Polymyxin B Dosing in Obese and Underweight Adults

To the Editor—Sandri et al [1] recently reported important population pharmacokinetic data on intravenous polymyxin B in critically ill patients. They conclusively demonstrate that the dosage of polymyxin B should not be based on kidney function. Although no specific dosage regimen is recommended, the inference from this work is that polymyxin B should be dosed on total body weight (TBW). Unfortunately, the results presented by the authors appear to contradict this conclusion [1]. Dosing polymyxin B on TBW may actually lead to overexposure in morbidly obese patients and underexposure in underweight patients. The mathematical assumptions and limitations of TBW-based dosing have recently been reviewed and serve as the basis for this alternate viewpoint [2].

The area under the concentration-time curve (AUC) to minimum inhibitory concentration ratio is considered to be the pharmacokinetic–pharmacodynamic index that has been linked to antibacterial effect for this class of agents [3, 4]. The AUC is dependent on the dose and clearance (CL) of a drug (AUC = dose/CL). To achieve isometric AUC values in a population, the dose should be modified in proportion to CL [2]. Sandri et al [1] evaluated 24 patients with a median TBW of 62.5 kg (range, 41–110 kg), with inclusion of one 250-kg patient. No patients between 110 kg and 250 kg were evaluated. Figure 3 in their manuscript demonstrates that the range of polymyxin B CL to be distributed between approximately 1.0 to 2.5 L/hour, and an average population estimate of 1.87 L/hour is reported [1]. The exception to this CL distribution is an outlier of approximately 5 L/hour, observed in the 250-kg patient. Figure 3 also shows that the patient with the highest TBW-scaled CL of 0.06 L/hour/kg had a creatinine clearance of 100 mL/minute, and an unscaled polymyxin B CL of 2.5 L/hour. This patient likely represents the 41 kg (2.5 L/hour + 0.06 L/hour/kg) individual [1]. The 250-kg patient has a polymyxin B CL that is only 2-fold higher than the 41-kg patient (5 L/hour vs 2.5 L/hour), so the daily dose should only vary by 2-fold in order to achieve the same AUC.

Dosing on TBW such as 2.5 mg/kg/day will lead to calculation of a 103 mg (41 kg) and 625 mg (250 kg) daily dose of polymyxin B that is 6-fold different between these extremes of body weight. If the “best” dose of polymyxin B is at least 200 mg/day [1, 5], then the 41-kg patient will be underdosed and the 250-kg patient potentially overdosed. A linear and proportionate relationship should exist between TBW and drug CL for this body size metric to be optimal to scale drug doses [2]. This is rarely the case, and the authors note that the CL of polymyxin B actually scaled “slightly better” with an allometric (nonlinear) assumption (TBW0.75). Clinicians should exercise caution with the suggested approach of dosing polymyxin B on TBW, especially among patients at the extremes of TBW.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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