Integration of Continuous Renal Replacement Therapy in a Meropenem Population Pharmacokinetics Model in Critically Ill Children

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KEYWORDS pediatric drug therapy, population pharmacokinetics

In a recent issue of Antimicrobial Agents and Chemotherapy, Saito et al. (1) published an interesting meropenem population pharmacokinetics (PK) model in 34 critically ill children. In addition to body weight, they succeeded to integrate the following relevant covariates with respect to critical illness status: estimated glomerular filtration rate (GFR), systemic inflammatory response syndrome, and continuous renal replacement therapy (CRRT) (1). However, we believe that the implementation of CRRT on PK parameters should be discussed.

In the publication, CRRT influenced the central volume of distribution (V_c) with an increase of 66%. This large percentage might need to be qualified and detailed. First, it is likely that the circuit of extracorporeal membrane oxygenation (ECMO) might contribute to this increase. The authors indicate that the lack of patients impedes the implementation of ECMO on PK parameters. However, it should be emphasized that the ECMO is probably already included along with the CRRT covariate. Moreover, patients with extracorporeal circuits often experience a large fluid overload, and other covariates could be a surrogate of CRRT, such as ascites or edema. Finally, we believe that the adsorption in the extracorporeal circuit might increase artificially the V_c . Although the authors mentioned that there is no loss of meropenem in the CRRT circuit, the stated reference showed that there was an adsorption of 9% (2). This amount is yet significant for critically ill children for which an increase of dose is recommended. Other studies have shown this expected impact of CRRT on meropenem, since this is a hydrophilic small molecule (molecular weight of 383 g/mol) with very low protein binding (2%) (3).

Unfortunately, Saito et al. could not demonstrate the effect of CRRT on clearance (CL) due to the small sample size, despite high dialysate and filtrate flow rates. In recent *ex vivo* studies, both the high dialysate and filtrate flow rates influenced the meropenem elimination (2, 3). CRRT has already been included in a meropenem population PK model in critically ill children but without reflecting the values of the flow rates (4).

To conclude, we acknowledge the contribution of Saito et al. to the understanding of the specificity of the PK of meropenem in critically ill children. Developing population PK models in pediatric intensive care units is mandatory given the high between-subject variability in the PK parameters, especially for the patients undergoing extracorporeal therapies. Standard dosing regimens do not consider all of the covariates and might lead to a risk of inadequate exposure (5). Their study provides strong evidence to take specific covariates into account for this vulnerable population but would be strengthened by a more extensive discussion.

ACKNOWLEDGMENT

We declare no conflict of interest.

Citation Béranger A, Bouazza N, Oualha M. 2021. Integration of continuous renal replacement therapy in a meropenem population pharmacokinetics model in critically ill children. *Antimicrob Agents Chemother* 65:e02542-20. <https://doi.org/10.1128/AAC.02542-20>.

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For the author reply, see <https://doi.org/10.1128/AAC.02592-20>.

Published 18 March 2021

REFERENCES

1. Saito J, Shoji K, Oho Y, Kato H, Matsumoto S, Aoki S, Nakamura H, Ogawa T, Hasegawa M, Yamatani A, Miyairi I. 16 November 2020. Population pharmacokinetics and pharmacodynamic implementation of meropenem in critically ill pediatric patients. *Antimicrob Agents Chemother* <https://doi.org/10.1128/AAC.01909-20>.
2. Sime FB, Pandey S, Karamujic N, Parker S, Alexander E, Loutit J, Durso S, Griffith D, Lipman J, Wallis SC, Roberts JA. 2018. Ex vivo characterization of effects of renal replacement therapy modalities and settings on pharmacokinetics of meropenem and vaborbactam. *Antimicrob Agents Chemother* 62:e01306-18. <https://doi.org/10.1128/AAC.01306-18>.
3. Purohit PJ, Elkomy MH, Frymoyer A, Sutherland SM, Drover DR, Hammer GB, Su F. 2019. Antimicrobial disposition during pediatric continuous renal replacement therapy using an ex vivo model. *Crit Care Med* 47:e767. <https://doi.org/10.1097/CCM.0000000000003895>.
4. Rapp M, Urien S, Foissac F, Béranger A, Bouazza N, Benaboud S, Bille E, Yi Z, Gana I, Moulin F, Lesage F, Renolleau S, Tréluyer J, Hirt D, Oualha M. 2020. Population pharmacokinetics of meropenem in critically ill children with different renal functions. *Eur J Clin Pharmacol* 76:61–71. <https://doi.org/10.1007/s00228-019-02761-7>.
5. Hartman SJF, Brüggemann RJ, Orriëns L, Dia N, Schreuder MF, de Wildt SN. 2020. Pharmacokinetics and target attainment of antibiotics in critically ill children: a systematic review of current literature. *Clin Pharmacokinet* 59:173–205. <https://doi.org/10.1007/s40262-019-00813-w>.