Improving dialytic removal of protein-bound uremic toxins using binding competitors: An *in silico* long term kinetic study

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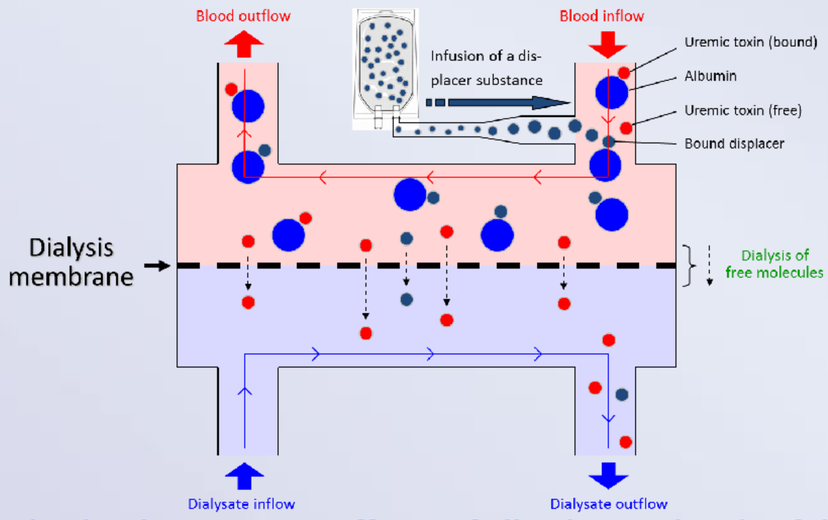
BACKGROUND

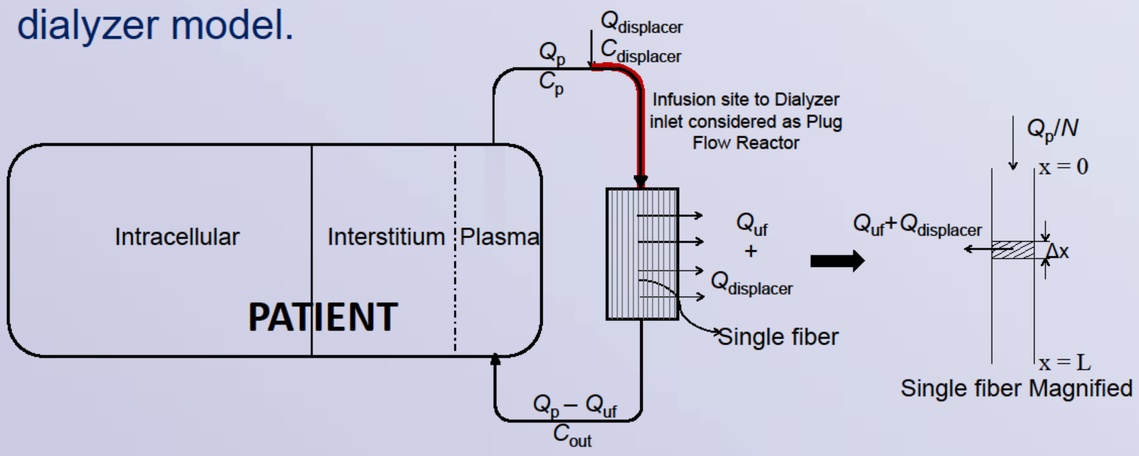
- Protein-bound uremic toxins (PBUTs) are recognized for a myriad of deleterious effects in HD patients and as potential contributors towards mortality due to,[1]
  - × Cardiomyopathy
  - × Cognitive dysfunction
  - × Inflammation and oxidative stress
- PBUT removal is severely limited due to strong protein-binding.
  - 90-98% bound for the prototypical PBUTs indoxyl sulfate and p-cresyl sulfate. This results in a low free fraction of these PBUTs (which determines the diffusion gradient).
- Improving the free fraction using binding competitors (displacers) has improved the *ex vivo* dialytic removal of indoxyl sulfate (IS) by ~300%.[2]



- What is the long-term effect of displacer *in vivo*? We explored this using mathematical model.

METHODS

- We developed a novel mathematical model describing PBUT kinetics during HD. The model comprises a patient model, a dialyzer tubing model where the displacer is infused, and a dialyzer model.



- We first tested the model output in a conventional HD setting and confirmed the model reliability based on correct estimation of reduction ratio and total removal.

$$P + T \underset{k_2}{\overset{k_1}{\rightleftharpoons}} PT$$

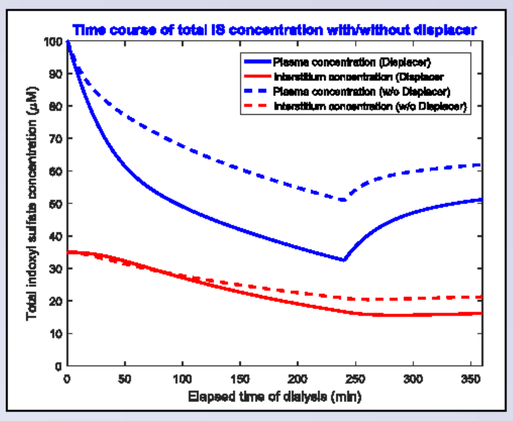
$$P + D \underset{k_4}{\overset{k_3}{\rightleftharpoons}} PD$$

Separation is based on competitive binding between PBUT and displacer (governed by law of mass action kinetics)

- The model was then used along with displacer infusion and accounting for competitive binding. We simulated 4-hr HD treatments: Q_p 250 mL/min, Q_d 500 mL/min, initial total IS conc. 100 µmol/L, albumin conc. 4 g/dL, ultrafiltration volume 2.4L, ibuprofen elimination half-life 2 hrs, and Optiflux F180NR dialyzer with fiber length 23 cm, fiber inner radius 105 µm, and 12300 fibers.
- We chose IS with a free fraction of 8% in human plasma. Ibuprofen was chosen as test displacer substance, 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 equilibrium association constant (1.76×10^5 M^{-1} vs. 2.26×10^4 M^{-1}) [3].

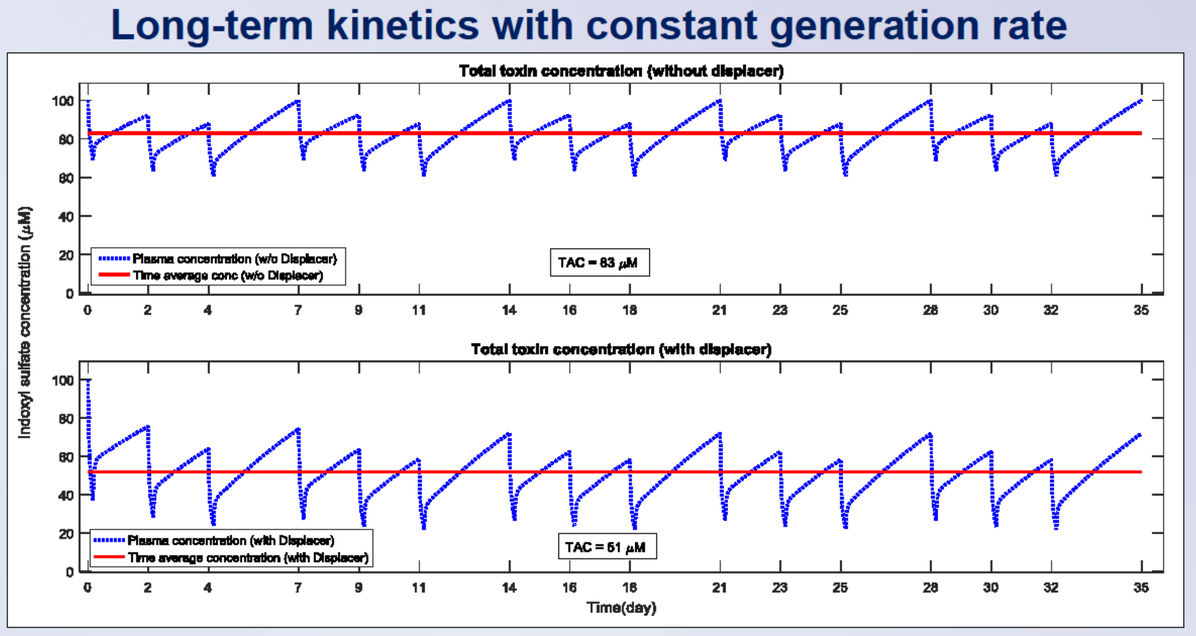
RESULTS

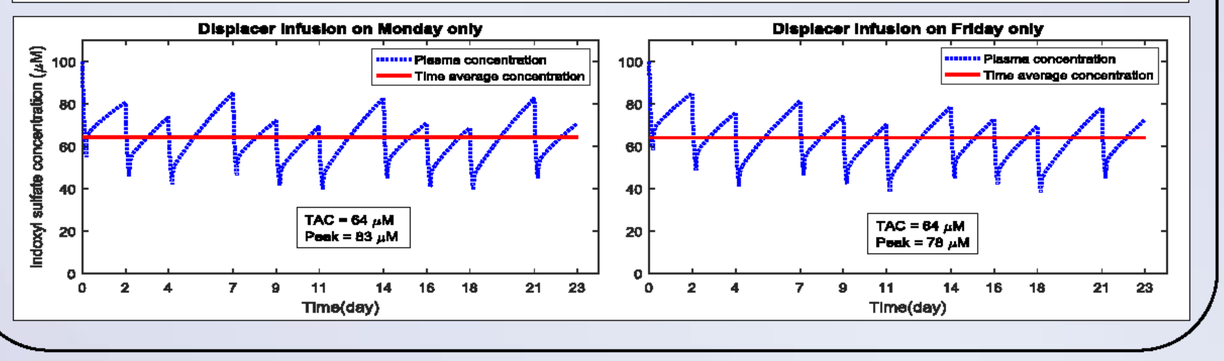
Parameter	Definition	Value
$K_{A,toxin}$	Albumin-IS equilibrium association constant	2.26×10^4 M^{-1}
$K_{A,displacer}$	Albumin-Ibuprofen eqbm. association constant	1.76×10^5 M^{-1}
D_{in}	Ibuprofen conc. in constant infusion (800 mg/200 mL saline) → FDA approved limit	0.0194 M
$K_{ip,T}$; $K_{ip,D}$	Free toxin/displacer mass transfer coefficient between interstitium and intracellular space	1500 mL/min
$K_{ie,T}$	Free toxin mass transfer coefficient between interstitium and intracellular space	300 mL/min
$KoA_{T/D}$	Membrane mass transfer coefficient for toxin and displacer	700 mL/min
k_1 ; k_3	Association constant for protein-toxin and protein-displacer interaction, resp.	3.7×10^5 $M^{-1}min^{-1}$



Measure	w/o Displacer	With Displacer
Reduction Ratio	42%	63%
Removal (µmoles)	402	484

Long-term kinetics with constant generation rate





CONCLUSIONS

- Binding competitors can significantly improve the removal of strongly bound PBUTs.
- Our *in silico* simulations suggest a significant improvement of ~20% in total IS removal during a single dialysis session with displacer infusion.
- Long term displacer infusion reduces the time-averaged concentration (TAC) from 83 µM in without displacer scenario to 51 µM in with displacer (~39% drop), and free concentration from 5.2 to 3.2 µM (~60% drop).
- Displacer infusions Monday vs. Friday are quantitatively similar, but latter is preferable in a clinical scenario, as it reduces peak concentrations. Such insights can only be obtained via a modeling approach. Single session displacer use results in ~23% drop in TAC.

References

1. Sirich, T.L., et al. Protein-bound molecules: a large family with a bad character. Semin Nephro 2014.
2. Tao, X., et al., Improved dialytic removal of protein-bound uraemic toxins with use of albumin binding competitors: an in vitro human whole blood study. Sci Rep, 2016. 6.
3. Lin, J.H *et al.*, Protein binding as a primary determinant of the clinical pharmacokinetic properties of non-steroidal anti-inflammatory drugs Clin Pharmacokinet, 1987, 12(6): p. 402-432.

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