Reply to Pai

To the Editor—We thank Dr Pai for highlighting the importance of optimal dosing of polymyxins [1]. As described in our original paper [2], a number of commonly used approaches to account for body size were extensively evaluated via population modeling and covariate analysis. These body size models included allometric and linear scaling by both total body weight (TBW) and lean body weight (LBW), the latter requiring calculations using TBW, height, and sex [3]. All of these 4 body size models resulted in unbiased and adequately precise population-predicted polymyxin B concentrations, in contrast to the base model without scaling. As mentioned in our paper, utilizing allometric or linear scaling by LBW did not provide a benefit in reducing the unexplained (ie, random) between-subject variability (BSV) in clearance and volume of distribution compared to allometric or linear scaling by TBW. As also reported in our paper, allometric scaling by TBW (ie, [TBW/70 kg]0.75) provided only a marginal reduction in the BSV of clearance compared to linear scaling by TBW. Dosing via an allometric approach is substantially more complex than dosing by milligrams per kilogram TBW, and this additional complexity did not appear to be justified by the marginal reduction in BSV. For this reason, Monte Carlo simulations were based on linear scaling by TBW [2].

Dr Pai focused on 2 potential “outlier” patients [1]. It should be noted that any patient population, particularly the critically ill, may contain patients with extreme body size–adjusted clearance values. If each patient was dosed based on individual body size to achieve a specific polymyxin target area under the curve (AUC), the 41-kg patient would be underdosed by 48%–56% with any of the 4 scaling approaches, including scaling by LBW. The 250-kg patient would be overdosed by 27% based on linear scaling with TBW, but would be underdosed by 26%–39% based on linear or allometric scaling by LBW and by 66% without any scaling. Therefore, dose-adjusting for body size by any method would allow more accurate dosing of the 250-kg patient compared to no scaling. It is critical to suggest an optimized dosing approach based on the entire available patient population; considering all 24 patients [2], the accuracy of dosing by different scaling methods was very similar. Therefore, we reported the most clinician-friendly scaling approach (ie, dosing as milligrams per kilogram TBW).

Although our comprehensive covariate analysis identified body size as the only patient covariate influencing polymyxin B clearance in our population, clearly other as yet unidentified factors may exist. As stated in the conclusions [2], further clinical studies on polymyxin B pharmacokinetics and pharmacodynamics are urgently needed. This certainly includes future studies on polymyxin B pharmacokinetics in obese patients, which will enable researchers to make specific dosage recommendations for this patient population.

Notes

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Corinella B. Landersdorfer,1,2 Cornelia B. Landersdorfer, Roger L. Nation,3 Alex Forrest, Ana M. Sandri,4 Alexandre P. Zavascki,3 and Jian Li2,5
1Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; 2School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo; 3Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; 4Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; 5Infectious Diseases Service, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil

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