Medication Removal by Apheresis

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Objectives

- Review basic pharmacokinetics and its relevance in drug removal by therapeutic apheresis (TPE)
- Review the removal by therapeutic apheresis of medications commonly used in patients undergoing therapeutic apheresis
- Discuss approaches/strategies in managing drug removal by therapeutic apheresis
Resources


Questions

• Can TPE remove drugs? How much?
• What are the factors affecting TPE drug removal?
• Can TPE drug removal harm patients?
• Is dose, frequency, timing adjustment necessary?
• Can TPE be used for therapeutic drug removal?
Case 1

- Patient is a 63-year-old female with myasthenia gravis receiving TPE. The patient’s immunosuppression regimen includes: mycophenolate mofetil 1000 mg in the morning and 1500 mg in the evening

- Do you need to adjust the dose, frequency, and timing for mycophenolate due to TPE?
  - A. Yes
  - B. No
Case 2

- Patient is a 56 y. o. man s/p renal transplant and was found to have extremely elevated tacrolimus level. You are asked to perform TPE to reduce the drug level. You would

A. Start TPE right away
B. TPE is not indicated
C. RBC exchange may be considered
Case 3A

- Patient is a 45 y. o. woman with relapsing TTP. Patient has a ADAMTS-13 inhibitor with titer of 8. You are two weeks into daily TPE, patient still remains thrombocytopenia. Hematology consult decides to give a dose of rituximab. They are consulting you regarding the timing of TPE.
Case 3A

You will recommend the following:

A. Continue daily TPE without rituximab

B. Stop daily TPE and give rituximab

C. Continue daily TPE 24 hours after rituximab

D. Continue daily TPE 48 hours after rituximab, but give high dose plasma infusion on the day without TPE
Case 3B

- Patient is also given Phenytoin for seizure control. The nursing staff is worried about the impact of drug removal by TPE. You would recommend:

A. Continue daily TPE without dose adjustment
B. Continue daily TPE with additional dose of Phenytoin
C. Continue daily TPE and give Phenytoin right before the TPE procedure
D. Continue daily TPE and give Phenytoin right after the TPE procedure
Basic Pharmacokinetics

• How the body affects medication after administration
  • Absorption - the process of a substance entering the blood circulation.
  • Distribution - the dispersion or dissemination of substances throughout the fluids and tissues of the body.
  • Metabolism - the irreversible transformation of compounds into metabolites.
  • Excretion (clearance) - the removal of the substances from the body.
Basic Pharmacokinetics

- $T_{\frac{1}{2}}$ beta: elimination half life
- $T_{1/2}$ alpha: the distribution half life
- Area Under Curve: reflects the actual body exposure to drug after administration of a dose of the drug and is expressed in mg*h/L.
Basic Pharmacokinetics
The volume of distribution (VD): volume that a drug occupies (assume it is uniformly distributed), to provide the same concentration as it is in blood plasma.

- If VD is greater, more of it is distributed in tissue (i.e. not in plasma).

- Total Drug

\[ \text{Total Drug} = \text{Drug Conc} \times \text{Total Volume (Vd or VD)} \]

- Total Volume (VD) = Total Drug/Drug Conc.
Basic Pharmacokinetics

- VD: not a physiologic value; a reflection of a drug distributes throughout the body depending on solubility, charge, size, etc.
- Determined by the physiologic volume of blood and tissues and how the drug binds in blood and tissues.
- The units for Volume of Distribution: liter/kg body weight, often used as L.
- Children typically have higher VD than that for adults
- Population variation
Basic Pharmacokinetics

- Plasma
- Extracellular Fluid
- Intracellular Fluid
- Other Fluids
- Fat
Basic Pharmacokinetics

- **Fat**: Small Vd, and high protein bound, high removal.
Basic Pharmacokinetics

- Plasma
- Extracellular Fluid
- Intracellular Fluid
- Fat
- Other Fluids

Large Vd, and high tissue/other fluid bound
Low removal
<table>
<thead>
<tr>
<th>Sample Drug</th>
<th>VD</th>
<th>Property/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.1 L</td>
<td>plasma protein binding.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>8L</td>
<td>plasma protein binding.</td>
</tr>
<tr>
<td>NXY-059</td>
<td>8L</td>
<td>Highly-charged hydrophilic molecule.</td>
</tr>
<tr>
<td>Theophylline, Ethanol</td>
<td>30L</td>
<td>High distribution in total body water.</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>15000L</td>
<td>Lipophilic, sequestered into total body fat.</td>
</tr>
</tbody>
</table>
Removal by TPE

- All solutes in plasma, including drugs, can be removed
  - Drug overdose treatment by TPE
  - Drug adjustment during TPE
- How much can be removed is the question
- For therapeutic removal: >30%
- Not well studied, limited evidence
- Effective removal:
  - Low volume of distribution (VD): <0.2
  - And high plasma protein binding: >80%
In general, drug infusion and the extravascular distributive phase should be complete (as measured by using t1/2a) before the start of TPE. Avoid administration right before TPE if possible.

For continuous infusion drugs that mostly distributed in plasma:

\[
\text{Infusion rate} = \text{endogenous clearance} \times C_{ss} + \text{plasma exchange clearance}
\]

\[
\text{Plasma exchange clearance} = \frac{\text{Plasmapheresate}}{\text{area under curve during TPE}}
\]
Removal by TPE

Assessment of Drug removal by TPE

• Mid apheresis level or levels right after apheresis in the distribution phase (re-equilibration) overestimate the drug removal.

• Level post (several hours) distribution phase (re-equilibration) can detect rebound (from tissue bound).

• Pre (right before TPE) and post (after re-equilibration).

• Plasma waste drug level and volume.
Removal by TPE

A. The amount of drug removed =
Drug concentration in removed plasma waste (g/L) x total volume of removed plasma (L)

B. Total body drug stores =
Serum conc. of drug (mg/L) x Vd (L)

C. % of total body drug removal =
(The amount of drug removed / total body drug store) x 100%

Maldonado et al, Transplantation 91, e3-4
Removal by TPE

Maldonado et al, Transplantation 91, e3-4

<table>
<thead>
<tr>
<th></th>
<th>TPE 1</th>
<th>TPE 2</th>
<th>TPE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA Blood level Pre (mg/mL)</td>
<td>10.1</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>MPA Blood level Post (mg/mL)</td>
<td>3</td>
<td>3.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Duration of procedure (min)</td>
<td>75</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>MPA level in plasma waste (mg/mL)</td>
<td>4.4</td>
<td>3.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Plasma waste volume (mL)</td>
<td>3210</td>
<td>3056</td>
<td>3056</td>
</tr>
<tr>
<td>Estimated MPA removal by TPE (mg)</td>
<td>14.124</td>
<td>11.9184</td>
<td>5.8064</td>
</tr>
<tr>
<td>Estimated body MPA stores (mg)</td>
<td>545.4</td>
<td>432</td>
<td>459</td>
</tr>
<tr>
<td>% of MPA removal by TPE</td>
<td>2.59%</td>
<td>2.76%</td>
<td>1.27%</td>
</tr>
</tbody>
</table>

Vd = 4 L, and 97% albumin bound
Case 1

- Patient is a 63-year-old female with myasthenia gravis receiving TPE. The patient’s immunosuppression regimen includes: mycophenolate mofetil 1000 mg in the morning and 1500 mg in the evening.

- Do you need to adjust the dose, frequency, and timing for mycophenolate due to TPE?
  - A. Yes
  - B. No
# Removal by TPE (immunosuppressant)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>VD</th>
<th>Plasma protein binding</th>
<th>Property/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone/ prednisolone</td>
<td>0.6–0.7 L</td>
<td>90–95%</td>
<td>1. 1% removal; 2. No need to adjust dose; 3. If possible, administer after TPE</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>13 L</td>
<td>90-98%</td>
<td>1. 1% removal; 2. No need to adjust dose; 3. If possible, administer after TPE; 4. 50% in RBC</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.8 L</td>
<td>23%</td>
<td>1. Suspect little removal 2. administer after TPE recommended</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0.6 L</td>
<td>30%</td>
<td>1. Suspect little removal 2. administer after TPE recommended</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Large (98 L?)</td>
<td>low</td>
<td>1. Little removal by TPE; 2. largely in RBC</td>
</tr>
</tbody>
</table>
Case 2

- Patient is a 56 y. o. man s/p renal transplant and was found to have extremely elevated tacrolimus level. You are asked to perform TPE to reduce the drug level. You would

A. Start TPE right away
B. TPE is not indicated
C. RBC exchange may be considered
## Removal by TPE (Ab)

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>&lt;0.3L</td>
<td>Plasma protein (76% IgM, 45% IgG)</td>
<td>1. T1/2: 12-40 days. 2. Multi-component, with 48% distributed intravascularly. 3. Give post TPE recommended</td>
</tr>
<tr>
<td>Rituximab</td>
<td>3L</td>
<td>No/plasma protein</td>
<td>1. Anti-CD20, target on B cells (not plasma cells). 2. T1/2 (distribution): 1-3 days; T1/2 (elimination): 20 days. 3. TPE removes (63% if 1 PV), but no impact on immediate effect</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>0.12 L</td>
<td>In plasma</td>
<td>1. T1/2: 2-3 days. 2. T-cell depletion is usually observed in 1 to 3 days. 3. Mean peak plasma level: 4-8 hours. 4. reported TPE removal for Serum sickness. 5. Give post TPE recommended</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>5-9 L</td>
<td>In plasma</td>
<td>1. 65 % removal; 2. If possible, administer after TPE; 3. Supplemental dose may be needed. 4. monoclonal antibody directed against the alpha chain of interleukin-2 (IL-2) receptors</td>
</tr>
<tr>
<td>Natalizumab (TYSABRI®)</td>
<td>5.7 + 1.9 L</td>
<td>In plasma</td>
<td>1. Removal after 3 TPE (over a 5-8 day interval) was approximately 70-80%, use in PML</td>
</tr>
</tbody>
</table>
Removal by TPE

- Median time to CD19 < 5%: 3 days (range 1–14 days)
- Median time to CD19 < 1%: 6.5 days (range 3–14 days).
- Rituximab was removed by TPE (65%) when done within 24 h post administration.
- The effect of rituximab’s action was unaffected despite its removal by TPE.
• Despite removal of significant amounts of rituximab by TPE, peripheral blood B cell depletion was achieved in all patients.

• Even though one-third of patients had elevated circulating CD19% at presentation, the median time to B cell depletion (CD19 < 5%) was only 3 days.

• There was no correlation between the time to B cell depletion and the rituximab level after the first dose or the number of PEX after rituximab
Case 3A

- Patient is a 45 y. o. woman with relapsing TTP. Patient has a ADAMTS-13 inhibitor with titer of 8. You are two weeks into daily TPE, patient still remains thrombocytopenia. Hematology consult decides to give a dose of rituximab. They are consulting you regarding the timing of TPE.
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D. Continue daily TPE 48 hours after rituximab, but give high dose plasma infusion on the day without TPE
Case 3B

- Patient was also given Phenytoin for seizure control. The nursing staff was worried about the impact of drug removal by TPE. You would recommend:

A. Continue daily TPE without dose adjustment

B. Continue daily TPE with additional dose of Phenytoin

C. Continue daily TPE and give Phenytoin right before the TPE procedure

D. Continue daily TPE and give Phenytoin right after the TPE procedure
Case 3B (Phenytoin)

- Highly protein bound (~90%)
- Vd of approximately 0.55 L/kg in patients without end-stage renal disease
  - One TTP case: removed 10% of total body stores, and required dosage adjustments to maintain therapeutic levels.
  - Other additional studies: TPE removed 2.8% to 5% of total body stores (Due to change in Vd in renal failure pts and increased binding to albumin) and free phenytoin did not change significantly
Case 3B

- Patient was also given Phenytoin for seizure control. The nursing staff was worried about the impact of drug removal by TPE. You would recommend:

A. Continue daily TPE without dose adjustment

B. Continue daily TPE with additional dose of Phenytoin

C. Continue daily TPE and give Phenytoin right before the TPE procedure

D. Continue daily TPE and give Phenytoin right after the TPE procedure
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<tr>
<td>Aspirin</td>
<td>0.1-0.2 L</td>
<td>80-90%</td>
<td>1. 7-32% removal. 2. dose adjustment may be necessary</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.04-0.07 L</td>
<td></td>
<td>1. Removal. 2. Give after TPE if needed*</td>
</tr>
<tr>
<td>Low MW Heparin</td>
<td>0.04-0.06 L</td>
<td>90–95%</td>
<td>1. ? Removal. 2. Divide dose or give after TPE. 3. anti-Xa activity decreased by TPE</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>12.2 L</td>
<td>90-98%</td>
<td>1. T1/2 of 1-2 hrs. 2. Give after TPE if needed*</td>
</tr>
<tr>
<td>Dabigatran (PRADAXA)</td>
<td>50-70 L</td>
<td>30%</td>
<td>1. Little removal by TPE*?; 2. Hemodialysis</td>
</tr>
<tr>
<td>XARELTO (rivaroxaban)</td>
<td>50L</td>
<td>92-95%</td>
<td>1. Little removal by TPE*?; 2. oral factor Xa inhibitor</td>
</tr>
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| Digoxin       | 5-8 L| 20-30%                 | 1. Early TPX effect on its pharmacokinetics (?), give after TPE (or at least 2 hours before) if possible  
                 |      |                        | 2. <1% removal in steady stage                                                  |
| Propranolol   | 4L   | 90%                    | 1. T1/2 beta decreased from 4.3 to 1.1 h after TPE; 2. Removal was reported     |
| Varapamil     | 2.4-6.2 L | 90%                | 1. Removal by TPE was reported in overdose                                        |
| Diltiazem     | 5 L  | 77-93 %                | 1. Removal by TPE was reported in overdose                                        |
| Amiodarone    | 60 L | 95%                    | Little removal by TPE                                                            |
Factors affecting drug removal by TPE

- Drug level in blood
  - Low volume distribution (<0.2)
  - High protein bound (>80%)
  - During distribution (after drug administration, $t_{1/2a}$)

- TPE dependent:
  - Length of TPE/Volume of exchange
  - No. of consecutive
  - Replacement fluid?
Conclusion

Check if low VD and high protein bound/plasma protein

- No
  - No specific action need but avoid pre-TPE administration*
  - No specific action need but avoid pre-TPE administration*

- Yes
  - Check if evidence for significant drug removal
  - Yes
    - Dose-justification# avoid pre-TPE administration*
  - No
    - No specific action need but avoid pre-TPE administration*

* NA for premedication or medication required during procedure
# NA if TPE removal does not affect drug effect
• Drug removal by TPE is complex
• Decision making depends on prior evidence (very limited and imperfect design) and exact clinical case
• Many factors can affect drug removal by TPE including length of procedure
• TPE drug removal may not always alter effect.
• Determine the drug removal by plasma waste is more reliable, when necessary.
Supplemental dosing may be considered for highly protein-bound drugs with low volumes of distribution (Vd)