Reply to Béranger et al., “Integration of Continuous Renal Replacement Therapy in a Meropenem Population Pharmacokinetics Model in Critically Ill Children”

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We welcome Béranger et al.'s response (1) to our recent publication (2), and we agree that the effect of continuous renal replacement therapy (CRRT) on pharmacokinetic parameters for meropenem (MEM) should be discussed. As Béranger et al. pointed out, extracorporeal membrane oxygenation (ECMO) was probably a component of the CRRT covariate, and it may have contributed to the increase in central volume of distribution. In fact, the circuit priming volume for ECMO can be several times higher than the pediatric patient's blood volume, and hemodilution effect is inversely related to age (3).

For patients receiving CRRT and ECMO, large fluid overload, ascites, and edema should also be considered covariates. We had constructed the model with these complications as covariates for the pharmacokinetic model of MEM independently. However, these factors were not included as covariates in our final model.

We also recognize that high rates of dialysate and filtrate flow can influence MEM elimination (4, 5), and the values of the flow rates for CRRT should have been included in our model (6). Although information on the flow rates for CRRT was complete and the rates were considered covariates, the continuous flow rate values were not included in our model because they did not appear significant in our analysis. Only eight pediatric patients (23.5%) in this study received CRRT, and three of those eight were receiving ECMO. Our study was probably underpowered for effective analysis of flow rate as a covariate for improvement of the pharmacokinetic model.

As Béranger et al. indicated, the interaction between MEM and ECMO/CRRT tubing may significantly change the pharmacokinetic behavior of MEM. Specific physicochemical characteristics that must be considered include molecular size, pK_a and degree of ionization, lipophilicity, and plasma protein binding (7). Furthermore, according to extensive *ex vivo* data, the degrees of lipophilicity and protein binding significantly affect the proportion of drug sequestered within the ECMO and CRRT circuits. Studies of ECMO circuits have demonstrated significant sequestration of MEM in the circuit. Also, drug sequestration varies in different circuits, oxygenators, and pumps used. Wildschut et al. reported that MEM recovery at 180 min in ECMO circuits with a neonatal centrifugal pump ranged from 76.4% to 101.7% (8). Although the material used in their oxygenators was polypropylene, the same phenomenon has occurred in oxygenators composed of polymethylpentene hollow fibers, which are widely used in current ECMO systems (9). Because MEM is a

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hydrophilic compound and its protein binding is low, the decrease in the ECMO/CRRT circuit may be explained by the instability of MEM at high temperatures or in aqueous solutions (10, 11).

We did not evaluate MEM sequestration in the ECMO circuit or in the CRRT tubing. A large-scale study is therefore necessary to determine the effect of CRRT settings and ECMO on MEM pharmacokinetics in pediatric patients.

As Béranger et al. proposed, integration of CRRT in a MEM population pharmacokinetics model is urgently needed to ensure appropriate MEM therapy in critically ill pediatric patients receiving CRRT, ECMO, or both.

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