Optimal Levetiracetam Dosing in Neurological ICU Patients With Augmented Renal Clearance

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To the Editor:

Valdes et al (1) concluded that their study, which examined the population pharmacokinetics of levetiracetam in a critically ill neurosurgical population, found that this population required higher doses to achieve target levels. The study also found that augmented renal clearance (ARC), a phenomenon characterized by creatinine clearance (CrCl) greater than 130 mL/min/1.73m^2, is commonly described in critically ill patients, especially neurological ICU patients (1). A dose of at least 1000 mg of levetiracetam twice daily was required to lead to optimal results and reduced the odds of seizure by 68% compared with low-dose regimens (500 mg bid) (1).

A recent study by Sime et al (2) examined patients with severe trauma exhibiting ARC and found that it can alter the dosing requirement of renal-eliminated drugs. The objective of the study by Valdes et al (1) was to develop a pharmacokinetic model for levetiracetam in patients with severe traumatic brain injury (TBI) and aneurysmal subarachnoid hemorrhage (SBH) and to use it to describe optimal dosing regimens (2). The median trough concentration was reduced by 50% for every 40 mL/min/1.73 m^2 increase in urinary CrCl for the simulated intermittent dosing regimens (2). Some levels of ARC required simulated doses of at least 6 g/d (2). ARC in some ICU patients can be as high as greater than 350 mL/min/1.73 m^2 (2). The authors recommend a dose titration guided by measured CrCl and/or therapeutic drug monitoring (TDM), if available, to minimize the risk of seizures (2). ARC can be a challenging diagnosis as plasma creatinine is usually normal, and clinicians may easily miss it (3). To ensure accurate diagnosis and prevent any potential oversights, it is crucial to measure CrCl (3). The use of TDM is highly recommended to avoid underdosing of levetiracetam for the treatment or prevention of epilepsy (4). It is important to note that the recommended dose of 2 g/d, as proposed by Valdes et al (1), may often be insufficient to achieve optimal drug levels. A majority of patients may require IV doses of 6 g of levetiracetam per day to achieve a therapeutic dose, whereas a dose of 2 g/d is often subtherapeutic (1, 2). Patient populations with the highest reported incidence of ARC include those with major trauma, sepsis, TBIs, SBHs, and CNS infections (3). To evaluate the necessity of medication dosage adjustments, clinicians should consider screening ICU patients deemed high risk for ARC to assess CrCl by measuring 24-hour CrCl (5). There is a clear association between ARC and subtherapeutic antibiotic concentrations, and the literature suggests worse clinical outcomes (5). Therefore, the underdosing of antibiotics in a patient with ARC could increase the risk of treatment failure, as well as for levetiracetam (5). Finally, it is recommended to measure CrCl in ICU patients, as the occurrence is very high (between 30% and 65% of ICU patients), to avoid treatment failures and worse outcomes (5).

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The author replies:

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We wholeheartedly agree with the comments made by Honore and Blackman (1), and support the use of targeted levetiracetam dosing in the ICU setting. Indeed, in our study, 36% of subjects that who high-dose levetiracetam (750–1000 mg bid) did not reach target serum levels, and of the 26 patients with a documented clinical or electrographic seizure, 27% had received high-dose levetiracetam (as opposed to 500 mg bid) (2). Hence, our data indicate that a substantial proportion of patients require doses greater than 1000 mg bid. Augmented renal clearance plays a significant role in achieving target levetiracetam levels, and higher creatinine clearance was significantly associated with increased seizure risk in our study, due primarily to lower steady-state levetiracetam levels. Creatinine clearance should be considered when selecting maintenance levetiracetam doses, in conjunction with drug-level monitoring.

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