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Levetiracetam Pharmacokinetics in a Patient with Intracranial Hemorrhage Undergoing Continuous Veno-Venous Hemofiltration

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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 78
Final Diagnosis: Right thalamic intraparenchymal hemorrhage with intraventricular extension
Symptoms: Altered mental status • left sided weakness
Medication: Levetiracetam
Clinical Procedure: Continuous renal replacement therapy
Specialty: Critical Care Medicine

Objective: Unusual or unexpected effect of treatment

Background: Levetiracetam is an antiepileptic drug frequently used in critically ill patients. Levetiracetam is primarily eliminated as a parent compound via glomerular filtration and requires dose adjustment in renal insufficiency, but the literature on patients receiving continuous veno-venous hemofiltration (CVVH) is scant.

Case Report: We report the levetiracetam pharmacokinetic profile of a patient being treated with levetiracetam 1000 mg intravenously every 12 h who required continuous veno-venous hemofiltration (CVVH). The patient underwent CVVH utilizing a high-flux polyethersulfone membrane filter. The blood flow rate was 250 ml/min, and the predilution replacement therapy fluid flow rate was 2000 ml/h. After achieving presumed steady-state on levetiracetam 1000 mg q12h, serial plasma samples (pre- and post-filter) and effluent samples were drawn at 2, 4, 6, 8, and 10 h. Levetiracetam concentrations were determined utilizing LC-MS/MS. The levetiracetam maximum concentration (C_{max}), minimum concentration (C_{min}), half-life, area under the concentration-time curve (AUC_{0-12}), clearance (CL), and volume of distribution (Vd) were 30.7 µg/ml, 16.1 µg/ml, 12.9 h, 272 mg·hr/L, 3.68 L/h, and 0.73 L/kg, respectively. The sieving coefficient was 1.03±0.08. CVVH represented 61.3% of the total levetiracetam clearance. The patient was maintained on CVVH for 24 consecutive days and then transitioned to intermittent hemodialysis and remained seizure-free.

Conclusions: CVVH is highly effective in removing levetiracetam from circulating plasma. Due to the effective removal, standard doses of levetiracetam are required to maintain adequate plasma concentrations. Dose reductions utilizing HD or estimated creatinine clearance recommendations will likely lead to subtherapeutic levels, especially if higher CVVH flow rates are used.

MeSH Keywords: Anticonvulsants • Critical Care • Dialysis • Hemofiltration • Pharmacokinetics

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902709

Background

Levetiracetam is an antiepileptic drug approved by the Food and Drug Administration (FDA) for the treatment of partial-onset seizures, myoclonic seizures in patients with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures [1]. Levetiracetam use is increasing in the critically ill population and is frequently selected over other antiepileptic options due to its proven efficacy, limited drug interactions, minimal adverse effect profile, and ease of use [2–5]. Recent evidence shows levetiracetam may also improve cerebral edema in patients with neurologic injuries [6]. Levetiracetam has a large dosing range (1000–3000 mg/day) with a 6–8-h half-life in healthy adults with normal renal function. It exhibits linear pharmacokinetics, with 66% of the drug eliminated renally via glomerular filtration as unchanged drug and has recommended dose adjustments for renal impairment [1,7–12]. Levetiracetam has a molecular weight of 170.21 g/mol, a Vd of 0.5–0.7 L/kg in healthy patients, a Vd of 0.43±0.11 L/kg in the neurocritical care population, and is minimally protein-bound within the plasma [1,10,13]. Acute kidney injury develops in 5% to 25% of patients admitted to an ICU. Approximately 6% of these patients require renal replacement therapy during their admission [14]. Given these properties, levetiracetam is likely to be removed via continuous renal replacement therapy [15].

Previous reports have described systemic levetiracetam clearance in patients undergoing various continuous renal replacement therapy (CRRT) strategies. These reports had complicating factors such as inclusion of patients with acute liver dysfunction, limited sampling strategies, concomitant use of extracorporeal membrane oxygenation, and a lack of effluent concentrations to determine clearance associated with CRRT; these factors may limit applicability to other critically ill patients requiring CRRT [16–18]. We report the case of a patient with an intraparenchymal hemorrhage on CRRT who received seizure prophylaxis therapy with intravenous levetiracetam. Additionally, we describe the pharmacokinetics and clearance of levetiracetam during continuous veno-venous hemofiltration (CVVH).

Case Report

A 78-year-old, 93.2 kg man presented to the University of Colorado Hospital Emergency Department as a stroke alert with acute mental status changes and left-sided weakness. The patient underwent a non-contrasted computerized tomography (CT) scan, which demonstrated a right thalamic intraparenchymal hemorrhage with intraventricular extension, and was intubated in the Emergency Department. A CT angiography did not reveal any evidence of a vascular malformation or aneurysm. The patient was transferred to the Neurosurgical-ICU where levetiracetam therapy was initiated at 1000 mg intravenously every 12 h for seizure prophylaxis, consistent with institutional practice.

One day following admission, the patient developed acute tubular necrosis (SCr 3.14 mg/dL) secondary to contrast-induced nephropathy, leading to oliguric renal failure requiring CVVH for volume status management in the setting of hemodynamic instability. The patient underwent CVVH using a NxStage System One dialysis machine with NxStage Cartridge Express and filter (high-flux polyethersulfone membrane with 1.5-m^2 membrane surface area). The blood flow rate was 250 ml/min, and the predilution replacement therapy fluid, PureFlow™ B Solution 4K/2.5 Ca^{++}, flow rate was 2000 ml/h. Pre-filter anticoagulation was not used. The ultrafiltration rate was adjusted hourly to keep the patient's volume status net-even. The patient produced 76 ml of urine in the 12 h during which the pharmacokinetic analysis was performed. The levetiracetam dosing regimen was 1000 mg intravenously given over 15 minutes every 12 h. Steady-state levetiracetam pre-filter, post-filter, and effluent concentrations were drawn on day 9 of therapy when the levetiracetam was assumed to be at pharmacokinetic steady-state. The patient was maintained on CVVH for 24 consecutive days and then transitioned to intermittent hemodialysis and remained seizure-free without any noted adverse effects from the levetiracetam therapy. The patient was discharged to a skilled nursing facility for rehabilitation and dialysis. Proxy consent was obtained for plasma and effluent samples and publication of subsequent findings from the patient's medical decision-maker.

Pre-filter plasma (4 ml) and effluent samples (10 ml) were collected for measurement of levetiracetam concentration at 2, 4, 6, 8, and 10 h after administration. A 12-h timed urine collection was collected for measurement of urinary levetiracetam clearance. Levetiracetam concentration were determined using a previously described liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at the University of Colorado Medicinal Chemistry Core Laboratory (University of Colorado Anschutz Medical Campus, Aurora, CO) [19].

Plasma and dialysate concentration-time data for levetiracetam were analyzed by standard noncompartmental pharmacokinetic modeling [20]. The apparent terminal elimination rate constant (k_e) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. The levetiracetam peak concentration (C_{max}) 15 min after the start of the infusion and the minimum concentration (C_{min}) at 12 h following administration were extrapolated from the measured concentrations and calculated k_e ($C_t = C_1 \cdot e^{-kt}$). Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_e$. The area under the concentration-time curve from time zero to the end of the 12-h dosing interval ($AUC_{0–12}$) was

Table 1. Pharmacokinetic parameters in healthy subjects and CVVH.

Parameter	Healthy subjects [22]	CVVH
C_{max} (µg/ml)	71.7	30.3
C_{min} (µg/ml)	14.1	16.1
K (h^{-1})	0.0968	0.0538
Half-life (h)	7.16	12.9
$AUC_{0–12}$ (mg·hr/L)	371.9	272
Cl_s (L/h)	3.78	3.68
Vd (L)	41.0	68.3
Vd (L/kg)	0.56	0.73
Sieving coefficient	–	1.03
Cl_{cvvh} (L/h)	–	2.25
Fr_{CVVH} (%)	–	61.3
Ultrafiltrate $AUC_{0–12}$ (mg·hr/L)	–	279

C_{max} – maximum plasma concentration; C_{min} – minimum plasma concentration; K – elimination rate constant; $AUC_{0–12}$ – area under the plasma concentration-time curve 0–12 h; Cl_s – systemic clearance; Vd – volume of distribution; Cl_{cvvh} – CVVH clearance.

calculated by the linear trapezoidal summation method. Total systemic clearance (CL_s) was calculated as dose/$AUC_{0–12}$. Since levetiracetam was determined (based on observed half-lives) to be at steady-state during the sampling period, the volume of distribution (V_d) was calculated as dose/(k_e×$AUC_{0–12}$). Additional pharmacokinetic parameters specific to the CVVH procedure were also calculated. Sieving coefficient (Sc) was calculated as the ratio of the ultrafiltrate $AUC_{0–12}$ to the plasma $AUC_{0–12}$. Drug clearance contributed by CVVH (CL_{CVVH}) in the predilution mode was calculated via the formula CL_{CVVH}=Quf×Sc×[Qb/(Qb+Qrf)], where Quf is the total ultrafiltration rate (hemofiltration + net ultrafiltration), Qub is the extracorporeal blood flow, and Qrf is the predilution replacement therapy fluid flow rate. Fractional clearance by CVVH (Fr_{CVVH}), which is the portion of total systemic clearance contributed by CVVH, was calculated using the ratio of CL_{CVVH} to CL_s. The amount of levetiracetam eliminated by CVVH was also estimated from the $AUC_{0–12}$ of the ultrafiltrate concentration-time curve and the ultrafiltration rate. All calculations were made by programming pharmacokinetic equations into Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA).

The pharmacokinetic analysis occurred on day 9 of levetiracetam therapy and day 8 of CVVH therapy. CVVH was run at a dose of 26.7 ml/kg/h with a blood flow rate of 250 ml/min and a predilution replacement therapy fluid flow rate of 2000 ml/h.

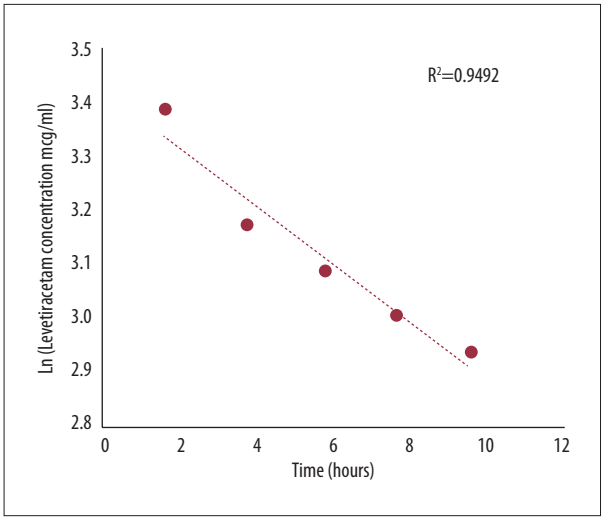

Figure 1. Levetiracetam plasma elimination curve. Displays log_e transformation of the plasma concentrations.

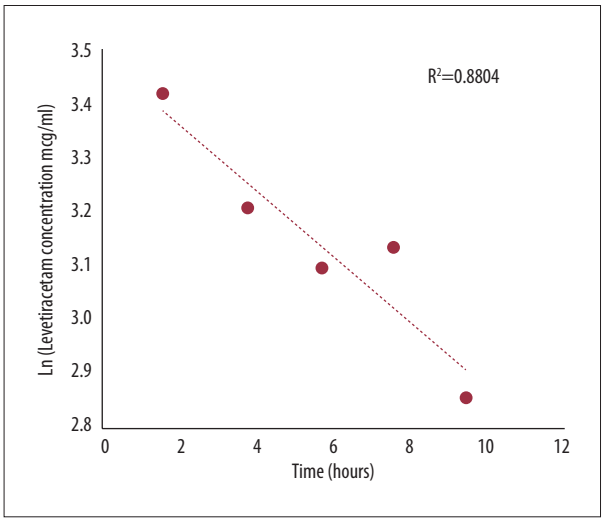

Figure 2. Levetiracetam effluent elimination curve. Displays log_e transformation of the effluent concentrations.

Most of the pharmacokinetic parameters evaluated are reported in Table 1. The plasma and effluent levetiracetam elimination curves are illustrated in Figures 1 and 2, respectively. The ultrafiltrate $AUC_{0–12}$ was 279 mg·h/L and 70.3% of the dose was recovered in the effluent. Urinary clearance represented 0.003% of the total levetiracetam clearance and 0.63% of the dose was recovered in the urine.

Discussion

In our patient, levetiracetam did not accumulate and was readily removed with CVVH therapy. Given the broad range of clinical applications within a variety of critically ill populations maintaining adequate therapeutic concentrations, with

target trough ranges of 6–20 µmg/ml having been suggested, likely reduces the risks of therapeutic failure [10,21,22]. The C_{min} with the dosing regimen of 1000 mg every 12 h was within the previously reported target range. The half-life of levetiracetam was prolonged, at 12.9 h, compared to the half-life of 6–8 h in healthy volunteers and 5.2 h in neurocritically ill patients [10,13]. A reduction in total clearance was anticipated because the prescribed ultrafiltration rate of 2000 ml/h approximates the renal function of a patient with moderate renal impairment (~Cl_{Cr} of 30 ml/min/1.73 m^2). Despite this estimated decreased renal function, the systemic clearance of levetiracetam in our patient was similar to that of healthy volunteers, at 3.68 and 3.78 L/h, respectively [11,23]. The difference in half-life despite similar systemic clearance is likely attributable to the difference in total Vd between reported healthy subjects and our patient. The ability of CVVH to effectively remove levetiracetam from circulating plasma is further highlighted by the reported sieving coefficient of 1.03. To the best of our knowledge this is the first report of the sieving coefficient of levetiracetam. Given the free movement of levetiracetam, the reported filter clearance is purely a function of ultrafiltrate and blood flow rate. Clinicians should carefully consider ultrafiltrate and blood flow rate when selecting a dosing regimen for levetiracetam for a patient receiving CRRT.

A Cl_{Cr} of 30-50 ml/min/1.73 m^2 is commonly used when choosing drug dosing regimens for patients receiving usual ultrafiltration rates during CVVH. The FDA-approved labeling for levetiracetam recommends a dose of 500 mg every 12 h for patients with an estimated clearance of 30 ml/min/1.73 m^2 [1]. Our data suggest that this recommendation in patients on CVVH may result in subtherapeutic levetiracetam plasma concentrations. In our patient, CVVH clearance at an ultrafiltration rate of ~2000 ml/h was responsible for >60% of the levetiracetam clearance, and total systemic clearance resembled that reported in patients with a ClCr >60 ml/min/1.73 m^2. Clearance would be expected to increase if higher ultrafiltration rates are utilized. We estimate the CL_{CVVH} would increase to 3.64 L/h and 4.76 L/h if the predilution replacement therapy fluid flow rate was increased to 4000 ml/h and 6000 ml/h, respectively. These estimated changes in CL_{CVVH} would require clinically significant dose adjustments to maintain the same plasma levetiracetam concentrations.

Currently, there are only 3 reports evaluating the elimination of levetiracetam via CRRT. Two of these case reports used a single steady-state trough concentration for each of their pharmacokinetic evaluations, introducing possible error due to the use of population estimates [16,18]. Comorbidities such as hepatic failure and the need for extracorporeal membrane oxygenation also complicate the evaluation of the role CRRT plays in levetiracetam [17,18]. The present report used an extensive sampling strategy including effluent sampling to isolate the role CVVH in the elimination of levetiracetam and to establish a sieving coefficient for levetiracetam, but is limited in that the sample was a single patient, and by pharmacokinetic differences within the neurocritically ill. Globally, levetiracetam therapeutic drug monitoring is limited as there is not an established relationship between plasma concentrations and clinical efficacy of levetiracetam. Further evaluation is needed in a more heterogeneous patient population with an increased sample size to establish the full effects of CRRT on levetiracetam clearance.

Conclusions

CVVH is highly effective in removing levetiracetam from circulating plasma. Due to the effective removal, standard doses of levetiracetam are required to maintain adequate plasma concentrations. Dose reductions utilizing HD or estimated CrCl recommendations will likely lead to subtherapeutic concentrations and may increase risk of seizure, especially if higher CVVH flow rates are used.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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