A mathematical model of protein-bound uremic toxin kinetics during hemodialysis and effect of toxin displacement

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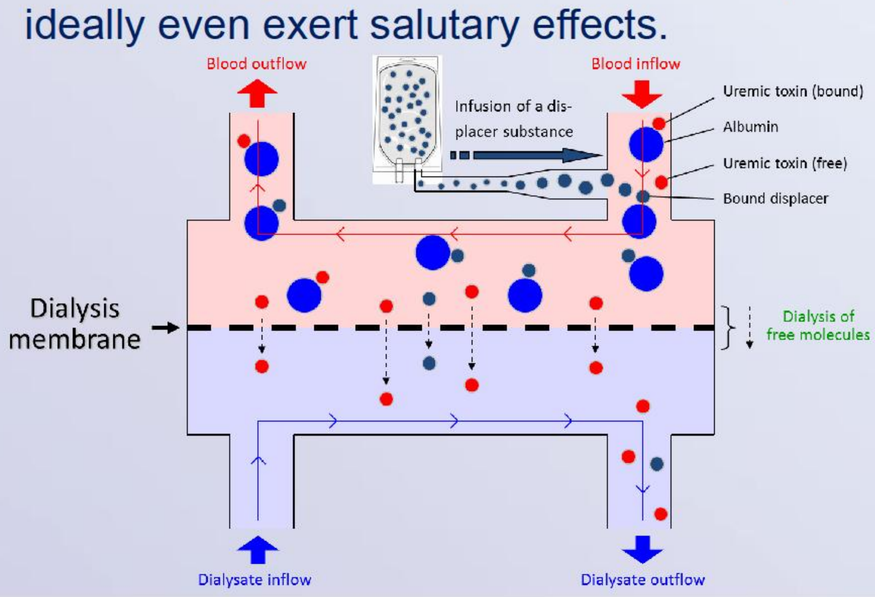
Background

- Protein-bound uremic toxins (PBUTs) exert numerous deleterious effects in Hemodialysis (HD) patients [1].
  - × Inflammation and oxidative stress
  - × Cardiomyopathy
  - × Cognitive dysfunction …
- PBUT removal is severely limited in conventional HD or in convection based Hemodiafiltration (HDF).
  - High binding affinity towards plasma proteins (primarily albumin): 90-98% for the prototypical PBUTs indoxyl sulfate and p-cresyl sulfate.
  - Consequently, the free fraction of these PBUTs (which determines the diffusion gradient as well as the convective removal) is low.

Concept

- Infuse binding competitors (*displacer*) in the arterial blood line [2]. (Concept has been successfully validated *in vitro* [3].) Displacer should,
  - ✓ Exhibit higher affinity towards albumin binding site(s) where toxins bind.
  - ✓ Be metabolized/eliminated without need for dialysis.
  - ✓ Not exert any deleterious effects on the patient, and ideally even exert salutary effects.



Materials and Methods

- We developed a comprehensive mathematical model describing PBUT kinetics during HD, covering the kinetics in the patient (3-compartments: plasma, interstitial, intracellular), between displacer infusion site and dialyzer, and in the dialyzer.
- The model was then used to quantify the effect of displacer infusion on dialytic PBUT removal during simulated 4-hr HD treatments (Q_p: 250 mL/min; initial total IS conc.: 100 µmol/L; albumin conc.: 4 g/dL; ibuprofen half-life: 2 hrs; Q_{uf}: 750 mL/hr; Optiflux dialyzer with fiber length 23 cm, fiber radius 90 µm, 12,000 fibers; displacer infusion site 50 cm upstream of dialyzer)
- For the PBUT, we chose indoxyl sulfate (IS), a prototypical PBUT with a free fraction of approx. 8% in human plasma. As a displacer substance, we chose ibuprofen, which is commercially available for i.v. infusion and binds to the same primary binding site on albumin as IS (Sudlow site II), but with a markedly higher association constant (1.76×10^5 M^{-1} vs. 2.3×10^4 M^{-1}) [4].

References

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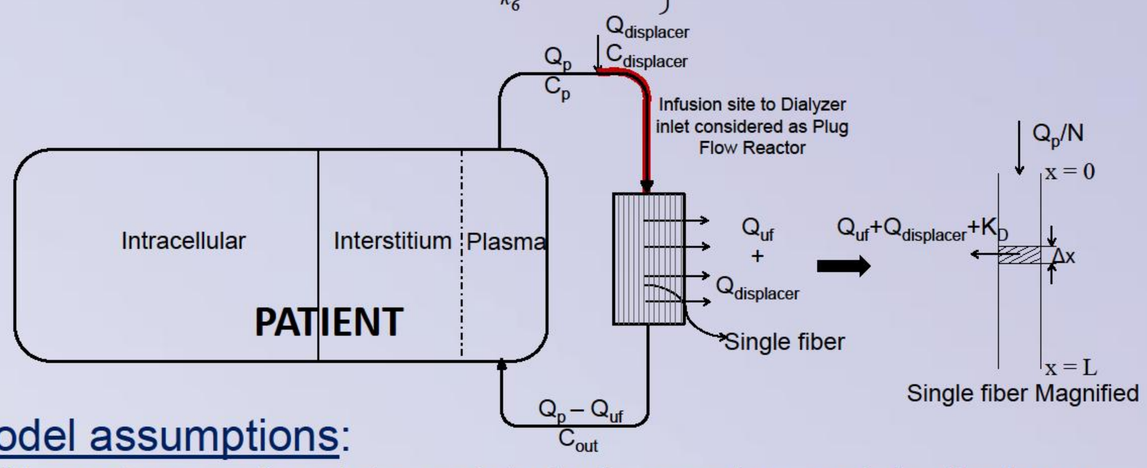
Mathematical Model

- Multi-compartment patient model
- Dialyzer model to show spatiotemporal change in toxin concentration

$$P + T \underset{k_4}{\overset{k_3}{\rightleftharpoons}} PT$$
$$P + D \underset{k_6}{\overset{k_5}{\rightleftharpoons}} PD$$

Law of mass action kinetics



Model assumptions:

- No exchange of protein, protein-toxin complex, protein-displacer complex between plasma and interstitial compartment.
- Blood flow distribution in each fiber is uniform. All fibers perform identically.

Model parameters:

Parameter	Definition	Value
$K_{A,toxin}$	Albumin-IS association constant	2.26×10^4 M^{-1}
$K_{A,displacer}$	Albumin-Ibuprofen association constant	1.76×10^5 M^{-1}
D_{in}	Ibuprofen conc. in constant infusion (800 mg/200 mL) → FDA approved limit	0.0194 M
$K_{ip,T}$; $K_{ip,D}$	Plasma-interstitium mass transfer coefficient for free toxin and free displacer, resp.	2000 mL/min
$K_{D,T}$; $K_{D,D}$	Dialyzer clearance of free toxin and free displacer, resp.	150 mL/min
k_3 ; k_5	Forward rate constant for protein-toxin and protein-displacer interaction, resp.	10^6 $M^{-1}min^{-1}$

Results

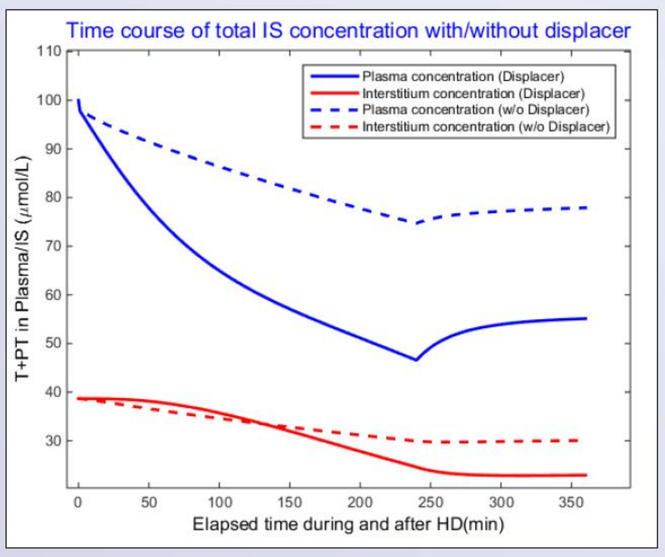


Figure depicts total IS concentration time course during 4 hrs of HD and 2 hrs of rebound after HD. Table compares IS reduction ratio (RR) and total dialytic IS removal with and without displacer infusion.

$$RR = \left(1 - \frac{(T+PT)_{240}}{(T+PT)_0}\right) \times 100$$

$$\text{Whole body total IS amount } (IS_{total}) = (T+PT)_{pl} V_{pl} + (T+PT)_{is} V_{is}$$

$$\text{Dialytic Removal} = IS_{total}\big|_{t=0} - IS_{total}\big|_{t=240}$$

Measure	w/o Displacer	With Displacer
Reduction Ratio	33.8% [5]	53.5%
Dialytic removal	437 µmoles	486 µmoles

11.3% improvement in dialytic removal

Conclusions

- Our *in silico* simulation reveals a significant improvement of approx. 11% in total IS removal during a single dialysis session with displacer infusion, which may potentially translate into improved patient outcomes.
- Our model provides insights into the complex kinetics of PBUTs during dialysis and allows quantification of PBUT removal with various displacer substances and infusion profiles. This may serve as a foundation for the development of clinical studies aimed at validating the PBUT displacement concept *in vivo*.

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