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

<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

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www.kidigo.org
IMPACT OF $\text{CL}_D$

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

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

BUT CLEARANCE ESTIMATES MUST BE COMPARABLE


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RECOVERY METHOD

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

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

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

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:
\[ CL_P = \frac{U \cdot V}{P} \]
\[ CL_B = \frac{U \cdot V}{B} \]

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

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

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

$Q_{EFF}^* = \left[ (1 - Hct) + (RBC/P) (HCT) \right] Q_{MEAS}$
KINETIC MODEL USED TO ANALYZE HEMODIALYSIS DATA*

3-Compartment Model

\[ V_F \]

\[ V_S \]

\[ V_C \]

\[ CL_F \]

\[ CL_S \]

\[ CL_R \]

\[ CL_{NR} \]

\[ CL_D \]

Dialysis Machine

\[ \frac{Q_{PK}-CL_D}{Q_{PK}} \]

Post Dialyzer

“V”

Dialysate


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FICK CLEARANCE EQUATION

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

\[ CLA = QA - QV \]

\[ QV = QA - CLA \]

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


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PARAMETER CHANGE REQUIRED TO MODEL DIALYSIS PK

3-Compartment Model

V_c

V_F

V_S

C_L_F

C_L_S \times G

C_L_R

C_L_{NR}

Dialysis Machine

\frac{Q_{PK} - C_L_D}{Q_{PK}}

C_L_D

Dialysate

Post Dialyzer

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REDUCTION IN CL_S DURING AND AFTER HEMODIALYSIS

77% ↓ in CL_S

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IMPLICATIONS OF ↓ CLS FOR DIALYSIS TREATMENT OF DRUG TOXICITY*

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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

<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>

**DIALYSIS V_D ESTIMATE:**

\[ V_D = \frac{\text{DRUG REMOVED}}{\Delta \text{CONCENTRATION}} \]
SEQUESTRATION OF DRUG IN SOMATIC TISSUES

BIOPHASE

DIALYSIS

CL_D

CL_E

CL_F

CL_S

7L

14L

83L

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NEED FOR INTRADIALYZER TRANSFER OF RESULTS*

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

\( Q \) = 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

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DIALYSIS CLEARANCE VS. DIALYZER BLOOD FLOW *

\[ \text{CL}_D \text{ (mL/min)} \]

\[ \text{Q (mL/min)} \]

* 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

NEED FOR INTRADIALYZER TRANSFER OF RESULTS*

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