PART 1: PK IN PATIENTS REQUIRING HEMODIALYSIS

PHARMACOKINETICS IN PATIENTS REQUIRING RENAL REPLACEMENT Rx

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1857 - 1938
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

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ELIMINATION BY DIFFERENT ROUTES

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<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 PHARMACOKINETIC ANALYSIS

Diagram showing a medical device with labeled parts:

- Venous
- Arterial
- Dialysate Solution
- Dialysate Collection
- RECOVERED DRUG

Diagram illustrates a system for data sources in pharmacokinetic analysis.
IMPACT OF $\text{CL}_D$

$\text{CL}_E = \text{CL}_R + \text{CL}_\text{NR} + \text{CL}_D$
CRITERION FOR DIALYSIS EFFICACY*

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

BUT CLEARANCE ESTIMATES MUST BE COMPARABLE

GOALS OF DIALYSIS DISCUSSION

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

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*

\[ \text{CL}_D = Q \left(1 - e^{-P \cdot S/Q} \right) \]

- **Q** = Dialyzer Blood Flow
- **P \cdot S** = 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 ± 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·S RATIO FOR DRUG & STANDARD COMPOUND FOR DIALYZER BEING USED IN DIALYSIS STUDY (RECORD Q & RBC/PLASMA).

- THIS RATIO CAN BE USED TO ESTIMATE DRUG CLₐ FOR OTHER DIALYZERS AND OTHER Q VALUES IF P·S OF STANDARD COMPOUND FOR THAT DIALYZER IS KNOWN.

- NEED TO SELECT APPROPRIATE STANDARD COMPOUND (? CREATININE).
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RECOVERY CLEARANCE

THE GOLD STANDARD

\[
CL_D = \frac{C_D \cdot Vol_D}{A \cdot t}
\]

\[
CL_D = \frac{C_D \cdot Vol_D}{AUC_A}
\]
A-V DIFFERENCE METHOD
[FICK EQUATION]

\[ \text{CL} = Q \left( \frac{A - V}{A} \right) \]

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

**Q** = DIALYZER BLOOD FLOW

**A** = CONCENTRATION IN BLOOD COMING TO DIALYZER

**V** = CONCENTRATION IN BLOOD LEAVING DIALYZER

**E** = EXTRACTION RATIO
Renkin Equation:
\[ E = \left[ 1 - e^{-P \cdot S/Q} \right] \]

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

In Each Case:
\[ CL = Q \cdot E \]
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
IMPACT OF SELECTED BLOOD FLOW ON CLEARANCE ESTIMATES

RECOVERY: $\text{CL}_P = \frac{U \cdot V}{P}$  \hspace{1cm} $\text{CL}_B = \frac{U \cdot V}{B}$

FICK: $\text{CL}_P = Q_{PK} \left( \frac{A-V}{A} \right)$  \hspace{1cm} $\text{CL}_B = Q_B \left( \frac{A-V}{A} \right)$

If $P < B$: $\text{CL}_P > \text{CL}_B$, so $Q_{PK} > Q_B > Q_P$

**S0:** Use $Q = \text{BLOOD FLOW}$ if measuring [BLOOD]  
Calculate $Q_{PK}$ if measuring [PLASMA]  
*NEVER* use $Q = \text{PLASMA FLOW}$
**DRUG 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>

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

DIALYSIS SATURATION \( (S_p = C_d/C_r) \):

\[
CL_p = Q_d \frac{C_d}{C_r}
\]

RECOVERY CLEARANCE:

\[
CL_r = \frac{UV}{P \tau} = \frac{C_r V_d}{C_r \tau}
\]

BUT:

\[Q_d = \frac{V_d}{\tau}\]

SO EXPRESSIONS ARE EQUIVALENT
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   PATHOPHYSIOLOGIC CONSEQUENCES
DATA SOURCES FOR PHARMACOKINETIC ANALYSIS
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*


CONDUCT OF PK STUDIES IN HEMODIALYSIS PATIENTS

Chapter 6 – Principles of Clinical Pharmacology


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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.
KINETIC ANALYSIS OF HEMODIALYSIS FOR PROCAINAMIDE TOXICITY*

WAS DIALYSIS EFFICACIOUS?

• DIALYSIS INCREASED DRUG CLEARANCE > 30%
  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
<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>$CL_E$ (mL/min)</td>
<td>590</td>
<td>233</td>
<td>66.8</td>
<td>16.1</td>
</tr>
<tr>
<td>$CL_D$ (mL/min)</td>
<td></td>
<td></td>
<td>68.3</td>
<td>45.8</td>
</tr>
<tr>
<td>$V_{dβ}$ (L/kg)</td>
<td>1.80</td>
<td>1.76</td>
<td>0.76</td>
<td>0.63</td>
</tr>
</tbody>
</table>
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

14L

83L

DIALYSIS

$CL_D$

$CL_E$

$CL_F$

$CL_S$
Efficacy of Extracorporeal Treatment of Drug Toxicity

• Total extent of drug removal may be compromised 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?

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

POSSIBILITIES:
- CAPILLARY BLOOD FLOW ($Q$) DECREASES
- CAPILLARY $P\cdot S$ PRODUCT DECREASES
- BOTH DECREASE
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*

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><strong>BLOOD FLOW</strong></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><strong>PS</strong></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. - $Q_S$*
CROSS SECTION OF MUSCLE SHOWING OPEN (○) & CLOSED (●) CAPILLARIES*

*From Krogh A. Nobel Lecture, December 11, 1920.
EFFECT OF ARGinine VASOPRESSIN (AVP) ON P•S*

RENIN-ANGIOTENSIN SYSTEM ACTIVATION DURING AND AFTER HEMODIALYSIS*

DIFFERENT MICROCIRCULATORY ACTIONS OF ANG II AND AVP OR NE
CONCLUDING PK THOUGHT

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

- IMPACT OF DIALYSIS-ASSOCIATED HEMODYNAMIC CHANGES (↓ CL<sub>S</sub>)

- IMPACT OF ↓ SPLANCHNIC BLOOD FLOW (↓ CL<sub>F</sub>) ON BIOAVAILABILITY

USE OF PK MODELS TO ELUCIDATE UNAPPRECIATED PHYSIOLOGY