patients receiving amikacin undergoing either HD and HDF

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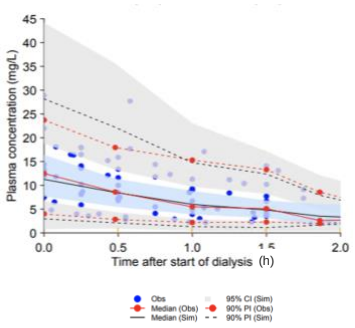
Results

- **Data:**
  - 20 patients
  - 30 occasions
  - 188 observations
- **Model:**
  - Distribution: 2 compartments
  - Dialysis CL: Michaels HD + HDF
  - Covariates:
    - Cartridge type
    - Coagulation in the dialyser



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Dialysis Efficiency and Clearance

Parameter	HD	HDF	HDF/HD %
Blood flow, Q_B (L/h)	18	21	17%
Dialysis Efficiency, $DE = \frac{CL_{B,i}}{Q_B}$	0.74	0.92	24%
Blood CL , $CL_{B,i} = DE \times Q_B$ (L/h)	13.3	19.3	45%

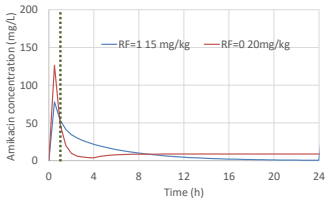
Clearance not Dialysis Efficiency is used to determine the dose

$$Dosing\ rate = CL_{B,i} \times Concentration_B$$

DE for HDF is 24% higher than HD. The change in CL is much bigger (45%) than the change in DE because of the additional increase in dialyser blood flow.

Slide 15	**Proposed Dosing** **Acceptable ranges:** AUC = 210-360 mg/L*h Peak (0.5h after inf end) = 45-60 mg/L Trough = 4-15 mg/L **HD** **HDF**	Simulated alternative dosing. To achieve AUC, peak (half an hour after the end of infusion) and trough levels within the acceptable range, 20 mg/kg is required for HD and 35 mg/kg for HDF. In clinical practice lower doses may be warranted.
Slide 16	**Conclusions** • The Michaels equation can be applied to countercurrent single pass dialyser and combined with convection clearance • We propose rational dosing regimens of amikacin for both HD and HDF • Our framework can be applied to model other drugs on HD and HDF	
Slide 17	Thank you for listening Laila.nassar@gmail.com	

Renal Function	Dose (mg/kg)	Dose timing (h)	AUC (mg/L*h)	Peak (mg/L)	Trough (mg/L)
1	15	0	258	54	0.4
0	20	0	279	48	8.7



Renal Function	Dose (mg/kg)	Dose timing (h)	AUC (mg/L*h)	Peak (mg/L)	Trough (mg/L)
1	15	0	258	54	0.4
0	35	0	336	49	10.4