PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

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FIRST DESCRIPTION OF HEMODIALYSIS IN ANIMALS*

ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD OF LIVING ANIMALS BY DIALYSIS

JOHN J. ABEL, LEONARD G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, December 18, 1913

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WILLEM J. KOLFF, M.D. (1911 - )
## Elimination by Different Routes

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<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

Venous

Arterial

Dialysate Solution

Dialysate Collection

RECOVERED DRUG

V

Q

A
IMPACT OF CL_D

\[ C_{L_E} = C_{L_R} + C_{L_{NR}} + C_{L_D} \]
**CRITERION FOR DIALYSIS EFFICACY**

\[ CL_{EC} > 30\% \left[ CL_{R} + CL_{NR} \right] \]

**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
RENKIN DIALYSIS EQUATION*

\[ CL_D = Q (1 - e^{-P/Q}) \]

Q = DIALYZER BLOOD FLOW

P = PERMEABILITY-SURFACE AREA PRODUCT OF DIALYZING MEMBRANE

NEGLECTS: BOUNDARY EFFECTS, ULTRAFILTRATION

* From Renkin EM. Tr Am Soc Artific Organs 1956;2:102-5
DETERMINANTS OF PERMEABILITY TERM (P or P \cdot 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*  
\[ 1.28 \pm 0.23 \]

RATIO OF FREE WATER DIFFUSION COEFFICIENTS  
\[ 1.23 \]

DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW*

* 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 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).
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FICK EQUATION

\[
\begin{align*}
CL &= Q \left[ \frac{A - V}{A} \right] \\
E &= \left[ \frac{A - V}{A} \right]
\end{align*}
\]

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

Renkin Equation:
\[ E = [1 - e^{-P/Q}] \]

Fick Equation:
\[ E = \left[ \frac{A - V}{A} \right] \]

In Each Case:
\[ CL = Q \cdot E \]
RECOVERY CLEARANCE

THE GOLD STANDARD

\[ CL = \frac{U \cdot V}{P \cdot t} \]

U = DIALYSATE CONCENTRATION
V = DIALYSATE VOLUME
t = DIALYSIS TIME
P = MEAN PLASMA CONCENTRATION
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:  \[ CL_p = \frac{U \cdot V}{P} \quad \text{and} \quad CL_B = \frac{U \cdot V}{B} \]

FICK:  \[ CL_p = Q_{PK} \left( \frac{A - V}{A} \right) \quad \text{and} \quad CL_B = Q_B \left( \frac{A - V}{A} \right) \]

IF \( B > P \), then \( CL_p > CL_B \), SO: \( Q_{PK} > Q_B > Q_p \)
NAPA IN RBC IS DIALYZED

<table>
<thead>
<tr>
<th>FLOW PARAMETER</th>
<th>MEAN VALUE (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{PK}$</td>
<td>223</td>
</tr>
<tr>
<td>$Q_{MEAS}$</td>
<td>195 (p &lt; 0.2)</td>
</tr>
<tr>
<td>$Q_{EFF}^*$</td>
<td>217 (p &gt; 0.2)</td>
</tr>
</tbody>
</table>

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

DIALYSIS SATURATION \((EC = C_d/C_p)\):

\[ CL_d = Q_d \frac{C_d}{C_p} \]

RECOVERY CLEARANCE:

\[ CL_d = \frac{UV}{P\tau} = \frac{C_d V_d}{C_p\tau} \]

BUT:

\[ Q_d = \frac{V_d}{\tau} \text{ SO EXPRESSIONS ARE EQUIVALENT} \]
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PATHOPHYSIOLOGIC CONSEQUENCES
DATA SOURCES FOR FICK EQUATION

DIAGRAM:
- V: Venous
- Q: Arterial
- A: Recovered Drug
- Dialysate Solution
- Dialysate Collection

Equation:

\[ \text{Equation} \]
KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

FICK CLEARANCE EQUATION

\[
\begin{align*}
CL &= Q \left( \frac{A - V}{A} \right) \\
CLA &= QA - QV \\
QV &= QA - CLA \\
V &= \left( \frac{Q - CL}{Q} \right) A
\end{align*}
\]
TWO PROBLEMS WITH FIXED-PARAMETER MODEL*

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

KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS*

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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.
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*

CRITERION FOR DIALYSIS EFFICACY*

\[ \text{CL}_{EC} > 30\% \left( \text{CL}_R + \text{CL}_{NR} \right) \]

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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PA</td>
<td>NAPA</td>
<td>PA</td>
<td>NAPA</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>2.5</td>
<td>6.2</td>
<td>10.5</td>
<td>35.9</td>
</tr>
<tr>
<td>$\text{CL}_E$ (mL/min)</td>
<td>590</td>
<td>233</td>
<td>66.8</td>
<td>16.1</td>
</tr>
<tr>
<td>$\text{CL}_D$ (mL/min)</td>
<td></td>
<td></td>
<td>68.3</td>
<td>45.8</td>
</tr>
<tr>
<td>$V_{d\beta}$ (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?

USUAL \( V_d \) ESTIMATE:
\[
V_d = \frac{\text{DOSE GIVEN}}{\Delta \text{CONCENTRATION}}
\]

DIALYSIS \( V_d \) ESTIMATE:
\[
V_d = \frac{\text{DRUG REMOVED}}{\Delta \text{CONCENTRATION}}
\]
SEQUESTRATION OF DRUG IN SOMATIC TISSUES

BIOPHASE

7L

DIALYSIS

CL_P

CL_E

CL_F

CL_S

14L

83L
EFFICACY OF EXTRACORPOREAL TREATMENT OF DRUG TOXICITY

• TOTAL EXTENT OF DRUG REMOVAL MAY BE COMPROMIZED BY ↓ CL_S.

• ↓ CL_S 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.

• ↓ CL_S 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 $P\cdot S$ PRODUCT DECREASES
- BOTH DECREASE
RENKIN EQUATION*

\[ CL = Q \left(1 - e^{-\frac{P}{Q}}\right) \]

Q = capillary blood flow

P = capillary permeability coefficient-surface area product (sometimes denoted P\•S).

MULTICOMPARTMENTAL MODEL OF INULIN AND UREA KINETICS*

**Basis for Kinetic Heterogeneity of Interstitial Fluid Space**

<table>
<thead>
<tr>
<th>Effective Pore Size</th>
<th>Capillary Structure</th>
<th>Primary Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Fenestrated</td>
<td>Splanchnic Bed</td>
</tr>
<tr>
<td>Small</td>
<td>Continuous</td>
<td>Somatic Tissues</td>
</tr>
</tbody>
</table>
ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS
INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY
UREA (●) AND INULIN (▲) KINETICS DURING AND AFTER HEMODIALYSIS*

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

RELATIONSHIP BETWEEN BLOOD FLOW (Q) AND CL₁ *

UREA AND INULIN KINETICS DURING AND AFTER HEMODIALYSIS

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BEFORE</th>
<th>DURING</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD FLOW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q_S (mL/min)</td>
<td>1991</td>
<td>199</td>
<td>405</td>
</tr>
<tr>
<td>Q_F (mL/min)</td>
<td>2332</td>
<td>2591*</td>
<td>2965*</td>
</tr>
<tr>
<td>C.O. (mL/min)</td>
<td>4399</td>
<td>2790</td>
<td>3370</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INULIN (mL/min)</td>
<td>186</td>
<td>169</td>
<td>238</td>
</tr>
<tr>
<td>UREA (mL/min)</td>
<td>1649</td>
<td>1541</td>
<td>2164</td>
</tr>
</tbody>
</table>

* ESTIMATED AS C.O. - Q_S
RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*

DIFFERENT MICROCIRCULATORY ACTIONS OF ANGIOTENSIN II AND AVP*

EFFECT OF ARGinine VASOPRESSIN (AVP) ON P•S*

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HEMODIALYSIS-ASSOCIATED 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
RESPONSE OF CRAMPING AND NONCRAMPING PATIENTS TO TILT*

ACTIONS OF ANGIOTENSIN II & SYMPATHETIC NERVOUS SYSTEM

Arterial

Venous

Sympathetic Nervous System

\( R_A \)

\( A_{\text{II}} \)

\( R_v \)

\( R_{A/R_v} \)

P \cdot S

\( A_{\text{II}} \)

Sympathetic Nerves

\( \downarrow \)

Normal

\( \uparrow \)

\( \downarrow \)
ONLY SOME PATIENTS HAVE DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS*

AUGUST KROGH
1920 NOBEL LAUREATE
CROSS SECTION OF MUSCLE SHOWING OPEN (O) & CLOSED (●) CAPILLARIES*

*From Krogh A. Nobel Lecture, December 11, 1920.
CAPILLARY DERECRUITMENT (OPEN (○) & CLOSED (●) CAPILLARIES)

OPEN CAPILLARIES IN MUSCLE CROSS SECTION
PATHOGENESIS OF DIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS

HEMODIALYSIS \[ \text{NaCl, MANNITOL} \]

PLASMA VOLUME CONTRACTION \[ \text{ACE INHIBITOR} \rightarrow \text{PRAZOSIN} \]

MODULATED SYMPATHETIC ACTIVATION

PERIPHERAL VASOCONSTRICTION

DERECRUITMENT OF MUSCLE CAPILLARIES

IMPAIRED MUSCLE OXYGENATION

SKELETAL MUSCLE CRAMPS
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 (↓ CL_S)
- IMPACT OF ↓ SPLANCHNIC BLOOD FLOW (↓ CL_F) ON BIOAVAILABILITY