Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in CKD

Section Leaders:

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Outline

- The paradigm and the problem
- Impact of CKD on pharmacokinetics
- Determination of drug dosing guidelines
- Determination of individualized patient dose
- Breakout group discussion points

Paradigm and the Problem

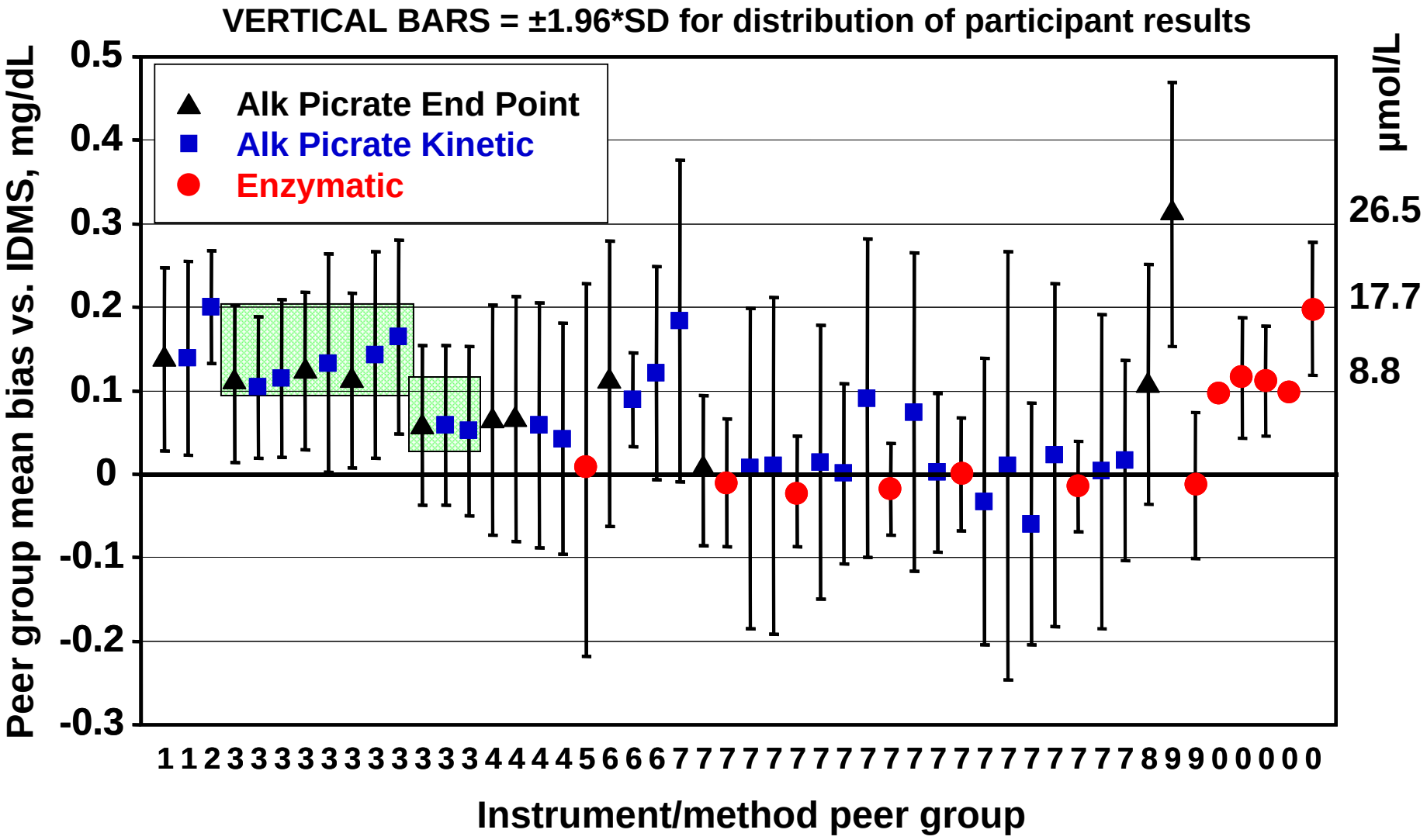
- PK studies in patients with CKD are performed "*when drug or its active metabolites exhibit a narrow therapeutic index and when excretion and/or metabolism occurs primarily via renal mechanisms*"
- GFR (or dialysis modality) is assumed to capture all aspects of the effect of kidney disease on PK of a drug, under the "intact nephron hypothesis"
- ***The problem:*** No incorporation of other factors that may not correlate with GFR, but are present in patients with CKD, eg hyopoalbuminemia or drug interactions

Impact of CKD on Pharmacokinetics

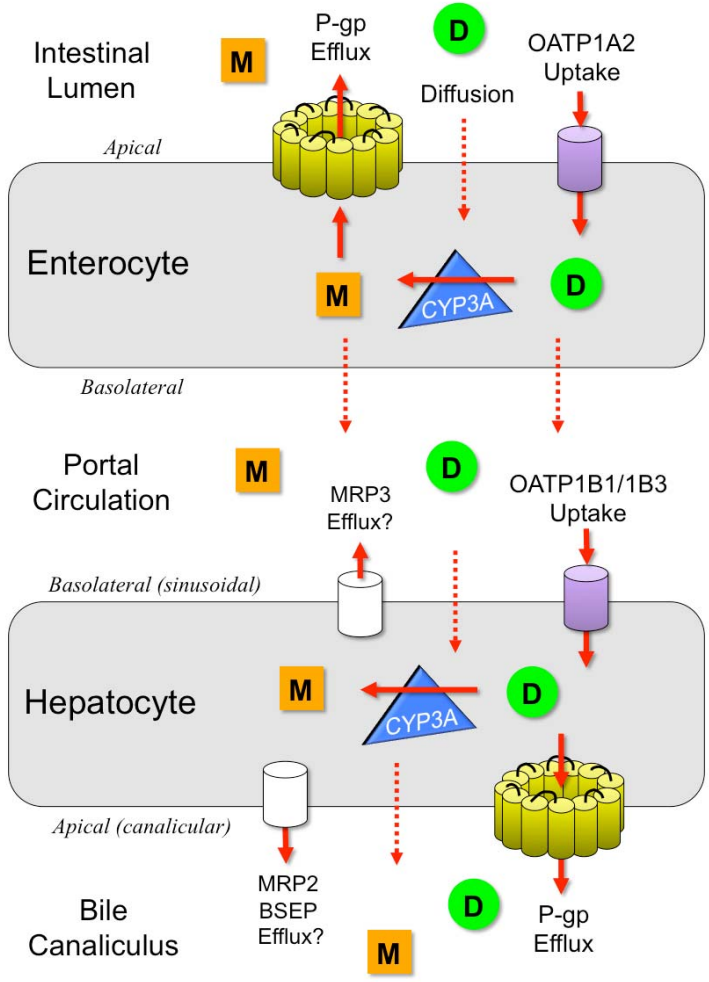
Factors involved in PK	Kidney disease effects	Measured specifically for incorporation into drug dosage
Absorption	+	N
Intestinal and first pass metabolism	+	N
Distribution	++	N
Clearance		
Renal	+++	Y
Nonrenal	++	N

Number of '+' indicates magnitude of available data

CAP, 2003, Fresh Frozen Serum, N = 5624
Creatinine = 0.90 mg/dL (79.7 µmol/L)



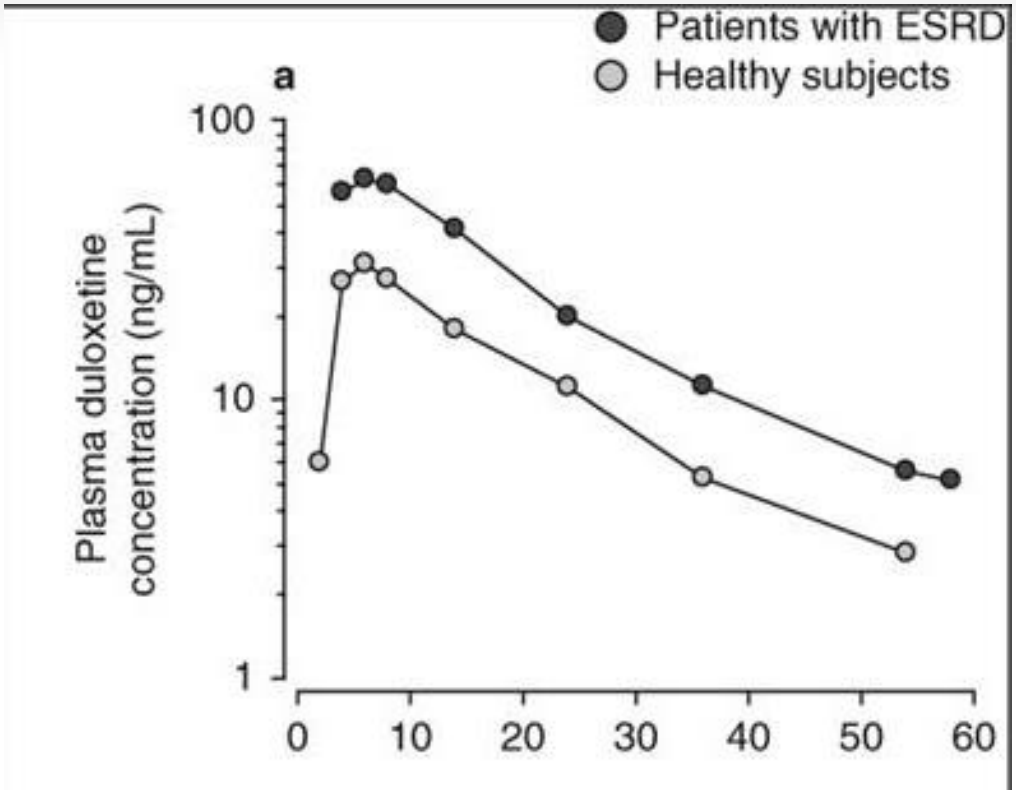
Miller et al. Arch Pathol Lab Med 2005;129:297-304

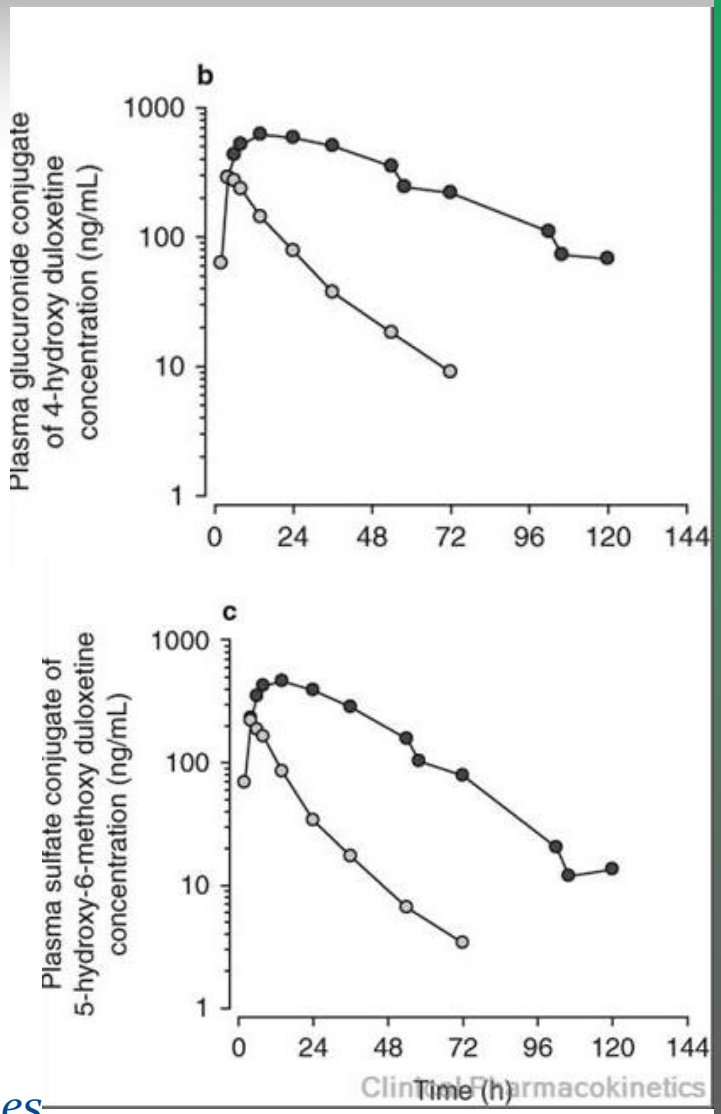


- Fexofenadine and midazolam are both CYP3A4 substrates.
- CL of Fexofenadine reduced in CKD
  - 2.8 fold higher AUC compared to control
- CL of Midazolam unchanged in CKD

Nolin TD, et al. J Am Soc Nephrol 2009;20:2269-76

Duloxetine pharmacokinetics in CKD





Kidney Disease: Improving Global Outcomes

Lobo ED, et al. Clin Pharmacokinet 2010;49:311-321

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Duloxetine pharmacokinetics in CKD

Parameter	Status	Least squares geometric mean	P-value
Glucuronide conjugate of 4-hydroxy duloxetine			
Cmax [ng/mL]	ESRD	585	0.0006
	Healthy control	235	
AUC_{∞} [ng●hr/mL]	ESRD	36,686	0.0001
	Healthy control	3936	

Calculation of daptomycin dose

- Kidney disease (CrCl < 30 mL/min) increases risk of daptomycin failure by ~80%
- Package labeling for CrCl < 30 mL/min and hemodialysis
  - 4-6 mg/kg every 48 hrs or after hemodialysis session
- Conflicting data regarding proper schedule and dose
  - Should dose be increased, interval adjusted?
  - Should dose be given during hemodialysis?

Comparison of Daptomycin PK

Parameter	Study A[1]	Study B[2]
C_{max} (µg/mL)	60 ± 7	51 ± 29
AUC_{0-68} (µg * hr/mL)	1351 ± 151	NA
AUC_{0-72} (µg * hr/mL)	NA	1520 ± 585
$C_{min\ (68hrs)}$ (µg/mL)	10.9 ± 3.3	NA
$C_{min\ (72hrs)}$ (µg/mL)	NA	7.5 ± 3.9

[1]Salama NN, et al. Nephrol Dial Transplant 2010;25:1279-84. [2]Patel N, et al. Abstract 2514; 49th ICAAC Meeting, San Francisco, CA, September 12-15, 2009

Development of Drug Dosing Guidelines: *Half-life*

- Used to predict time to steady state

$$T_{1/2}=0.693\ V_d/Cl$$

- If $T_{1/2}$ changes due to Vd vs Cl, then has different implications for dose adjustment
  - Δ Vd→ Loading dose adjustment
  - Δ Cl → Maintenance dose

- The relative magnitude of an effect of CKD on Vd vs Cl may change as the GFR falls

Development of Drug Dosing Guidelines: *Loading dose*

- Required if long half life and need to achieve steady state rapidly

- In the absence of a loading dose
  - Time to reach 90% of max concentration is 3.3 X $T_{1/2}$
  - If this is too long relative to the clinical situation, then require loading dose

$$\text{Loading dose} = (C_{initial})\ (V_d)$$

$$\frac{\text{Usual loading dose}}{\text{Modified loading dose}} = \frac{\text{Normal } V_d}{\text{patient's } V_d}$$

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Development of Drug Dosing Guidelines: *Maintenance Dose*

- ***Goal:*** Dosing regimen that maintains the desired steady-state drug concentrations as would occur if the patient did not have CKD
- Change in clearance requires a change in dose to maintain drug concentration

$$Maintenance\ dose = (C_{average})\ (Cl)$$

- Strategies
  - Continuous infusion: modify rate of infusion
  - Intermittent dosing:
    - Vary dose: Constant levels
    - Vary frequency: Possible fluctuating levels

Measuring Drug Levels

- Total drug vs active drug
  - E.g. Phenytoin
- Importance of hypoalbuminemia

Determination of Individualized Patient Dose

Factor	Method of Ascertainment	Modify
Clearance	eGFR/eCrCl	Maintenance
Volume of distribution	Level of drug after initial dose*	Loading
Urgency of clinical situation	Clinical judgment	Loading
Impact of fluctuations in steady state levels	Clinical judgment	Maintenance
Patient's financial situation	Clinical judgment	Maintenance
Medication interactions	Profile review	Loading, maintenance

*Difficult to ascertain for drugs where levels not routinely available, or for oral drugs

Dialysis

- Removes drug either intermittently or continuously
- Total clearance of drug dependent on
  - Residual kidney function
  - Dialysis clearance
  - Non-renal clearance
- Clearance dependent on
  - Drug properties (e.g. MW, hydrophilicity, PPB, Vd)
  - Dialysis properties (e.g. flow rate, volume, duration)
  - Membrane properties (e.g. pore size, surface area)