Plasmaphoresis/exchange (PLEX) and levetiracetam dosing – are first principles accurate?

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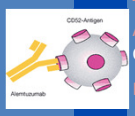
Background: PLEX can remove drugs from plasma however limited guidance on drug dosing is available in literature. This effect can be crucial especially where a correlation exists between serum drug level and biological effect and for drugs which have a narrow therapeutic window.

Objective: Describe effects of PLEX on levetiracetam

Multiple Sclerosis (MS):

Autoimmune disease caused by immune cells attacking the CNS demyelination.



4 types:

- Clinically isolated syndrome
- Relapsing-remitting MS (RRMS)

(active/ not active, worsening or not worsening)

- Primary progressive
- Secondary progressive

Alemtuzumab:

Action: recombinant human monoclonal antibody. Binds to CD52 antigen on surface of B and T lymphocytes

Indications: Active RRMS, CLL

Side effects: Autoimmune disorders (thyroid dysfunction, immune TTP, nephropathies: can occur up to 5 years post dosing); Infusion related reactions; Lymphopenia (Exacerbated if JC virus antibody status +); Liver dysfunction

Monitoring: FBC + WCC diff; UEC (monthly); TFT (prior + every 3 months until 48 months post last dose and prn); skin cancers (prior and during treatment)

Definitions:

Apheresis: The process of removing a specific component from blood temporarily.

Plasmaphoresis: Method removing blood plasma, separating it from cells, transfusing the cells back into patient. Used to remove antibodies in treating autoimmune conditions.

Plasma exchange: (PLEX): Duration: 2-3 hours

Removal of plasma from withdrawn blood (plasmapheresis) AND re-transfusion (RBC, WBC, Plt) and type-specific fresh-frozen plasma back into the donor; albumin, FFP commonly used.

PLEX removes antibodies located in plasma. Used to treat: MS, Myasthenia gravis, TTP, Polyneuropathies eg. Acute inflammatory demyelinating polyneuropathy = Guillian Barre Syndrome.

Clinical Features

Presentation:

24-year-old Caucasian female

- multiple sclerosis (MS) treated with alemtuzumab, last dosed 7/12 previous.
- Other Rx: thyroxine 100mcg daily carbamazepine 100mg bd (recently commenced)
- New onset focal seizures characterised by neck and tongue twitching
- Resulted in referral to ED and progression to two tonic-clonic seizures.
- Provisional differential diagnoses were partial status epilepticus and alemtuzumab-associated immune reconstitution.

Past medical history:

JC virus serology positive May 2014

MS Dx 2014

- Rx: alemtuzumab (Lemtrada ®)
  - Aug 2016(x5), 2017(x3)

Related complications:

- Idiopathic thrombocytopenia (ITP) - resolved
- Hypothyroidism with a normal T4
  - Ab positive
  - Rx. Thyroxine
- Immunosuppression

Bloods on admission:

- Carbamazepine = 4.6 (25/4/18 @ 11:00) not trough (NR=5-10)
- Ser cr remained stably low throughout (range: 32-48 umol/L)

Case Progress:

25 day admission included prolonged ICU stay: invasive ventilation and deep sedation, refractory seizures occurred.

Workup included:

- Unremarkable: lumbar puncture (negative cultures and limbic encephalitis screen) and brain biopsy.
- Remarkable EEG (epileptiform activity), MRI (new, progressing lesions).

Diagnosis:
Alemtuzumab-associated autoimmune encephalitis was suspected.

Drug	valproate		carbamazepine		levetiracetam	
NR (mg/L)	50-100		5-10		12-46	
Dosing frequency	BD		TDS		BD	
PLEX No.	1.	2.	1.	2.	1.	2.
PLEX duration	2hr 25min	1 hr 45min				
Baseline trough	23	↑dose	6.7	-	6	-
Post PLEX	55	49	5.7	6.1	4	3
Post PLEX trough	40 (not trough)	42	3.8	5.2	5*	10*

Table 1: Drug levels at baseline, post-PLEX and trough

Interventions - Management included:

- Aciclovir 10mg/kg tds iv (initially)
- Multiple antiepileptics with up titration:
  Levetiracetam iv load 1g then 500mg bd iv
  Clonazepam 0.5mg bd po
  Carbamazepine CR 200mg bd
  Phenytoin 15mg/kg iv load then 300mg daily iv
  Sod. valproate 1.5g bd iv
  Gabapentin 300mg bd po
- Midazolam and Propofol infusions
- 3% saline infusions - Low Na^+ (128)
  - ? 2^0 to carbamazepine
- IV methylprednisolone 1g 5/7 with ongoing prednisolone orally
- IV immunoglobulin 5/7
- x5 PLEX courses.

Case Progress:

Prior to PLEX the ICU pharmacist investigated its potential effects on antiepileptic drug levels.
Literature recommendations are limited.
Pharmacokinetic characteristics of drugs likely to be removed:
high protein binding (PB)(>80%)
and/or Vd<0.2L/kg.

Literature suggested:

- carbamazepine/ valproate not removed

Others are based on first principles:

- levetiracetam
  - low PB, Vd=0.5-0.7L/kg, removal unlikely
- gabapentin
  - low PB, Vd=0.8L/kg, removal unlikely
- clonazepam (can be given PRN).

Baseline, post-PLEX and trough levels were taken, following pharmacist advice. (Table 1.)

- Levels showed neither agent dramatically removed – as predicted
- *? Due to redistribution
- Levetiracetam levels were low throughout. Reporting delays prevented level-related dosage adjustment.

Outcomes:

- Patient recovered well and was discharged to the ward for ongoing seizure monitoring.
- CSF studies were negative for antibodies
- Discharged home
  - Multiple antiepileptics - weaned
  - Follow-up with Neurology, EEG
  - Approved for 3 then 6 months IVIG
  - Subsequently to be treated with Ocrelizumab

Discussion:

New literature messages: Removal is LESS if:

- PLEX done after tmax, ie. minimises concentration in plasma for removal.
- Drug shorter t1/2 (<2hours), ie less time in plasma.
  - Decline in level may be due to PK not PLEX.
- Drug allowed to distribute fully, ie less concentration in plasma.
  - This can be > Vd/PB contribution and then not be removed.
  - Time to complete distribution complicated by "elimination organ" dysfunction eg acute kidney injury

Caution:

- Ensure to sample long enough after PLEX to show post-PLEX redistribution from extravascular tissue back into plasma otherwise over est. PLEX removal.
  Eg carbamazepine and phenytoin are not removed.
- Correlation: serum drug level and biological effect must exist otherwise clinical effect of PLEX on drug NOT important.

BUT it is much more than PB and Vd = "imperfect proxies"
→ Drug dependent and clinical factors
→ 2017 Review: 60 peer reviewed articles mainly case reports, no RCT
→ Dose after PLEX if possible
→ Calculating waste plasma levels are most reliable indicator of removal by PLEX

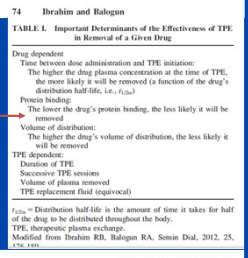

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TABLE I. Important Determinants of the Effectiveness of TPE in Removal of a Given Drug

Drug dependent
Time between dose administration and TPE initiation:
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., $t_{1/2\alpha}$)
Protein binding:
The lower the drug's protein binding, the less likely it will be removed
Volume of distribution:
The higher the drug's volume of distribution, the less likely it will be removed
TPE dependent:
Duration of TPE
Successive TPE sessions
Volume of plasma removed
TPE replacement fluid (equivocal)

$t_{1/2\alpha}$ = Distribution half-life is the amount of time it takes for half of the drug to be distributed throughout the body.
TPE, therapeutic plasma exchange.
Modified from Ibrahim RB, Balogun RA. Semin Dial. 2012, 25, 170–180.

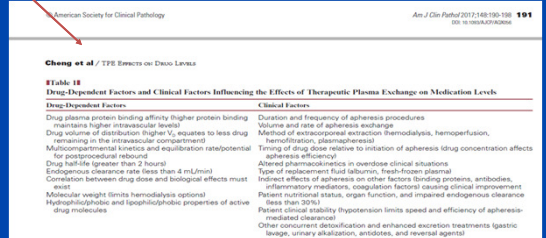
The American Society for Clinical Pathology — Am J Clin Pathol 2017;148:190-198 191

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Table 18
Drug-Dependent Factors and Clinical Factors Influencing the Effects of Therapeutic Plasma Exchange on Medication Levels

Drug-Dependent Factors	Clinical Factors
Drug plasma protein binding affinity (higher protein binding maintains higher intravascular levels)	Duration and frequency of apheresis procedures
Drug volume of distribution (higher V_d equates to less drug remaining in the intravascular compartment)	Volume and rate of apheresis exchange
Multicompartmental kinetics and equilibration rate/potential for postprocedural rebound	Method of extracorporeal extraction (hemodialysis, hemoperfusion, hemofiltration, plasmapheresis)
Drug half-life (greater than 2 hours)	Timing of drug dose relative to initiation of apheresis (drug concentration affects apheresis efficiency)
Endogenous clearance rate (less than 4 mL/min)	Altered pharmacokinetics in overdose clinical situations
Correlation between drug dose and biological effects must exist	Type of replacement fluid (albumin, fresh-frozen plasma)
Molecular weight (limits hemodialysis options)	Indirect effects of apheresis on other factors (binding proteins, antibodies, inflammatory mediators, coagulation factors) causing clinical improvement
Hydrophilic/phobic and lipophilic/phobic properties of active drug molecules	Patient nutritional status, organ function, and impaired endogenous clearance (less than 30%)
	Patient clinical stability (hypotension limits speed and efficiency of apheresis-mediated clearance)
	Other concurrent detoxification and enhanced excretion treatments (gastric lavage, urinary alkalization, antidotes, and reversal agents)

Drug	PB %	Vd L/kg	tmax	t1/2 (hour)	Cleared
Valproate iv	80-95	0.1-0.4	7.3-10 min	8-12	metab
Levetiracetam po	<10	0.5-0.7	iv ? Po = 1hr	7-8	renal
carbamazepine	70-80	0.8-1.9	12 hr	16-24 Less with phenytoin	metab
gabapentin	<3	58L = 0.8 (70kg)	2 hr	5-7	renal

Table 2: Antiepileptic PK

Conclusion:

First principles appear useful in guiding levetiracetam dosing recommendations for PLEX, no dramatic removal. Ideally monitor levels when seizure control is crucial. Reduced reporting times would enhance clinical relevance.

Future work will explore waste plasma levels post PLEX.