PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

October 21, 2010

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JOHN JACOB ABEL
1857 – 1938

Photograph of Professor John Jacob Abel, 1857-1938, in a laboratory.

FIRST DESCRIPTION OF HEMODIALYSIS IN ANIMALS*

Reproduction of the Table of Contents from an article entitled On The Removal of Diffusible Substances from the Circulating Blood of Living Animals by Dialysis by John J. Abel et al from the Pharmacological Laboratory of the Johns Hopkins University. Received for publication, December 18, 1913.

*** From: Abel JJ, et al. J Pharmacol Exp Ther 1914;5:275-317.**

WILLEM J. KOLFF, M.D. (1911 -)

Photograph of Dr. Willem J. Kolff, developer of the first functioning artificial kidney (1943).

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

Illustration of these sources in a dialysis machine.

IMPACT OF CL_D

Formula showing that CLR, CLNR and CLD are additive.

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.

GOALS OF DIALYSIS DISCUSSION

DISCUSSION OF DIALYSIS CLEARANCE
- MECHANISTIC – RENKIN APPROACH
- EMPIRICAL
  - FICK EQUATION
  - RECOVERY CLEARANCE

CLINICAL STUDIES OF DIALYSIS PK
- MODEL PROSPECTIVE STUDY
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PHYSIOLOGIC CHANGES DURING DIALYSIS
- USE OF KINETIC METHODS FOR ANALYSIS
- PATHOPHYSIOLOGIC CONSEQUENCES

EUGENE RENKIN
PROFESSOR EMERITUS AT UC DAVIS

Photograph of Professor Eugene Renkin

RENKIN DIALYSIS EQUATION*

Equation showing dialyzer blood flow and permeability-surface area product of dialysis membrane.

Neglects: Boundary effects, ultrafiltration.

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

DETERMINANTS OF PERMEABILITY TERM (P or P · S)

DIALYZER MEMBRANE CHARACTERISTICS
- **MEMBRANE SURFACE AREA**
- **MEMBRANE THICKNESS**
- **MEMBRANE POROSITY**

- **DRUG BINDING TO PLASMA PROTEINS**
- **SOLUTE SIZE AND DIFFUSIVITY**

DIALYZER PERMEABILITY VS. FREE WATER DIFFUSION COEFFICIENTS

Procainamide/NAPA:

RATIO OF DIALYZER PERMEABILITY COEFFICIENTS*	**1.29 ± 0.22**
RATIO OF FREE WATER DIFFUSION COEFFICIENTS	**1.23**

*** From Gibson TP et al. Clin Pharmacol Ther 1976;20:720-6.**

DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW*

Chart showing dialysis clearance vs. dialyzer blood flow and the impact of P.S. values for urea (high), creatinine, phosphate, and phenol red (low).

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

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 CLD FOR OTHER DIALYZERS AND OTHER Q VALUES IF P OF STANDARD COMPOUND FOR THAT DIALYZER IS KNOWN.

NEED TO SELECT APPROPRIATE STANDARD COMPOUND (? CREATININE).

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RECOVERY CLEARANCE

The gold standard equation for clearance.

U = DIALYSATE CONCENTRATION
V = DIALYSATE VOLUME
t = DIALYSIS TIME
P = MEAN PLASMA CONCENTRATION

A-V DIFFERENCE METHOD
[FICK EQUATION]

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

EXTRACTION RATIO

The Renkin Equation and the Fick Equation terms for extraction ratio.

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

Equation showing recovery and equation showing the Fick approach.

NAPA IN RBC IS DIALYZED

Chart comparing flow parameters.

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

DIALYSIS SATURATION VS. RECOVERY CLEARANCE

Formula for dialysis saturation and formula for recovery clearance.

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DATA SOURCES
FOR FICK EQUATION

Graphic illustration of venous (V) and arterial (A) bloodflow and dialysate solution into dialysate collection – recovered drug

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

Chart showing 3-compartment model

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

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

Chart showing 3-compartment model and dialysis machine.

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

FICK CLEARANCE EQUATION

TWO PROBLEMS WITH FIXED-PARAMETER MODEL*

Chart illustrating these two problems.

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

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

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

Chart showing 3-compartment model and dialysis machine.

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

REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS*

Charts illustrating reduction in slow intercompartmental clearance.

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

CONDUCT OF PK STUDIES IN HEMODIALYSIS PATIENTS

Chapter 6 – Principles of Clinical Pharmacology

Atkinson AJ Jr, Umans JG: Pharmacokinetic Studies in Hemodialysis Patients. Clin Pharmacol Ther 2009;86:548-52.

CDER, FDA: Draft Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling. http://www.fda.gov downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM204959.pdf

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CASE HISTORY

A 67 year-old woman became lethargic and confused and developed hypotension, renal insufficiency, junctional tachycardia and intraventricular conduction delay after ingesting an estimated 7gm of procainamide (PA). Plasma PA and NAPA concentrations were 57 µg/mL and 55 µg/mL, respectively.

CASE HISTORY (cont.)

Hemodialysis was performed for 4 hr. By the end of the second hour BP was maintained in the range of 110/80 mm Hg without vasopressor therapy. At the end of dialysis, the patient was alert and oriented although only 340 mg of PA and 470 mg of NAPA had been removed by this procedure.

DIALYSIS CASE HISTORY (cont.)

Fifteen hours after dialysis, PA and NAPA levels were 9.2 µg/mL and 33 µg/mL, respectively. The patient had returned to normal sinus rhythm with QRS = 0.12 sec.

KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*

Chart illustrating this analysis and drug removal during dialysis.

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

CRITERION FOR DIALYSIS EFFICACY*

Formula showing that dialysis clearance must be greater than 30% of total organ clearance to be effective.

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

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**
t1/2 (hr)	**2.5**	**6.2**	**10.5**	**35.9**
CLE (mL/min)	**590**	**233**	**66.8**	**16.1**
CLD (mL/min)			**68.3**	**45.8**
Vdβ (L/kg)	**1.80**	**1.76**	**0.76**	**0.63**

ESTIMATION OF V_d

Question: Why was distribution volume estimate so much lower in patient than in normal subjects?

Formulas comparing the usual with the dialysis estimates.

SEQUESTRATION OF DRUG IN SOMATIC TISSUES

Chart illustrating this effect with a 3-compartment model.

EFFICACY OF EXTRACORPOREAL TREATMENT OF DRUG TOXICITY

- TOTAL EXTENT OF DRUG REMOVAL MAY BE COMPROMIZED BY ↓ CLS.

- ↓ CLS FROM SOMATIC TISSUES CAN ACCELERATE ↓ IN DRUG CONCENTRATION TO WHICH VITAL ORGANS (CNS, HEART) ARE EXPOSED AND RESULT IN A BENEFICIAL CLINICAL RESPONSE > EXTENT OF DRUG REMOVAL.

- ↓ CLS FROM SOMATIC TISSUES ALSO ATTENUATES POST-DIALYSIS REBOUND.

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WHY DOES $CL_S \downarrow$ DURING DIALYSIS ?

POSSIBILITIES:

CAPILLARY BLOOD FLOW DECREASES

CAPILLARY P x S PRODUCT DECREASES

BOTH DECREASE

MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*

Illustration of this model.

*** From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.**

BASIS FOR KINETIC HETEROGENETIY OF INTERSTITIAL FLUID SPACE

Chart comparing effective pore size with capillary structure and primary location in splanchnic and somatic tissues.

ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS

Photomicrograph.

INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

Photomicrograph.

UREA (●) AND INULIN (▲) KINETICS DURING AND AFTER HEMODIALYSIS*

Chart illustrating the kinetics during and after hemodialysis.

*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

EFFECT OF MOLECULAR WEIGHT (M) ON SOLUTE DIFFUSIVITY (D)*

Chart illustrating this activity.

*** From Henderson LW: *In*: Brenner BM, Rector FC Jr. The Kidney. 1976, p. 1643-71.**

RELATIONSHIP BETWEEN BLOOD FLOW (Q) AND CL_I* (intercompartmental clearance)

Chart illustrating this relationship.

*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

UREA AND INULIN KINETICS DURING AND AFTER HEMODIALYSIS

Chart showing the flow and permeability parameters before, during and after.

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*

Chart illustrating this system activation during and after hemodialysis.

*** From Bowsher DJ, et al. J Lab Clin Med 1985;105:489-97.**

DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*

Chart illustrating actions of angiotensin II and AVP.

*** From Atkinson AJ Jr: The Pharmacologist 1989;31:229-34.**

EFFECT OF ARGININE VASOPRESSIN (AVP) ON P● S*

Chart illustrating this effect.

*** From Atkinson AJ Jr: The Pharmacologist 1989;31:229-34.**

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HEMODIALYSIS-ASSOCATED SKELETAL MUSCLE CRAMPS

COMPLICATE MORE THAN 20% OF HEMODIALYSIS SESSIONS

OCCUR MORE FREQUENTLY IN SOME PATIENTS THAN OTHERS

PATHOGENESIS UNCLEAR

SYMPTOMATIC THERAPY: NaCl, MANNITOL

PREVENTIVE THERAPY: NaCl INFUSION

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM

Chart illustrating these actions.

ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*

Chart comparing dialysis reaction with normal and cramper and noncramper.

*** Sidhom OA, et al. Clin Pharmacol Ther 1994;56:445-51**

CAPILLARY DERECRUITMENT
(OPEN (O) & CLOSED (●) CAPILLARIES)

8 OPEN CAPILLARIES IN MUSCLE CROSS SECTION.

PATHOGENESIS OF DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS

Chart illustrating the basis of dialysis-associated skeletal muscle cramps.

CONCLUDING THOUGHT

ALTHOUGH NON-COMPARTMENTAL ANALYSIS OF PK DATA IS CURRENTLY IN VOGUE, IT IS UNABLE TO PROVIDE INSIGHT INTO SOME IMPORTANT PHENOMENA:

- **IMPACT OF DIALYSIS-ASSOCIATED HEMODYNAMIC CHANGES (↓ CLS)**
- **IMPACT OF ↓ SPLANCHNIC BLOOD FLOW (↓ CLF) ON BIOAVAILABILITY**