Drug Removal by Therapeutic Plasma Exchange: a Wellness Check

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Objectives

• Upon completion of this presentation, the participant will be able to:

1. Discuss drug-related pharmacokinetics characteristics which lead to more efficient removal by therapeutic plasma exchange (TPE)

2. Apply knowledge in clinical scenarios as to how to handle medications in patients actively receiving TPE
Conflicts of interest statement

• No receipt of salary, royalties, honorarium, intellectual property rights/patent holder and consulting fees (e.g., advisory boards)
• No receipt of fees for non-CE services received directly from a commercial interest or their agents (e.g., speakers’ bureaus)
• No contracted research
• No ownership interest (stocks, stock options or other ownership interest excluding diversified mutual funds)
Outline

• Introduction

• Drug removal by TPE principles
  – Time between dose administration and TPE
  – Relation between the amount removed and biologic effect
  – How to assess the amount removed?

• Future directions
• A 55-year-old female patient status post allogeneic hematopoietic stem cell transplant for acute leukemia is on intravenous mycophenolate mofetil (MMF) 1g Q8H for the treatment of refractory gastrointestinal graft-versus-host-disease. She is initiated on TPE for the treatment of TTP:

  • IV Cellcept dose given at 8:00 a.m. over 2 hours

  • TPE initiated at ~8:30 a.m. for about 2 hours
Introduction

• Pharmacokinetics:
  – Trough (serum) total MMA* level prior to TPE = 1.8 mg/L
  – MMA concentration in waste plasma = 1.4 mg/L

Ratio waste plasma/patient’s serum concentration:

\[
\frac{1.4}{1.8} \times 100 = \sim 75\%
\]

TPE eliminated a substantial amount of IV MMA when it overlapped with the latter’s infusion for about 1.5 hours

* mycophenolic acid, the active ingredient of mycophenolate mofetil (MMF)
Introduction: another case

- Pediatric patient with pulmonary arterial hypertension awaiting lung transplant
- On Treprostinil (Remodulin®) IV infusion
- TPE scheduled pre-transplant and post-transplant
Introduction

• TPE is used in a host of renal, hematological and neurological indications (to name a few)

• The likelihood of patients actively receiving TPE to be on multiple oral (or IV) medications is high

• TPE can remove these medications and, as such, can affect their disposition and, by extension, their therapeutic action
Introduction: Question #1

• Most of the literature evaluating drug removal by TPE is comprised of?

1) Case reports of overdose situations
2) Case reports of therapeutic dose situations
3) Phase II pharmacokinetics studies of overdose exposure
4) Phase II pharmacokinetics studies of therapeutic dose exposure
Introduction: Question #1

• Most of the literature evaluating drug removal by TPE is comprised of?

1) Case reports of overdose situations
2) Case reports of therapeutic dose situations
3) Phase II pharmacokinetics studies of overdose exposure
4) Phase II pharmacokinetics studies of therapeutic dose exposure
Introduction

• Of all published reports, approximately 25% are formal pharmacokinetic trials evaluating TPE’s impact on drug disposition

• The majority are case reports (predominately dealing with overdose exposure to medicines)

Drug removal by TPE: state of the literature

1. Variable ganciclovir concentrations in a critically ill patient receiving continuous renal replacement therapy and plasma exchange.
   Nunez-Nunez M, Bellapart J, O'Donoghue S, McWhinney B, Ungerer JP, Lipman J, Roberts JA.
   PMID: 24853257

2. Effect of therapeutic plasma exchange on coagulation parameters in patients on warfarin.
   Zantek ND, Morgan S, Zantek PF, Mair DC, Bowman RJ, Aysola A.
   PMID: 24000079

   PMID: 23296095

   Bastiaans DE, van Uden IW, Ruiterkamp RA, de Jong BA.
   PMID: 23222689
# Drug removal by TPE: state of the literature

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Type of Publication (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Amphotericin</td>
<td>case report (n=1)</td>
<td>overdose</td>
</tr>
<tr>
<td>2013</td>
<td>Dabigatran</td>
<td>?; n=1</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Rituximab</td>
<td>pharmacokinetic study (n=20)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Valproic acid</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Voriconazole</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Ganciclovir</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Warfarin</td>
<td>prospective observational study (n=8)</td>
<td>pharmacodynamic study per se</td>
</tr>
<tr>
<td>2015</td>
<td>Interferon</td>
<td>an open-label, single-center proof of concept study (n=6)</td>
<td>neutralizing antibodies assessed</td>
</tr>
<tr>
<td>2015</td>
<td>Bivalirudin</td>
<td>case report (n=1)</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>cisplatin</td>
<td>case report (n=1)</td>
<td>pediatric</td>
</tr>
<tr>
<td>2017</td>
<td>enoxaparin</td>
<td>Case report (n=1)</td>
<td>pediatric</td>
</tr>
</tbody>
</table>
Plentiful evidence

High-level evidence (more studies than case reports)
Outline

• Introduction

• Drug removal by TPE principles
  – *Time between dose administration and TPE*
  – Relation between the amount removed and biologic effect
  – How to assess the amount removed?

• Future directions
Drug Removal by TPE principles

- In general, drugs are likely to be removed if:
  - Low volume of distribution \((V_d)\) and/or
  - High rate of plasma protein binding

Some have proposed that TPE ability to remove drugs occurs when plasma protein binding of a substance is > 80% and when the \(V_d\) is <0.2 L/kg

Ibrahim RB, Balogun RA. *Semin Dial* 2012 ;25(2):176-89.
Drug Removal by TPE principles:
Not just $V_d$ and protein binding!

**TABLE 1. Important determinants of the effectiveness of TPE in removal of a given drug**

<table>
<thead>
<tr>
<th>Drug dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between dose administration and TPE initiation:</td>
</tr>
<tr>
<td>the higher the drug plasma concentration at the time of TPE, the more likely it will be removed (a function of the drug’s distribution half-life, i.e., $t_{1/2\alpha}$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein binding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>the lower the drug’s protein binding, the less likely it will be removed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume of distribution:</th>
</tr>
</thead>
<tbody>
<tr>
<td>the higher the drug’s volume of distribution, the less likely it will be removed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TPE dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of TPE</td>
</tr>
<tr>
<td>Successive TPE sessions</td>
</tr>
<tr>
<td>Volume of plasma removed</td>
</tr>
<tr>
<td>TPE replacement fluid (equivocal; please see text)</td>
</tr>
</tbody>
</table>

$t_{1/2\alpha} = \text{distribution half-life is the amount of time it takes for half of the drug to be distributed throughout the body}$

Ibrahim RB, Balogun RA. *Semin Dial* 2012;25(2):176-89.
Drug Removal by TPE principles:
Time between dose administration and TPE

- Strong correlation between drug concentration before initiating TPE and the amount removed by the procedure

**Figure 1.** Correlation between amount of cefepime removed (mg) by PE and cefepime plasma concentration (mg/dL) before PE.

Drug Removal by TPE principles:

Time between dose administration and TPE

• This correlation was also observed with:
  – aspirin
  – gentamycin
  – rituximab
  – thyroxine
  – vancomycin
  – valproic acid

• It is unclear if this parameter “trumps” the $V_d$ and protein binding effects but a drug with a small $V_d$ (~0.2L/kg) may be negligibly removed by TPE if given time to fully distribute
Drug Removal by TPE principles:
Time between Dose administration and TPE

- Similar findings were reported with the antibiotic ceftazidime

**Drug Removal by TPE principles:**
Time between dose administration and TPE

<table>
<thead>
<tr>
<th>TABLE 1. Drug Concentration Levels of Valproic Acid in Plasma and Plasmapherate</th>
<th>Total Concentration Valproic Acid (mg/L)</th>
<th>Unbound Concentration Valproic Acid (mg/L) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough level before dosing</td>
<td>43.6</td>
<td>4.7 (10.7%)</td>
</tr>
<tr>
<td>At start of plasmapheresis (3.5 h after dose)</td>
<td>80.1</td>
<td>8.5 (10.6%)</td>
</tr>
<tr>
<td>At end of plasmapheresis</td>
<td>44.2</td>
<td>4.0 (9.0%)</td>
</tr>
<tr>
<td>Plasmapherate (2.85 L)</td>
<td>45.5</td>
<td>4.1 (9.0%)</td>
</tr>
</tbody>
</table>

Immediate release formulation used

- Amphotericin overdose

Drug Removal by TPE principles:
Time between dose administration and TPE

- Drugs with a low $V_d$ (and low protein binding) are likely to be unaffected by TPE if given the time to distribute.

- Scarce published pharmacokinetic analysis with drugs who have a low $V_d$ (and high protein binding).

- While not giving drugs after TPE is customarily adopted, a drug like digoxin can be given immediately before TPE without any meaningful impact on its disposition.

Drug Removal by TPE principles:
Time between dose administration and TPE

Digoxin was eliminated by not more than **1.5%** even immediately after dosing

Question #2

Which drug is likely to be removed the most by TPE? Assume they’re all given 2 hours after TPE.

1) Ceftriaxone (protein binding 96%; 0.1 L/Kg)
2) Cyclosporin (protein binding 90-98% and $V_d$ 13 L/kg)
3) Digoxin (protein binding 25% and $V_d$ 8 L/kg)
4) Vancomycin (protein binding 70% and $V_d$ 0.4 L/kg)
Drug Removal by TPE principles:  
Answer to Question # 2

<table>
<thead>
<tr>
<th>Drug class, drug</th>
<th>PK characteristics: plasma protein binding; ( V_d^a )</th>
<th>TPE exchange</th>
<th>Drug removal</th>
<th>Time from last dose (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>1 g dose (10): 96%; 0.1 l/kg 2–3 g dose: 83%; 0.2 l/kg</td>
<td>Yes; 23–25% of dose (group 1; ( n = 6 ))</td>
<td>No; 5.7–16.6% of 2-g dose</td>
<td>3–15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No; 11.5–16.6% of dose (group 2; ( n = 6 ))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ibrahim RB, Balogun RA. *Semin Dial* 2012;25(2):176-89  
Drug Removal by TPE principles: *Time to distribution might be key*

Not all $V_d$s are equal

Outline

• Introduction

• Drug removal by TPE principles
  — Time between dose administration and TPE
  — **Relation between the amount removed and biologic effect**
  — How to assess the amount removed?

• Future directions
Drug Removal by TPE principles:
Relation between the amount removed and biologic effect

• In a significant number of compounds (e.g., B-blockers), blood levels do not correlate with clinical effects

• By extension, TPE may reduce blood levels of some drugs without altering their biologic effect

• e.g., monoclonal antibodies
Drug Removal by TPE principles: Relation between the amount removed and biologic effect: *Monoclonal Antibodies*

<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Plasma protein binding; $V_d$</th>
<th>Time from TPE</th>
<th>Extracted by TPE; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basiliximab</td>
<td>N/A; 4.8-8 L</td>
<td>&gt; 4 hours</td>
<td>Yes; ~65%</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>N/A; ~6 L</td>
<td>10-14 days</td>
<td>Yes; ~75%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>N/A; 2-5 L</td>
<td>see discussion</td>
<td>Yes – see discussion</td>
</tr>
</tbody>
</table>

Drug Removal by TPE principles: Relation between the amount removed and biologic effect: 

**Monoclonal Antibodies - Natalizumab**

**Figure 1** Effects of plasma exchange on serum concentration of natalizumab and α4-integrin saturation

A) 
- Historic controls (no PLEX; n=17)
- Site #1 (n=6)
- Site #2 (n=6)
- PLEX, Site #1
- PLEX, Site #2

B) 
- Prior to natalizumab

Relation between the amount removed and biologic effect: *Monoclonal Antibodies - Natalizumab*

- No pharmacokinetic analysis

Drug Removal by TPE principles:
Relation between the amount removed and biologic effect:
*Monoclonal Antibodies* - **Rituximab**
Distribution half-life ($t_{1/2\alpha}$)$\sim$1.5-3 days and elimination $t_{1/2}$ of $\sim$ 20 days

<table>
<thead>
<tr>
<th>Publications</th>
<th>Time of rituximab dose from TPE</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald V, et al. <em>J Thromb Haemost</em> 2010;8(6):1201-8</td>
<td>24 hours (?)</td>
<td><strong>Yes; ~70%</strong></td>
</tr>
<tr>
<td>Scully M, et al. <em>Blood</em> 2011;118(7):1746-53</td>
<td>At a minimum 4 hours</td>
<td>CD19+ B-cells depressed; ADAMTS13 activity increased and Anti-ADAMTS13 IgG decreased; appropriate hematologic response to TTP seen</td>
</tr>
<tr>
<td>Puisset F, et al. <em>Br J Clin Pharmacol</em> 2013;76(5):734-40</td>
<td>24-72 hours</td>
<td><strong>Yes; 47% - 54% (mostly with after the first session)</strong></td>
</tr>
</tbody>
</table>
Drug Removal by TPE principles: 
Relation between the amount removed and biologic effect: *Monoclonal Antibodies* - Rituximab

\[ \times \text{dose 1} \quad \times \text{dose 2} \quad \times \text{dose 3} \quad \times \text{dose 4} \]

**TPE**

exposure = or slightly higher than

\[ \times \text{dose 1} \quad \times \text{dose 2} \]

*Weekly intervals

** PK simulation

Drug Removal by TPE principles:

Drug Removal by TPE principles: Relation between the amount removed and biologic effect - Warfarin

- Patients on warfarin (n=8; 121 TPEs)

- Pre-procedure INR influences the post-INR increase

- Similar effect on Factor II and fibrinogen

Drug Removal by TPE principles: 
Relation between the amount removed and biologic effect – IFN-β

Drug Removal by TPE principles:

Check List

- Time between dose administration and TPE
  - distribution half-life \( t_{1/2\alpha} \)

- Plasma protein binding and \( V_d \)

- Relationship between plasma levels (and removed drug) and biologic effect (or pharmacodynamic \( t_{1/2} \) is important)
  - Despite being removed, the biologic effect of some monoclonal antibodies was unaffected.
  - That said, the optimal time cut-off between dose and TPE initiation for each monoclonal antibodies is ill-defined
Drug Removal by TPE principles:

Check List

✓ **Be wary:** pharmacokinetics tenets ($t_{1/2\alpha}$, plasma protein binding and $V_d$) can all change in:

**Overdose Situations**

e.g., ceftriaxone, levothyroxine
Outline

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Drug Removal by TPE principles:

Question # 3

- A patient presents with acute TTP and is slated for TPE. Which pharmacologic treatment can be given with TPE without its pharmacokinetics being affected by the procedure?

1) Drug A (started 4 hours before; $t_{1/2\alpha} = 0.5$ hours)
2) Drug B (started 2 hours before; $t_{1/2\alpha} = 0.5$ hours)
3) Drug C (started 4 hours before; $t_{1/2\alpha} = 24$ hours)
4) Drug D (started 2 hours before; $t_{1/2\alpha} = 24$ hours)
Drug Removal by TPE principles:

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3) Drug C (started 4 hours before; $t_{1/2\alpha} = 24$ hours)
4) Drug D (started 2 hours before; $t_{1/2\alpha} = 24$ hours)
Drug Removal by TPE principles:

Question # 4

• In your view, what is the most objective way to assess TPE influence on drug disposition?

1) calculate drug serum concentration before and after TPE
2) calculate TPE’s drug clearance
3) determine the amount of drug in waste plasma
4) determine TPE’s flow rate
Drug Removal by TPE principles:

Question # 4

• In your view, what is the most objective way to assess TPE influence on drug disposition?

1) calculate drug serum concentration before and after TPE
2) calculate TPE’s drug clearance
3) determine the amount of drug in waste plasma
4) determine TPE’s flow rate
Drug Removal by TPE principles: how to assess the amount removed?

- The “Vancomycin” example

<table>
<thead>
<tr>
<th>Publications type/# of patients</th>
<th>Endpoint</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report (n=1)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Reduction in serum concentration</td>
<td>Yes; ~ 49% reduction</td>
</tr>
<tr>
<td>Case report (n=1)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Reduction in serum concentration</td>
<td>Yes</td>
</tr>
<tr>
<td>Case report (n=1)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Reduction in serum concentration</td>
<td>Yes; ~ 27% reduction</td>
</tr>
<tr>
<td>Case report (n=1)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Reduction in serum concentration</td>
<td>No</td>
</tr>
<tr>
<td>PK trial (n=12)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Total body stores (derived from amount in waste plasma)</td>
<td>No; 6.3% of total body stores</td>
</tr>
</tbody>
</table>

PK=Pharmacokinetic

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Drug Removal by TPE principles: how to assess the amount removed?

- The **Vancomycin** example: explanation

  - The pitfalls of before/after TPE serum concentration evaluation:
    - It does not take into account post-redistribution from tissues
    - Overestimation of removal
Drug Removal by TPE principles: how to assess the amount removed?

- Even if drug clearance is increased on TPE, it does not mean that significant amount of the drug is removed by TPE.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE (y)</th>
<th>GENDER</th>
<th>Scr (mg/dL)</th>
<th>k_e (h⁻¹)</th>
<th>V_d (L)</th>
<th>Cl_Pe (L/h)</th>
<th>Cl_PE (L/h)</th>
<th>Cl_T (L/h)</th>
<th>% INCREASE IN Cl_T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>49.3 ± 19.2</td>
<td>3.2 ± 2.5</td>
<td>0.04 ± 0.03</td>
<td>49.2 ± 16.3</td>
<td>1.9 ± 1.2</td>
<td>1.6 ± 0.4</td>
<td>3.6 ± 1.1</td>
<td>285 ± 191</td>
<td></td>
</tr>
</tbody>
</table>

- Clearance relies on serum concentrations, which decline faster than tissue levels.

An example from the NCAA...sort of

% increase in PPG from 2014-2016:

$\frac{PPG\ (2016)}{PPG\ (2014)} = \frac{0.6}{0.2} \times 100 = 300\%$
Drug Removal by TPE principles: how to assess the amount removed?

- The **Valproic acid** example: 32% cleared by TPE but only 8.6% of total dose removed.

  - **The pitfalls of before/after TPE serum concentration evaluation:**
    - It does not take into account post-redistribution from tissues
    - Overestimation of removal

Drug Removal by TPE principles: how to assess the amount removed?

The pitfalls of before/after TPE serum concentration evaluation:

- The observed drop in serum concentration may not be due to TPE but normal endogenous elimination of the drug (e.g., cyclosporin removal*)

* red cell exchange

Drug Removal by TPE principles:

Other factors

• Concurrent renal failure
  – Observation suggesting a trend to remove more drug when patients with TPE have underlying renal dysfunction

• Replacement fluid
  – Equivocal (FFP and anticoagulants?)

Ibrahim RB, Balogun RA. *Semin Dial* 2012;25(2):176-89.
Introduction: *another case*

- Pediatric patients with pulmonary arterial hypertension awaiting lung transplant
- On Treprostinil (Remodulin®) IV infusion
- TPE scheduled pre-transplant and post-transplant
Future Directions

• Scant data with the following therapeutic apheresis procedures:
  – erythrocytapheresis (exception cyclosporin*)
  – leukapheresis
  – immunoadsorption
  – extracorporeal photopheresis

• Cyclosporin† (and tacrolimus ††) have been shown not to be affected by TPE as their major distributive compartment is mainly erythrocytes, not plasma

Plentiful evidence

High-level evidence (more studies than case reports)

Sound methodology

Future directions
Conclusion

• TPE has the ability to remove drugs

• The extent of the removal is a function of many factors, not the least of which are the drug’s own pharmacokinetics (at normal and overdose conditions)

• By removing the pharmacodynamic target, TPE can influence drug action – independent of the impact on the drug pharmacokinetics
Thank you