Conceptual evaluation of urea rebound in pediatric hemodialysis patients by a physiology-based pharmacokinetic simulation study

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Introduction

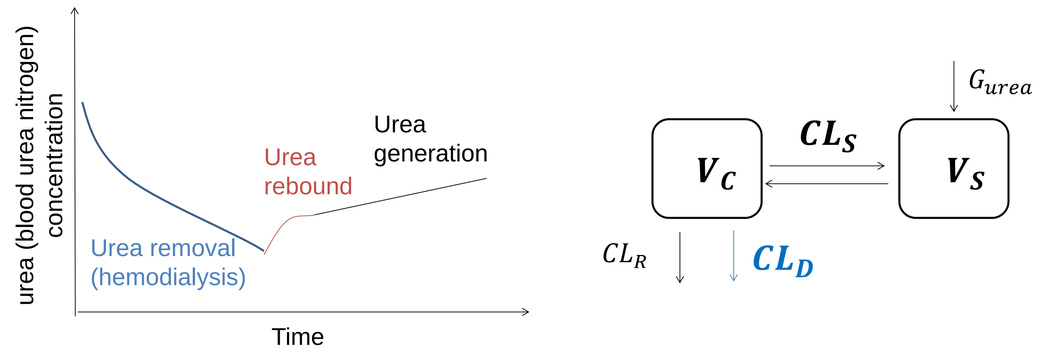
- Pediatric hemodialysis (HD) and monitoring strategies are mainly derived from adult studies, based on pre- and post-HD urea plasma concentrations.
- Accuracy of such HD evaluation approach depends on extent and duration of post-HD urea rebound.
- Rebound occurs due to redistribution of urea from slowly perfused (peripheral) to quickly perfused (central) body compartments.

Methods

1. Realistic typical (median) demographics and pediatric HD prescription parameters were calculated over weight-bands of 5 kg from a large registry (DaVita) with ≥20 patients and >130 HD sessions per weight-band.
2. Physiology-based kinetic changes in pediatrics (age-, weight, and gender-dependency of total body water[3,4], cardiac output[5], and fraction of skeletal muscle mass[6]) were used to scale published urea kinetic data[1,2] to those typical pediatric patients.
3. Typical urea concentration-time profiles during and after HD sessions were simulated for each weight band and time to regaining 95% of equilibrium between central and peripheral urea concentration after HD sessions was calculated.

Objective

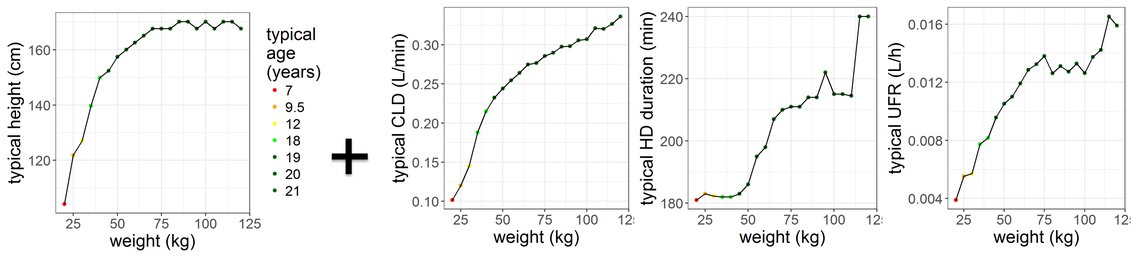
- **To predict urea rebound in paediatric HD patients,** using a physiology-based scaling approach of an urea kinetic model previously developed for adults[1,2].



Schematic illustration of urea rebound (*left*) **and the applied urea kinetic model** (*right*). The rebound is a result of the balance between the intensity of dialysis (**CL_D**, dialysis clearance of urea) and physiology-determined kinetic parameters (mainly **CL_S**: inter-compartmental clearance between slowly equilibrating compartments, but also **V_C**: central distribution volume, representing mainly splachnic tissues (organs in the abdominal cavity) and **V_S**: peripheral slowly perfused distribution volume, representing mainly somatic tissues (muscle, bone, fat)).
CL_R: residual renal urea clearance (absent in the majority of patients), **G_{urea}**: urea generation rate from protein catabolism (not influential shortly after dialysis) were ignored for simplicity in model simulations.

Results

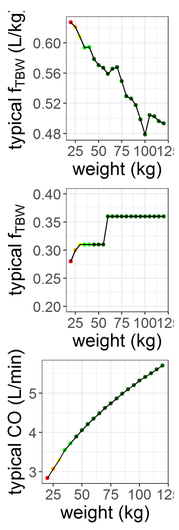
1. «Typical» pediatric patient demographics & hemodialysis prescription



Typical (median) patient demo-graphics per weight band.

Typical (median) hemodialysis (HD) prescription in pediatric patients per weight bands. **CL_D**: dialysis clearance of urea (calculated from Kt/V; mechanistic clearance according to Michaels 1966 underpredicted actual CL_D in low-weight patients). **UFR**: ultrafiltration rate.

2. Predicted physiology & change of kinetic parameters



(1) V_{tot} equals total body water (TBW):
f_{TBW}: fraction of TBW in L/kg). Weight: post-dialysis weight. $V_{tot} = V_S + V_C$.

$$V_{tot} = TBW, \quad with\ TBW = f_{TBW} \cdot weight$$

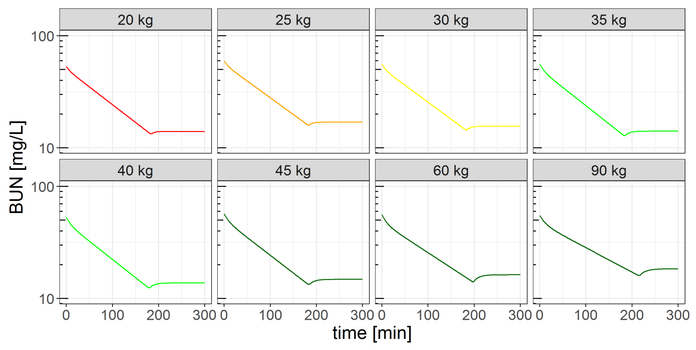
(2) V_S is proportional to the fraction skeletal muscle mass (f_{SMM}):
$f_{SMM,adult}$: reference value estimated in adults.
$f_{Vs,adult}$: fraction of V_S estimated in adults.

$$V_S = \frac{f_{SMM}}{f_{SMM,adult}} \cdot f_{Vs,adult} \cdot V_{tot}$$

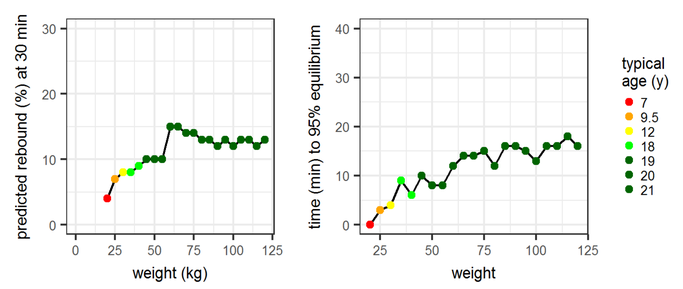
(3) CL_S depends on cardiac output (CO):
f_S: fraction of flow to slowly perfused tissues.
PS: Cappilary permeability-coefficient surface area product for urea.

$$CL_S = Q_S \cdot e^{\left(-PS/Q_S\right)}, \quad with\ Q_S = CO \cdot f_S$$

3. Simulated urea kinetics and rebound



Simulated typical concentration-time profiles of blood urea nitrogen (BUN) during and after typical HD sessions for each weight band.



Predicted typical urea rebound after typical HD sessions for each weight band.

Conclusions

- Urea kinetic simulations taking into account pediatric HD prescription parameters and physiology suggest that **time to equilibrium is *shorter* in pediatric** than in adult patients.
- Results can be utilized to design optimal sampling in urea kinetic studies in pediatric HD patients and to verify this finding.

References

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