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PRACTICAL PEARL

Augmented Renal Clearance of Vancomycin and Levetiracetam in a Traumatic Brain Injury Patient

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Abstract
Background Increased creatinine clearance and subsequent elevated antimicrobial clearance is evident in many traumatic brain injury (TBI) patients due to augmented renal clearance (ARC). Little is known about the effects of ARC on other renally-eliminated medications, such as the anti-epileptic drug levetiracetam.
Methods This is a case report of serum monitoring of vancomycin and levetiracetam in a 22 year old female with ARC after severe TBI.
Results The patient exhibited ARC of vancomycin as evidenced by her low serum concentrations with standard vancomycin dosing. Her estimated creatinine clearance based on vancomycin clearance was 243.9 ml/min. Serum concentrations also suggested ARC of levetiracetam. No toxicities for either medication were noted, even after dose adjustment to account for possible ARC.
Conclusions Vancomycin and levetiracetam both appear to be subject to ARC after TBI. Clinicians should be mindful that standard dosing of these agents may not achieve typical target concentrations in this clinical scenario.

Keywords Closed head injury · Pharmacokinetics · Antibiotic · Antiepileptic · Creatinine clearance

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Background and Purpose

Augmented renal clearance (ARC) is defined as enhanced renal elimination of solutes. ARC has been described in several different types of critical illness such as burn, polytrauma, and traumatic brain injury (TBI) [1–3]. Previous publications have described the enhanced elimination of monitorable drugs such as aminoglycosides and vancomycin, as well as antimicrobials that are not commonly monitored by serum concentrations such as meropenem and piperacillin [4, 5]. In the case of the beta-lactam antimicrobials, a high percentage of patients with ARC have subtherapeutic concentrations (69 %). In other cases, empiric dosing of agents such as vancomycin or amikacin results in lower than desired concentrations at the outset of therapy or yields prolonged periods with no detectable drug. It seems clear that in patients with ARC, drug exposure may be much lower than expected. We present a case of a TBI with ARC affecting vancomycin and the anti-epileptic drug, levetiracetam.

Summary of Case

The patient is a 22-year-old female who presented with a severe TBI after a motor vehicle collision with a tree. She was previously healthy, although she did have a remote history of a below-the-knee (BKA) amputation of her left lower extremity. Upon admission, she weighed 42.9 kg and was 157.4 cm tall (body surface area 1.26 m^2 when accounting for her BKA) [6]. Her post-resuscitation Glasgow Coma Score was 2-4-1T (E-M-V). The computerized tomography of her head showed traumatic subarachnoid hemorrhage and diffused cerebral edema. A ventriculostomy was inserted. Due to hypotension during the first day

of admission, a transthoracic ECHO was obtained, which demonstrated severe myocardial dysfunction, with an estimated ejection fraction of 20 %. She received judicious fluid resuscitation and vasopressor support to ensure her cerebral perfusion pressure was >60 mmHg. She was administered phenytoin for post-traumatic seizure prophylaxis. Over the first several days of her stay, she required numerous boluses of 23.4 % sodium chloride to treat her elevated ICP and occasional norepinephrine infusion to maintain cerebral perfusion pressure >60 mmHg. Over the first week of her ICU stay, her ejection fraction remained <30 % with moderate to severe global hypokinesis. Ultimately, she required a pentobarbital infusion for approximately 72 h for her refractory elevations in ICP (average infusion rate 3 mg/kg/h over days 3–7 of hospitalization) [7, 8]. Levetiracetam 1,000 mg IV twice daily was added due to suspicion of breakthrough seizures upon withdrawal of pentobarbital. This dose was empirically increased to 1,000 mg IV every 8 h on the second day of levetiracetam therapy.

Later in her ICU stay, vancomycin was initiated for empiric coverage of potential brain infection. On hospital day 10, and after six consecutive doses of vancomycin 750 mg IV q12h (17.5 mg/kg), a peak and trough concentration were obtained, which yielded lower than anticipated concentrations and suggested rapid vancomycin clearance (Fig. 1). Specifically, the vancomycin peak concentration was 14.5 mcg/ml and the trough was 2.2 mcg/ml. Estimated GFR was 200 ml/min and estimated creatinine clearance was 153.2 ml/min (209.5 ml/min standardized to body surface area) [6, 9, 10]. Estimated creatinine clearance based on vancomycin clearance was 243.9 ml/min [11]. Based on her pharmacokinetic parameters calculated from these concentrations, a new dose of 1,250 mg IV q8h should have yielded a peak of ~32.5 and a trough of 9.9 mcg/ml. A follow-up trough on the newly calculated regimen was nearly exactly as calculated (11 mcg/ml), which indicates her ARC remained elevated through the dosing period observed. The patient completed a 9-day course of therapy when the vancomycin was discontinued in light of negative serial cerebrospinal fluid cultures.

On hospital day 11, a levetiracetam trough sample was obtained after seven consecutive doses of levetiracetam 1,000 mg q8h (administered enterally). The concentration was 13 mcg/ml (Fig. 2). Later, on hospital day 12, after she had received a 4,000-mg loading dose of IV levetiracetam followed by two consecutive doses of levetiracetam 1,500 mg IV every 8 h, a peak levetiracetam concentration was obtained which was 34 mcg/ml. Renal function measurements were stable at this point as well (see Table 1 for a description of fluid intake and urine output during the vancomycin and levetiracetam sampling period). The trough concentration was not appropriately obtained and could not be assessed for this dose. Based on the typical levetiracetam linear pharmacokinetics in a one-compartment model and using population parameters for typical volume of distribution and elimination, both concentrations are drastically lower than would be estimated [12–14]. Based on population parameters for normal individuals, we would have estimated a peak concentration of ~60 mcg/ml and a trough of ~46 mcg/ml for this dosing scheme [15]. Unfortunately, we were unable to assess bioavailability of the enterally administered levetiracetam, though we are confident that a significant portion of the dose was absorbed, as has been demonstrated in the literature [13–15]. Although the concentrations obtained do not permit us to specifically define the levetiracetam pharmacokinetic parameters at steady state, it is evident that rapid levetiracetam clearance was a factor in this patient. We believe this is likely due to ARC, although increased plasma hydrolysis of levetiracetam (typically ~33 %) could also explain the elevated clearance [13]. We could not rule this out.

The analysis of her electroencephalograph during the time of the levetiracetam sampling did not show seizures,

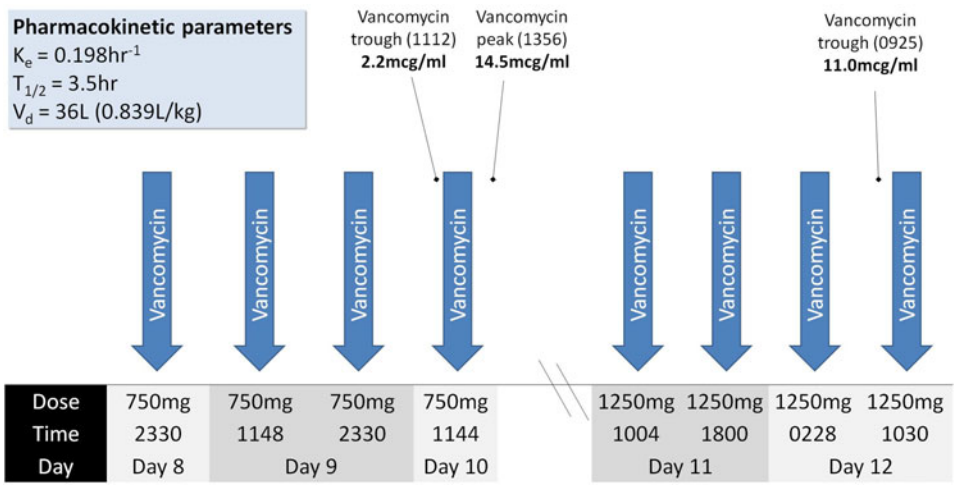

Fig. 1 Summary of vancomycin doses and concentrations. Serial vancomycin doses and timing of serum sampling. Vancomycin doses were given at a consistent schedule, and vancomycin peak and trough were obtained on day 10 at steady state. The calculated pharmacokinetic parameters suggest an elevated volume of distribution and augmented renal clearance of vancomycin

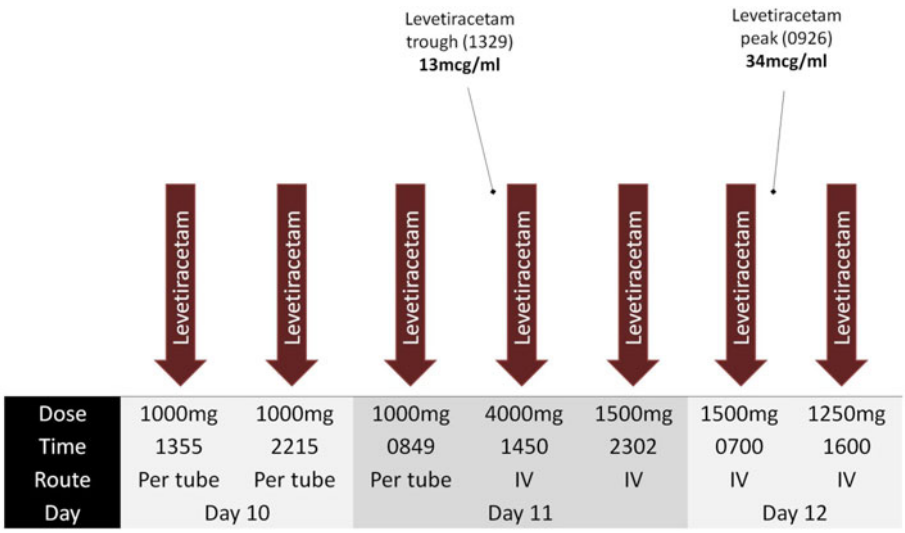

Fig. 2 Summary of levetiracetam doses and concentrations. Serial levetiracetam doses and timing of serum sampling. Levetiracetam doses were given at a consistent schedule, though the dose, formulation, and route of administration were changed between the time that the peak and trough were obtained. Given the high dose of levetiracetam, the serum concentrations suggest an augmented renal clearance and likely an elevated volume of distribution

Table 1 Description of fluid intake, urine output, and renal function measures during vancomycin and levetiracetam sampling period

	Day 8	Day 9	Day 10	Day 11	Day 12
23.4 % HTS (ml)	0	0	0	0	30
3 % HTS (ml)	1,858	1,963	1,855	0	0
1.5 % HTS (ml)	0	0	0	2,319	2,553
5 % albumin (ml)	0	0	750	0	250
NS (ml)	0	0	5,000	2,000	1,000
Other IV fluids (ml)[a]	1,236	1,170	1,018	1,646	2,435
Enteral nutrition/fluids (ml)	416	120	692	366	394
Fluid intake total (ml)	3,510	3,253	9,315	6,331	6,662
Urine output (ml)	5,375	5,885	8,010	7,800	6,995
Vasopressors used (dose range)	0	0	0	0	Norepinephrine 3–12 mcg/min
Serum creatinine (mg/dl)	0.33	0.33	0.39	0.34	0.39
Estimated CrCl (ml/min/1.72 m^2)	247	247	209	239	209
Estimated GFR (ml/min/1.73 m^2)	249	249	206	241	206

NS 0.9 % sodium chloride, *HTS* hypertonic saline infusion, *CrCl* creatinine clearance, *GFR* glomerular filtration rate

[a] Other IV fluids indicates intermittent medications administered intravenously. Our standard is to dilute medications in NS for parenteral administration

but showed only generalized slowing. No toxicity associated with levetiracetam was detected. On hospital day 15, a repeat transthoracic ECHO demonstrated return of normal cardiac function (ejection fraction 50–55 %). The patient was administered levetiracetam 1,500 mg per tube every 8 h. Ultimately, the patient was discharged from the hospital to a long-term care facility after a 60-day length of stay with a glasgow outcome score of 3.

Discussion

ARC has been previously reported in patients with severe TBI. ARC likely occurs in TBI patients (and other similarly critically ill individuals) due to several reasons. First, stress hormone concentrations are elevated in critical illness and cardiac function (and therefore GFR) is elevated. Renal blood flow increases as a result. Second, the fluid resuscitation strategies in supporting TBI patients often entail relatively high amounts of crystalloid intravenous fluids to maintain an adequate intravascular volume. Finally, cerebral perfusion pressure modulation often is necessary in TBI patients, typically by use of fluids or vasopressors. Increasing mean arterial pressure in this context also increases renal blood flow [1]. A more robust description of the mechanisms of ARC has been published elsewhere [3]. Nearly all of the reports to this point have focused on the pharmacokinetic variability of renally

eliminated antimicrobials, particularly aminoglycosides, and beta-lactams [3–5]. This is the first case report describing possible ARC in a TBI patient affecting vancomycin and a renally eliminated anti-epileptic agent, levetiracetam. This is significant for several reasons.

First, while vancomycin has been demonstrated to be affected by ARC in patients after surgery and burn, the impact of ARC on vancomycin has yet to be reported in the setting of TBI. Predictably, the vancomycin volume of distribution and systemic clearance were quite elevated. Inadequate dosing of vancomycin may lead to treatment failure, which is of particular concern in patients with potential brain infections, such as the patient we described. We typically target a trough concentration of ~15–20 mcg/ml [16]. The dose adjustment yielded a trough closer to our target range, but suggests that ARC can persist for a prolonged period after the initial insult causing critical illness.

Second, levetiracetam is similar to antimicrobials such as the beta-lactams in that serum concentration monitoring is not routinely performed. Levetiracetam is also primarily renally eliminated and therefore may be subject to the effects of ARC. This creates a scenario in the critically ill patient, where a "standard" dose of a commonly used agent may result in therapeutic failure. Clinicians would have difficulty in predicting failure due to the lack of routine serum monitoring. Empirically increasing doses of these agents may also be fraught with difficulty, due to the variability in clearance in critical illness. The pharmacokinetics of levetiracetam in patients with TBI has been described. In the study by Klein et al. a heterogeneous TBI population (mild to severe) received levetiracetam 55 mg/kg/day either via intravenous infusion, enterally, or orally [17]. This study suggested that the typical peak concentration of levetiracetam in a TBI population was ~60 mcg/ml, with a corresponding trough concentration of ~24 mcg/ml. Despite receiving nearly twice this amount as a maintenance dose (as well as previous, slightly lower dose levetiracetam therapy and a 4-g bolus dose, see Fig. 2), the young lady in our case report had significantly lower serum concentrations of levetiracetam. We attribute this to a likely increased volume of distribution and likely augmented renal clearance.

Levetiracetam is increasingly being recommended for use in TBI patients and other neurocritical care patients to prevent seizures [18, 19]. However, levetiracetam has little to no data to support routine use for indications such as post-traumatic seizure prophylaxis. Levetiracetam is also not included in the TBI treatment guidelines as an option for post-traumatic seizure prophylaxis [20]. The potential impact of ARC on levetiracetam exposure is yet another reason to employ this therapy with caution in critically ill patients.

An analysis of both of the agents monitored in this patient suggests possible ARC. For example, vancomycin clearance was 176 % greater than reported "normals" and 150 % greater than population parameters would suggest (normal vancomycin clearance ~67.7 ml/min, volume of distribution 0.52 l/kg) [21]. In fact, the vancomycin clearance more closely approximated that of a burn patient (143 ml/min). Based on our data, it is evident that creatinine clearance estimates such as modification of diet in renal disease (MDRD glomerular filtration rate estimate) and Cockcroft–Gault did not correlate well with measured levetiracetam or vancomycin clearance in this case [9, 10]. This is similar to previously reported data, which suggests that using creatinine clearance estimates to predict renal drug clearance in the case of ARC is inaccurate [22]. Interestingly, our patient had a somewhat unusual presentation in that she exhibited severe myocardial dysfunction and had a reduced ejection fraction for a prolonged duration after her TBI. Despite her low ejection fraction, clearance of the targeted medications was still augmented. This is likely due to the vasoactive support and fluid therapy we provided to ensure adequate cerebral perfusion, though many of her measured hemodynamic parameters did not improve to normal values despite cerebral perfusion pressure modulation.

Clinicians should be mindful of the potential impact of ARC in critically ill patients, particularly those with TBI. ARC in these patients may lead to serum or target site concentrations that are lower than anticipated based on standard dosing. This may lead to therapeutic failure. For medications where therapeutic drug monitoring is frequently available (aminoglycosides, vancomycin), proactive monitoring should be performed in order to ensure adequate serum concentrations. Dose modifications can easily be made for these medications to achieve surrogate dosing endpoints. If levetiracetam is indeed subject to the effects of ARC, this creates a much more problematic situation for clinicians, due to the relative lack of availability and utility of levetiracetam serum monitoring. A similar problem has been reported for beta-lactams antibiotics which are not routinely monitored [5]. In these situations, if serum monitoring is not timely or practical, a more specific assessment of renal function, such as a measured urine creatinine clearance, may be helpful.

Unfortunately, we did not obtain a measured creatinine clearance, such as an 8- or 24-h urine creatinine measurement as part of our processes of care for this patient. However, due to the relative lack of correlation of creatinine clearance estimates and the renal clearance for the various agents measured in this case report, a reasonable case could be made for routinely evaluating an 8-h creatinine clearance measurement in patients at risk of exhibiting ARC [23]. This may be more important for patients receiving medications possibly susceptible to the effects of ARC that are not routinely monitored such as levetiracetam or beta-lactams.

Conclusions

This is the first case of augmented renal clearance affecting vancomycin and levetiracetam clearance in a severe TBI patient. It is possible that many critically ill patients are underexposed to vital medications during the hyperdynamic phases of their illness, potentially leading to therapeutic failure and worse outcomes. Clinicians should be mindful of the possibility of ARC and closely monitor medications which may be affected (vancomycin, aminoglycosides, beta-lactams, levetiracetam, and other primarily renally eliminated drugs). Further investigation of the utility of levetiracetam in TBI patients and the typical pharmacokinetics in this population (particularly in the more severe population) is warranted before more widespread use of the agent can be advocated.

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