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FULL-LENGTH ORIGINAL RESEARCH

Levetiracetam dosing in patients receiving continuous renal replacement therapy

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Abstract

Objective: The study was aimed to define appropriate levetiracetam dosing regimens from available published pharmacokinetics (PK) studies in critically ill patients with and without cirrhosis receiving continuous renal replacement therapy (CRRT) via Monte Carlo simulation (MCS).

Methods: Mathematical pharmacokinetic models were developed using published demographic and PK data in adult critically ill patients with known variability and correlations between PK parameters. CRRT modalities (continuous venovenous hemofiltration and continuous venovenous hemodialysis) with different effluent rates were modeled. Levetiracetam regimens from available clinical resources were evaluated on the probability of target attainment (PTA) using pharmacodynamics (PD) target of the trough concentrations and area under the time-concentration curve within a range of 6–20 mg/L and 222–666 mg × hour/L for the initial 72 hours of therapy, respectively. Optimal regimens were defined from regimens that yielded the highest PTA. Each regimen was tested in a group of different 10,000 virtual patients.

Results: Our results showed the optimal levetiracetam dosing regimen of 750–1000 mg every 12 hours is recommended for adult patients receiving both CRRT modalities with two different effluent rates of 25 and 35 mL/kg/h. Child-Pugh class C cirrhotic patients undergoing CRRT required lower dosing regimens of 500–750 mg every 12 ours due to smaller non-renal clearance. Of interest, some of literature-based dosing regimens were not able to attain the PK and PD targets.

Significance: Volume of distribution, non-renal clearance, CRRT clearance, and body weight were significantly correlated with the PTA targets. Dosing adaptation in this vulnerable population should be concerned. Clinical validation of our finding is absolutely needed.

KEYWORDS

continuous renal replacement therapy, critically ill patients, drug dosing, levetiracetam, pharmacokinetics