PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

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Arthur J. Atkinson, Jr., M.D.
Adjunct Professor
Department of Molecular Pharmacology and Biochemistry
Feinberg School of Medicine
Northwestern University
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.

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

Photograph of Dr. Willem J. Kolff, developer of the first functioning artificial kidney (1943).
**ELIMINATION BY DIFFERENT ROUTES**

<table>
<thead>
<tr>
<th>MEASUREMENTS</th>
<th>RENAL</th>
<th>HEPATIC</th>
<th>DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD FLOW</td>
<td>+*</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>AFFERENT CONC.</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EFFERENT CONC.</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>ELIMINATED DRUG</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

*not actually measured in routine PK studies*
DATA SOURCES
FOR FICK EQUATION

Illustration of these sources in a dialysis machine.
IMPACT OF $\text{CL}_D$

Formula showing that CLR, CLNR and CLD are additive.
CRITERION FOR DIALYSIS EFFICACY*

$\text{CL}_{\text{EC}} > 30\% \ [\text{CL}_\text{R} + \text{CL}_\text{NR}]$

But clearance estimates must be comparable

GOALS OF DIALYSIS DISCUSSION

DISCUSSION OF DIALYSIS CLEARANCE
  MECHANISTIC – RENKIN APPROACH
  EMPIRICAL
    FICK EQUATION
    RECOVERY CLEARANCE
CLINICAL STUDIES OF DIALYSIS PK
  MODEL PROSPECTIVE STUDY
TREATMENT OF DRUG TOXICITY
PHYSIOLOGIC CHANGES DURING DIALYSIS
  USE OF KINETIC METHODS FOR ANALYSIS
PATHOPHYSIOLOGIC CONSEQUENCES
EUGENE RENKIN
PROFESSOR EMERITUS AT UC DAVIS

Photograph of Professor Eugene Renkin
RENNIN 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* 1.28 ± 0.23

RATIO OF FREE WATER DIFFUSION COEFFICIENTS 1.23

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.

\[ U = \text{DIALYSATE CONCENTRATION} \]
\[ V = \text{DIALYSATE VOLUME} \]
\[ t = \text{DIALYSIS TIME} \]
\[ P = \text{MEAN PLASMA CONCENTRATION} \]
A-V DIFFERENCE METHOD
[FICK EQUATION]

\[ Q = \text{DIALYZER BLOOD FLOW} \]
\[ A = \text{CONCENTRATION IN BLOOD COMING TO DIALYZER} \]
\[ V = \text{CONCENTRATION IN BLOOD LEAVING DIALYZER} \]
\[ E = \text{EXTRACTION RATIO} \]
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.

* $Q_{\text{EFF}} = [ (1 - \text{Hct}) + (\text{RBC}/P)(\text{HCT}) ] Q_{\text{MEAS}}$
DIALYSIS SATURATION VS. RECOVERY CLEARANCE

Formula for dialysis saturation and formula for recovery clearance.
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DATA SOURCES
FOR PHARMACOKINETICS ANALYSIS

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

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

Chart showing 3-compartment model and dialysis machine.

FICK CLEARANCE EQUATION

equation
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*

Chart illustrating these two problems.

**DURING DIALYSIS:** [A] AND [V] DROP MORE THAN EXPECTED FROM DRUG RECOVERY

**AFTER DIALYSIS:** CONCENTRATION REBOUND IS LESS THAN EXPECTED

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

Chart showing 3-compartment model and dialysis machine.

REDUCTION IN CL$_S$ DURING AND AFTER HEMODIALYSIS*

Charts illustrating reduction in slow intercompartmental clearance.

CONDUCT OF PK STUDIES IN HEMODIALYSIS PATIENTS

Chapter 6 – Principles of Clinical Pharmacology


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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.
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.
KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*

Chart illustrating this analysis and drug removal during dialysis.

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

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th></th>
<th>PATIENT</th>
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<tbody>
<tr>
<td></td>
<td>PA</td>
<td>NAPA</td>
<td>PA</td>
<td>NAPA</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>2.5</td>
<td>6.2</td>
<td>10.5</td>
<td>35.9</td>
</tr>
<tr>
<td>CLE (mL/min)</td>
<td>590</td>
<td>233</td>
<td>66.8</td>
<td>16.1</td>
</tr>
<tr>
<td>CLD (mL/min)</td>
<td></td>
<td></td>
<td>68.3</td>
<td>45.8</td>
</tr>
<tr>
<td>Vdβ (L/kg)</td>
<td>1.80</td>
<td>1.76</td>
<td>0.76</td>
<td>0.63</td>
</tr>
</tbody>
</table>
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$_S$ ↓ 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.

BASIS FOR KINETIC HETEROGENEITY 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.

RELATIONSHIP BETWEEN BLOOD FLOW (Q) AND CL\textsubscript{i}*

Chart illustrating this relationship.

UREA AND INULIN KINETICS
DURING AND AFTER HEMODIALYSIS

Chart showing the flow and permeability parameters before, during and after.
EFFECT OF ARGinine VASOPRESSIN (AVP) ON P•S*

Chart illustrating this effect.

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*

Chart illustrating this system activation during and after hemodialysis.

DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*

Chart illustrating actions of angiotensin II and AVP.

HEMODIALYSIS-ASSOCIATED
SKELETAL MUSCLE CRAMPS

COMPLICATE MORE THAN 20% OF HEMODIALYSIS SESSIONS

OCUR MORE FREQUENTLY IN SOME PATIENTS THAN
OTHERS

PATHOGENESIS UNCLEAR

SYMPTOMATIC THERAPY: NaCl, MANNITOL

PREVENTIVE THERAPY: NaCl INFUSION
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