Extracorporeal Clearance of Levetiracetam During Continuous Venovenous Hemofiltration in a Critically Ill Patient and New Dosing Recommendation

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Extracorporeal Clearance of Levetiracetam During Continuous Venovenous Hemofiltration in a Critically Ill Patient and New Dosing Recommendation

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Keywords

antiepileptic drugs, levetiracetam, epilepsy, continuous venovenous hemofiltration

Levetiracetam is a widely used antiepileptic drug; however, robust dosing recommendations for adult patients receiving continuous venovenous hemofiltration (CVVH) are lacking.[1] The present intermittent dosage recommendation of 1000 mg every 12 hours is based on 3 case reports.[2–4] Although useful, data on renal clearance, clearance by CVVH (CL_{CVVH}) and the maintenance dose multiplication factor (MDMF) are not available. We assessed whole-body clearance (CL_{TOTAL}), CL_{CVVH}, and levetiracetam MDMF during CVVH in the intensive care unit (ICU).

A 79-year-old man (admission body weight, 90 kg; height, 175 cm) presented with epilepsy. Medication on admission included carbamazepine, phenytoin, clobazam, and levetiracetam. Refractory status epilepticus and abdominal sepsis were diagnosed, requiring ICU admission. Mechanical ventilation was initiated for respiratory insufficiency. For the sepsis, amoxicillin/clavulanic acid, ceftriaxone, and gentamycin were initiated. Intravenous propofol and midazolam were started concurrently with continuous electroencephalographic monitoring to ensure a burst suppression pattern. On ICU day 3, anuric renal failure developed, and CVVH was started (Prismaflex system, Gambro) with an AN69ST hemofilter. Blood flow was set at 180 mL/min. The net ultrafiltrate rate was initially set at 0 mL/min. The ultrafiltrate flow rate was standardized at 55.6 mL/min. Citrate (Prismocitrate 18/0) was delivered prefilter at a rate of 1440 mL/h. Phoxilium was delivered postfilter at a rate of 1600 mL/h.

To prevent subtherapeutic levetiracetam concentrations, the daily dose was increased from 500 mg 3 times a day to intravenously 1000 mg twice a day, followed by therapeutic drug monitoring. Levetiracetam concentrations were measured at several points in plasma ($n = 6$), pre- and postfilter, and in ultrafiltrate samples ($n = 5$) using a validated reversed-phase high-pressure liquid chromatography method. On day 6, seizure activity was controlled.

All levetiracetam plasma values except one (41.2 mg/L) were within the therapeutic range of 5–25 mg/L (median, 12.4 mg/L).[5] Mw/Pharm 3.86 (MwPharm BV, Zuidhorn, The Netherlands) was used to calculate the pharmacokinetic parameters: apparent volume of distribution (V_d), 40.5 L; lean body mass-corrected V_d, 31 L; pre-CVVH initiation half-life ($t_{½}$), 20 hours; post-CVVH $t_{½}$, 7.2 hours. CL_{TOTAL} was 67.9 mL/min. CL_{CVVH} was 49.6 mL/min. Nonrenal clearance was 18.3 mL/min. Residual renal clearance was 0 mL/min. The median predilution-corrected sieving coefficient of the hemofilter was 0.89 (range, 0.88–0.94). The MDMF was 3.6. Despite best treatment, our patient died on ICU day 16 due to invasive candidiasis.

CVVH significantly contributed to overall levetiracetam clearance (73%). The half-life was comparable to that in patients with normal renal function (glomerular filtration rate > 90 mL/min/1.73 m^2).

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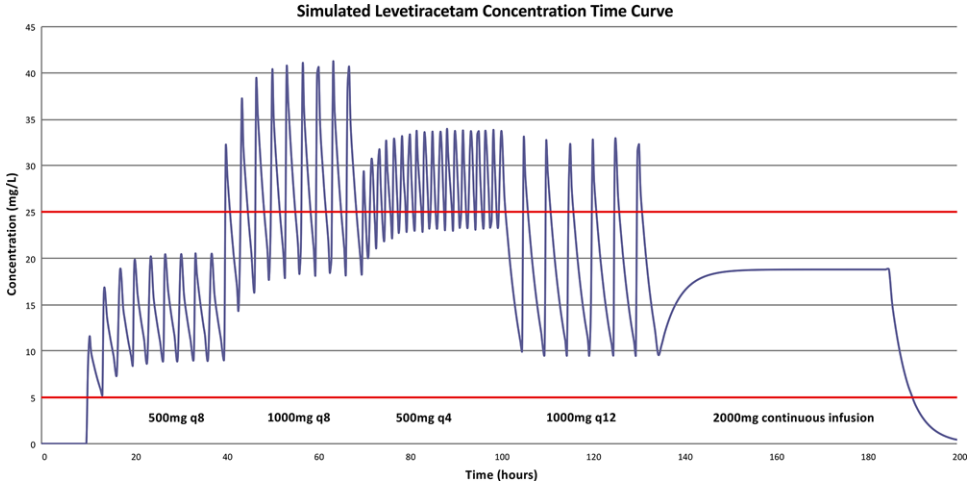

Figure 1. Pharmacokinetic simulations of levetiracetam based on pharmacological data derived from the present patient. The intermittent dosing situations (500 mg every 8 hours, 1000 mg every 8 hours, 500 mg every 4 hours, and the currently recommended intermittent dosing of 1000 mg every 12 hours) and the suggested new continuous dosing (2000 mg/24 h) are represented on the *x* axis. The results are recorded along the *y* axis. The solid red lines represent the therapeutic range of levetiracetam between 5 and 25 mg/L, with a goal steady-state concentration and target attainment of 19 mg/L.

Our new CVVH dosage regimen based on the calculated MDMF of 3.6 might prevent underdosing. In addition to the sieving coefficient of 0.89, a low-molecular-weight (170.2 DaD), low-protein bound fraction (10%), and low volume of levetiracetam distribution (< 0.7 L/kg) could all account for the significant CVVH clearance.[2,4] Based on our pharmacokinetic simulations, we recommend a levetiracetam dose adjustment of 2000 mg/24 h using continuous intravenous dosing in patients receiving CVVH (Figure 1). Moreover, our CVVH pharmacokinetic model revealed that continuous infusion achieves high target concentrations within the therapeutic range without an overdose risk.

Declaration of Conflicting Interests

The authors declare that they have nothing to disclose.

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