Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Drug Removal by Intermittent Renal Replacement Therapies

Section Leaders:

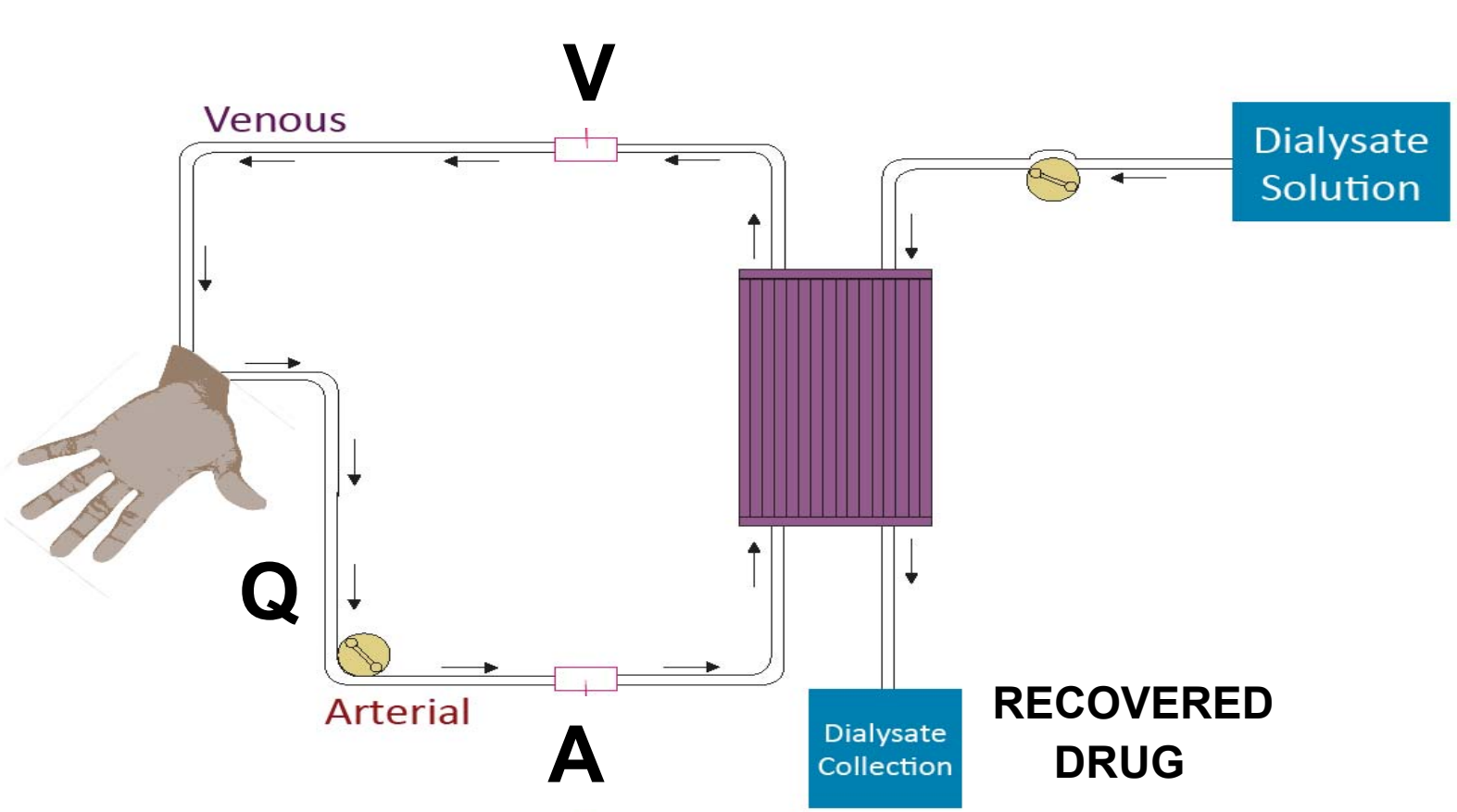
Arthur Atkinson and Jason Umans

ELIMINATION BY DIFFERENT ROUTES

MEASUREMENTS	RENAL	HEPATIC	DIALYSIS
BLOOD FLOW	+*	+*	+
AFFERENT CONC.	+	+	+
EFFERENT CONC.	0	0	+
ELIMINATED DRUG	+	0	+

*not actually measured in routine PK studies

DATA SOURCES FOR FICK EQUATION



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IMPACT OF CL_D

$$CL_E = CL_R + CL_{NR} + CL_D$$

CRITERION FOR DIALYSIS EFFICACY*

$$CL_{EC} > 30\% [CL_R + CL_{NR}]$$

BUT CLEARANCE ESTIMATES MUST BE COMPARABLE

*** Levy G. Am J Med 1977;62:461-5.**

RECOVERY METHOD

$$CL_D = \frac{C_D \cdot Vol_D}{\overline{A} \cdot t}$$

$$CL_D = \frac{C_D \cdot Vol_D}{AUC_A}$$

A-V DIFFERENCE METHOD

$$CL = Q \left[\frac{A - V}{A} \right]$$

Q = DIALYZER BLOOD FLOW
A = CONCENTRATION IN BLOOD COMING TO DIALYZER
V = CONCENTRATION IN BLOOD LEAVING DIALYZER

TWO DIALYSIS MYTHS

- NEED TO USE BLOOD CONCENTRATIONS WHEN CALCULATING BLOOD CLEARANCE

  BUT PLASMA CONCENTRATIONS PROPORTIONAL TO BLOOD CONCENTRATIONS, SO MAKES NO DIFFERENCE IN A/[A + V] RATIO

- NEED TO USE PLASMA FLOW WHEN CALCULATING PLASMA CLEARANCE

PLASMA VS. BLOOD CLEARANCE

RECOVERY : $CL_P = \frac{U \bullet V}{P}$ $CL_B = \frac{U \bullet V}{B}$

A - V DIFFERENCE: $CL_P = Q_{PK}\left(\frac{A-V}{A}\right)$ $CL_B = Q_B\left(\frac{A-V}{A}\right)$

$$\text{IF } B > P: CL_P > CL_B, \text{ SO: } Q_{PK} > Q_B > Q_P$$

NAPA IN RBC IS DIALYZED

FLOW PARAMETER	MEAN VALUE mL/min
Q_{PK}	223
Q_{MEAS}	195 ($p < 0.2$)
Q_{EFF}*	217 ($p > 0.2$)

$$* Q_{EFF} = [(1 - Hct) + (RBC/P) (HCT)] Q_{MEAS}$$

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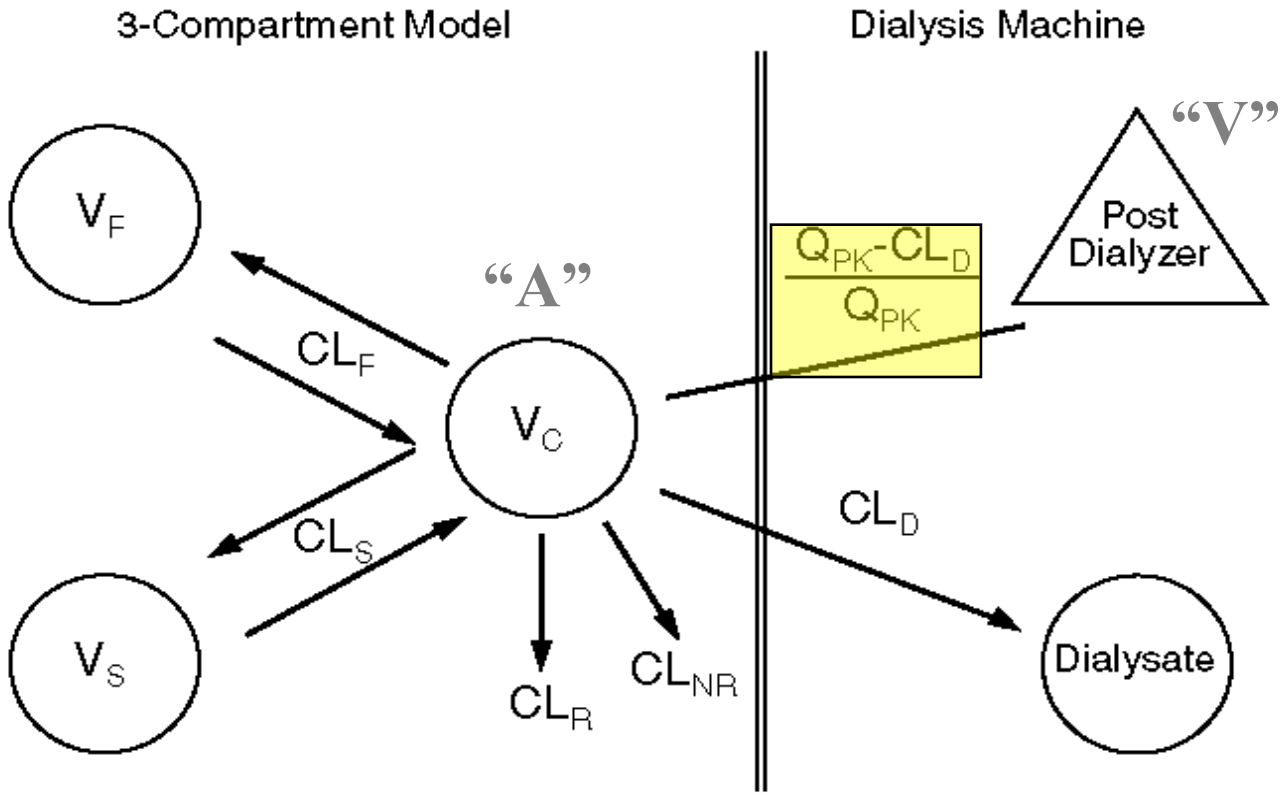
KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*



* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

FICK CLEARANCE EQUATION

$$CL = Q\left[\frac{A - V}{A}\right]$$

$$CLA = QA - QV$$

$$QV = QA - CLA$$

$$V = \left[\frac{Q - CL}{Q}\right]A$$

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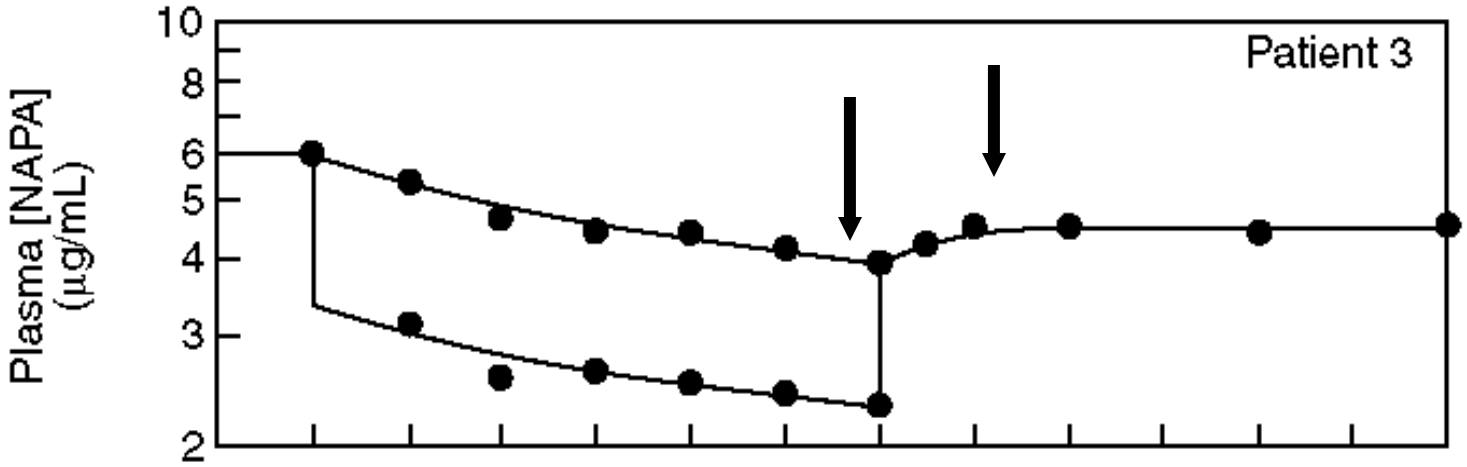
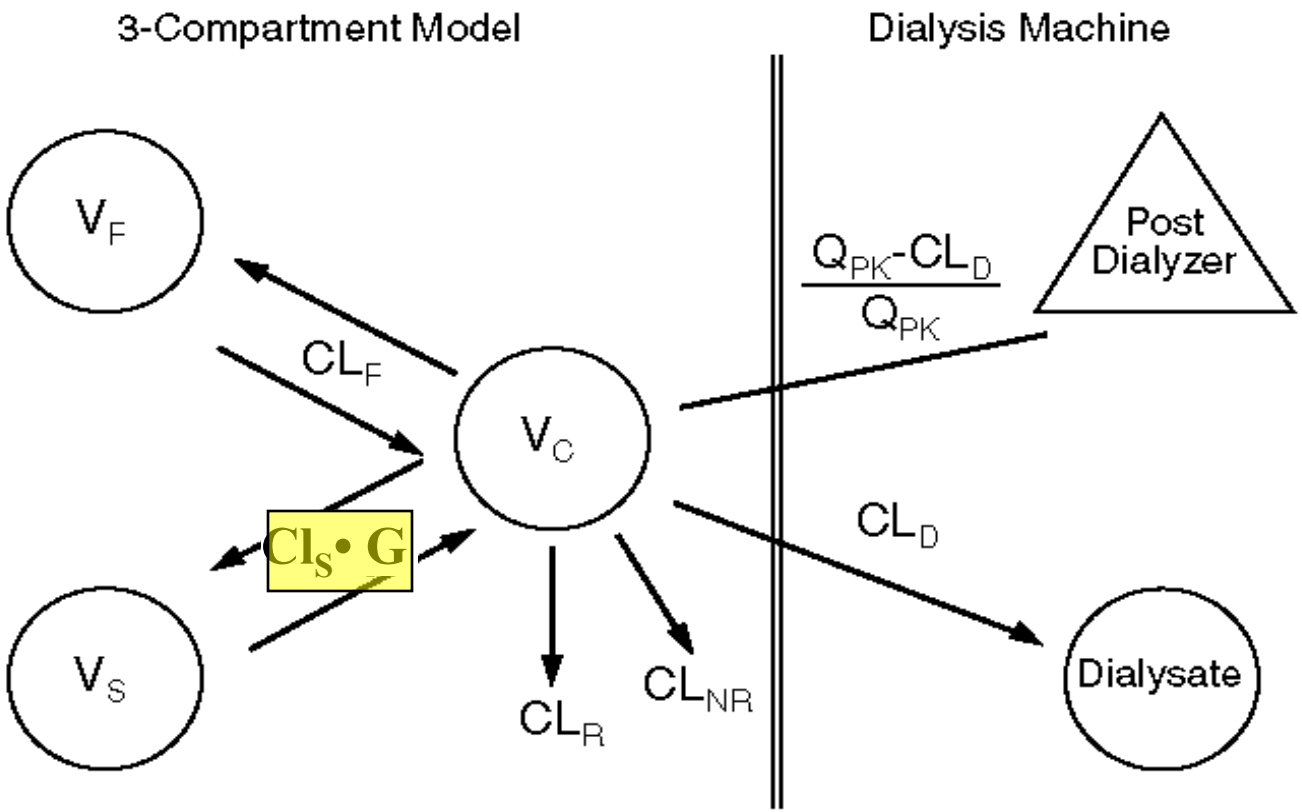
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*



1. **<u>DURING DIALYSIS</u>: [A] AND [V] DROP MORE THAN EXPECTED FROM DRUG RECOVERY**
2. **<u>AFTER DIALYSIS</u>: CONCENTRATION REBOUND IS LESS THAN EXPECTED**

* From Stec GP, et al. Clin Pharmacol Ther 1979;26:618-28.

PARAMETER CHANGE REQUIRED TO MODEL DIALYSIS PK



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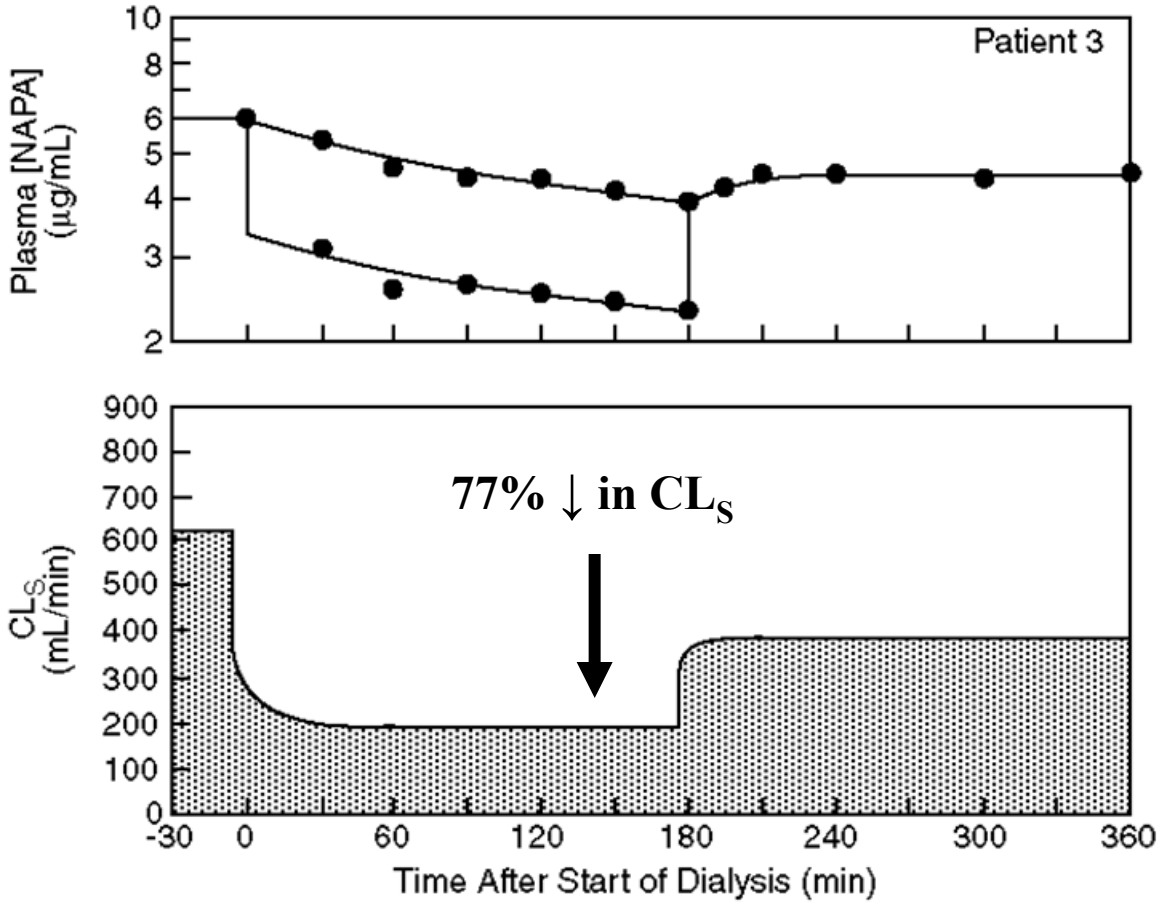
REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS



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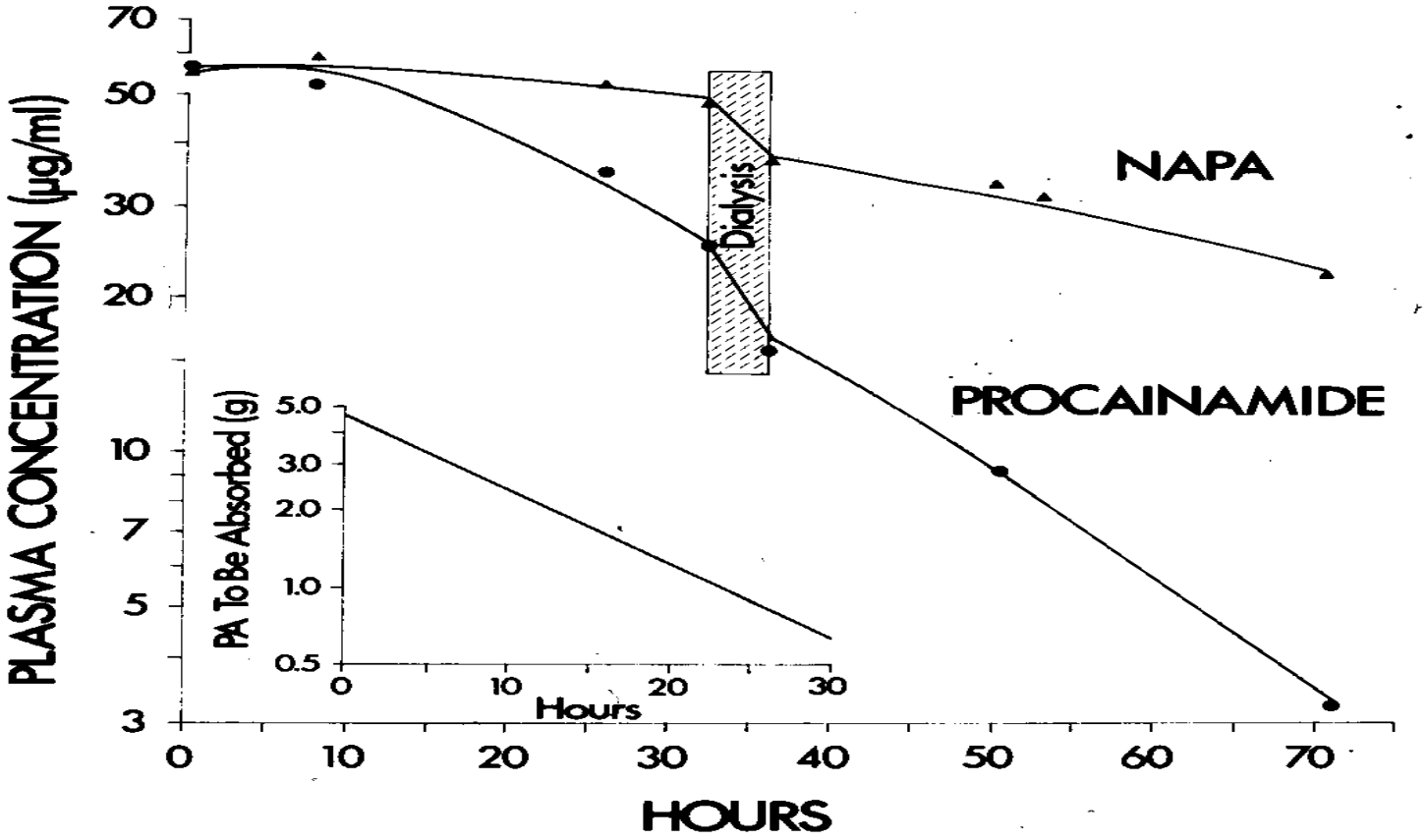
IMPLICATIONS OF ↓ CLS FOR DIALYSIS TREATMENT OF DRUG TOXICITY*



*** From: Atkinson AJ Jr, et al. Clin Pharmacol Ther 1976;20:585-92.**

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WAS DIALYSIS EFFICACIOUS?

- DIALYSIS INCREASED DRUG CLEARANCE
  PA – TWO FOLD
  NAPA – 3.8 FOLD
- BUT 4 hr OF DIALYSIS REMOVED < 1 gm of 7 gm DOSE
  340 mg PA
  470 mg NAPA
- HOWEVER, BLOOD LEVELS FELL SUBSTANTIALLY
  PA: 25.7 µg/mL → 15.5 µg/mL
  NAPA: 47.0 µg/mL → 35.5 µg/mL
  AND PATIENT'S CONDITION STABILIZED

PA & NAPA KINETICS IN TOXIC PATIENT

	NORMAL		PATIENT	
	PA	NAPA	PA	NAPA
$t_{1/2}$ (hr)	2.5	6.2	10.5	35.9
CL_E (mL/min)	590	233	66.8	16.1
CL_D (mL/min)			68.3	45.8
$V_{d\beta}$ (L/kg)	1.80	1.76	0.76	0.63

$$\textbf{DIALYSIS } V_D \textbf{ ESTIMATE: } V_D = \frac{\textbf{DRUG REMOVED}}{\Delta \textbf{ CONCENTRATION}}$$

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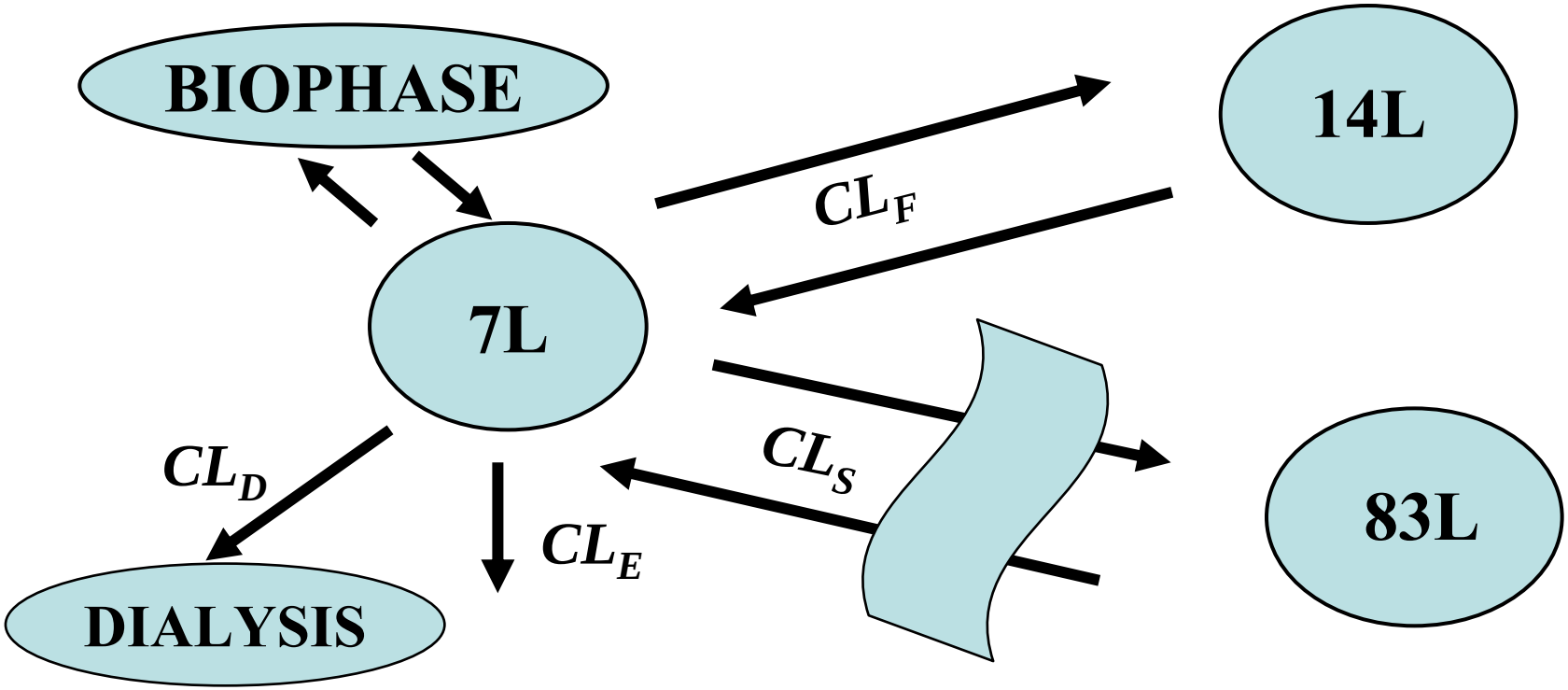
SEQUESTRATION OF DRUG IN SOMATIC TISSUES



NEED FOR INTRADIALYZER TRANSFER OFRESULTS*

$$CL_D = Q(1 - e^{-P \cdot S/Q})$$

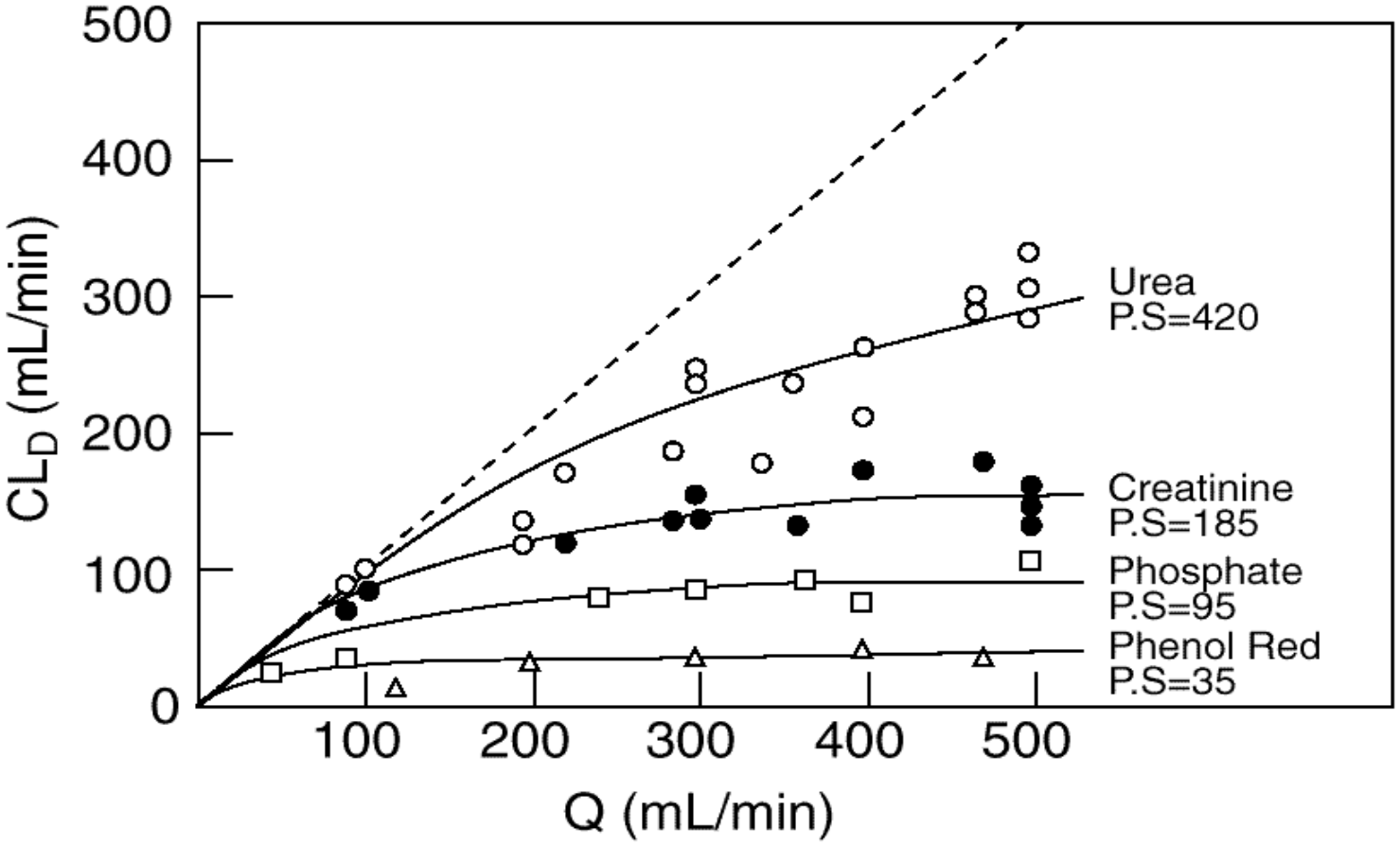
Q = DIALYZER BLOOD FLOW

P · S = PERMEABILITY-SURFACE AREA PRODUCT OF DIALYZING MEMBRANE

NEGLECTS: BOUNDARY EFFECTS, ULTRAFILTRATION

* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW *



* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5

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POSSIBLE USE FOR INTRA-DIALYZER TRANSFER OF RESULTS

- PERFORM PRELIMINARY *IN VITRO* STUDY TO OBTAIN P RATIO FOR DRUG & STANDARD COMPOUND FOR DIALYZER BEING USED IN DIALYSIS STUDY (RECORD Q & RBC/PLASMA).
- THIS RATIO CAN BE USED TO ESTIMATE DRUG CL_D FOR OTHER DIALYZERS AND OTHER Q VALUES IF P OF STANDARD COMPOUND FOR THAT DIALYZER IS KNOWN.
- NEED TO SELECT APPROPRIATE STANDARD COMPOUND (? CREATININE).

STABILITY OF P·S ACROSS 10 DIFFERENT DIALYZERS *

PROCAINAMIDE/NAPA:

RATIO OF DIALYZER P· S COEFFICIENTS*	**1.28 ± 0.23**
RATIO OF FREE WATER DIFFUSION COEFFICIENTS	**1.23**

*** Estimates of P·S based on *in vitro* CL_D results from Gibson TP et al. Clin Pharmacol Ther 1976;20:720-6.**

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