Monte Carlo Simulation to Determine Imipenem Dosing in Critically ill Patients Receiving Five Kidney Replacement Therapy Regimens

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Abstract

Introduction: The Tablo Hemodialysis System offers a range of kidney replacement therapy (KRT) options for critically ill patients with AKI. The use of a variety of dialysate flow rate, treatment duration & frequencies may clear drugs like imipenem differently than conventional devices. The purpose of this Monte Carlo Simulation (MCS) was to develop imipenem doses likely to attain therapeutic targets for a variety of KRT treatment combinations.

Methods: One compartment, pharmacokinetic models were developed using pertinent demographic data and pharmacokinetic parameters to predict imipenem exposure in 5,000 virtual anuric patients receiving 5 different KRT regimens. Imipenem dosing using 30-minute infusions were simulated to assess the probability of target attainment (PTA)(Table 1). Imipenem is co-formulated with cilastatin, but only imipenem was simulated. Usual and aggressive pharmacodynamic (PD) targets chosen were ≥40% free plasma concentrations above 1X or 4X the minimum inhibitory concentration (>40% fT >MIC or >40% fT>4xMIC) with the breakpoint MIC of 2 mg/L for *Pseudomonas aeruginosa*. Additionally, the potential risk of neurotoxicity was assessed using an accepted safety threshold (fT >MICx8). The smallest doses attaining PTA≥90% during 1-week of therapy were considered optimal.

Results: Imipenem doses attaining the two different efficacy targets in the 5 KRT settings are shown in the Table. Optimal doses attaining the aggressive efficacy (>40% fT>4xMIC) yielded total trough drug concentrations exceeding the safety threshold in many patients.

Conclusion: Standard imipenem dosing (500 mg Q8-12 hrs) attains usual PD targets for all KRT regimens, including sequential therapy (setting 3). More aggressive PD targets will require higher imipenem doses. These higher doses increase the possibility of imipenem neurotoxicity but were usually below the safety threshold used. These findings need clinical validation.

Introduction

The Tablo Hemodialysis System (Tablo) offers a range of kidney replacement therapy (KRT) options for critically ill patients with AKI. The use of the wide variety of dialysate flow rate and treatment duration & frequencies that are available may clear drugs like imipenem differently than conventional devices. Clinicians need antibiotic dosing recommendations for these new KRT flow rates to ensure that efficacious, non-toxic treatment can be given.
Monte Carlo Simulation (MCS) can be used in the absence of clinical pharmacokinetic trials to develop dosing schemes. The purpose of this MCS was to develop imipenem doses likely to attain therapeutic targets for a variety of KRT treatment combinations on Tablo.

Methods and Materials

- One compartment, 1st-order PK models were developed using demographics from a large KRT trial (Bagshaw 2020) & published imipenem PK parameters to predict one week of imipenem exposure in 5,000 virtual patients (>40 kg & anuric) receiving 5 different KRT regimens.
- Imipenem extraction coefficients [EC: SA or SC] were determined from all published imipenem studies using KRT. Transmembrane clearance (CL) from Tablo KRT was estimated using EC and effluent flow rates [Qeff: Qd or Quf] as follows: CL = EC x Qeff.
- Usual and aggressive pharmacodynamic (PD) targets chosen were ≥40% free plasma concentrations above 1X or 4X the minimum inhibitory concentration (>40% fT >MIC or >40% fT>4xMIC) with the breakpoint MIC of 2 mg/L for *P. aeruginosa*.
- The smallest doses attaining targets in ≥90% of subjects during 1-week of therapy were considered optimal.
- The safety of each dose was assessed by examining the frequency of trough free imipenem plasma concentrations exceeding > 8 times the MIC (fT >MICx8).
- Only imipenem concentrations (and not cilastatin) were considered in this MCS.

Body Weight and Pharmacokinetic Parameters Used

Body weight (kg)	88 ± 26 [40-177]
Vd (L/kg)	0.36 ± 0.15 {0.11-0.75]
Non-renal CL (ml/min)	89.2±31.9 [27.1-160.0]
Unbound fraction of drug	0.8 ± 0.16 [0-1]
Extraction coefficient	Qd 300 ml/min: SA = 0.34 ± 0.07 [0-1] Qd 100 ml/min: SA= 0.63± 0.12 [0-1] Qd 50 ml/min: SA = 0.82 ± 0.16 [0-1] Quf 5 ml/min: SC = 0.82 ± 0.16 [0-1]

Qd: dialysate flow rate; Quf: ultrafiltrate flow rate; SA: saturation coefficient; SC: sieving coefficient

Results - Sample Model 3 (Sequential Therapy)

Probability of Target Attainment (PTA) in 5000 Virtual Patients with Each Imipenem Dosing Regimen

Imipenem Dose	MIC (mg/L)	PTA (%) of 1-week		PTA (%) of Each Day						
		40% fT > MIC	100% fT > MIC	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
500 mg q12h post-HD	2	96.5	11.8	96.4	96.5	96.5	96.5	96.5	96.5	96.5
	8	11.2	0	7.1	11.2	11.6	11.6	11.6	11.6	11.6
750 mg q8h post-HD	2	99.9	54.4	99.9	99.9	99.9	99.9	99.9	99.9	99.9
	8	90.2	1.9	86.8	90.2	90.3	90.3	90.3	90.3	90.5
1g Loading Dose, 750 mg q8h post-HD	2	99.9	56.4	99.9	99.9	99.9	99.9	99.9	99.9	99.9
	8	90.5	4.2	90.7	90.4	90.4	90.4	90.4	90.4	90.4

The dose in yellow or green is the smallest imipenem dosing regimen attaining PD targets of [>40% fT>MIC] and >40% [fT>4xMIC] respectively

Dosing Recommendation Results

	Type	Effluent Flow Rate	Duration	Frequency	Optimal Imipenem Dose [Less Aggressive PD Target]	Preferred Optimal Imipenem Dose [More Aggressive PD Target]
1	HD	Qd 300 ml/min	4 hours	M-W-F	500 mg q12h post-HD	750 mg q8h post-HD
2	HD	Qd 300 ml/min	4 hours	Daily		
3	Sequential HD & UF	Qd 300 ml/min Quf 5 ml/min	HD 4 hours, then UF 20 hours	Daily		750 mg q8h post-HD or 1g LD, 750 mg q8h post-HD
4	PIKRT	Qd 100 ml/min	9 hours	Daily	500 mg q12h	1g q8h
5	Extended Therapy	Qd 50 ml/min	24 hours	Daily	500 mg q8h	750 mg q6h

Discussion & Conclusions

- MCS analysis predicted that alterations in KRT parameters will necessitate different imipenem doses to attain efficacy targets, but recommended doses for thrice weekly HD, daily HD, and sequential HD and UF were all the same.
- Imipenem has a substantially higher non-renal clearance in AKI than in ESKD. (Mueller BA, Pharmacotherapy 1991) AKI was modeled in this MCS. Patients with ESKD receiving Tablo would require lower doses than what appears in the table above.
- Toxicity was assessed using a trough free imipenem plasma concentrations exceeding > 8 times the MIC (fT >MICx8). Less than 12% of virtual patients receiving the recommended regimens exceeded this threshold in KRT settings 1 and 4..
- None of the simulated imipenem dosing regimens were optimal for a PD target of 100% fT >MIC.
- For patients with increased risk of neurotoxicity, optimal dose attaining less aggressive PD target or alternative antibiotic therapy may be considered.
- Therapeutic drug monitoring of imipenem would be valuable if available.
- These findings require clinical validation.

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