Antibacterial therapeutic drug monitoring in cerebrospinal fluid: difficulty in achieving adequate drug concentrations

Case report

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This report illustrates the difficulty in managing CNS infection in neurosurgical patients, the altered drug pharmacokinetics associated with critical illness, and the role that therapeutic drug monitoring (TDM) of CSF can play in assisting clinical decision making.

The authors present a case of external ventricular drain–related ventriculitis in a critically ill patient who initially presented with a subarachnoid hemorrhage. They discuss the physiological changes found in such patients, in particular augmented renal clearance (demonstrated in this patient by a measured creatinine clearance of 375 ml/min/1.73 m²), noting the effect this had on drug pharmacokinetics and leading to dosing requirements 2–3 times those recommended in standard regimens.

The authors consider the bacterial “kill” characteristics of 2 different antibacterial agents (meropenem and vancomycin) and describe the unique approach of using plasma and CSF TDM to achieve optimal drug exposure at the site of infection while limiting toxic side effects. The authors demonstrate that simply using plasma TDM as a surrogate marker for drug concentration in the CNS may lead to undertreatment, exemplified in this patient by CSF vancomycin concentrations as little as 13% of that in plasma. Finally, by measuring CSF and plasma ratios, the authors illustrate the disparity in pharmacokinetic properties between drugs, reminding the clinician of the importance of CNS penetration when selecting antibacterial agents in such cases.

This work raises an important hypothesis in the accurate prescription of antibacterial agents in neurological critical care, namely undertreatment in the context of augmented elimination and impaired target site penetration. However, prior to any recommendations regarding empirical dose modification, more data are clearly needed, particularly with respect to the safety and efficacy of such an approach. In this respect, the authors would advocate further research using TDM in the management of CNS infection in this setting, in addition to work defining plasma and CSF concentrations associated with antibacterial efficacy and toxicity.

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**Key Words** • subarachnoid hemorrhage • therapeutic drug monitoring • cerebrospinal fluid • infection

Abbreviations used in this paper: ARC = augmented renal clearance; AUC = area under the curve; CLCr = creatinine clearance; E = eye response; EVD = external ventricular drain; GCS = Glasgow Coma Scale; M = motor response; MIC = minimum inhibitory concentration; SAH = subarachnoid hemorrhage; TDM = therapeutic drug monitoring; V = verbal response.

Inspection of an EVD is common in the critically ill neurosurgical patient. The device plays an important role in the management of hydrocephalus and monitoring of intracranial pressure in acute neurosurgical emergencies, such as SAH. However, associated infection is a significant concern and is recognized as an important cause of morbidity and mortality in this setting. A meta-analysis in 2002 reported infection rates of 8.08% per EVD and 8.80% per patient. Factors associated with an increased risk of EVD-related infection include method of insertion, time in situ, physical interventions (such as irrigation or CSF sampling), and the presence of intraventricular or subarachnoid blood.

While identifying intracranial infection in such patients remains clinically challenging, timely application of appropriate antibacterial therapy remains a key principle of successful treatment. This is even more complex in the neurosurgical patient, as to ensure successful bacterial eradication, antibacterial therapy is reliant on achieving adequate drug concentrations.
ing, and maintaining, adequate drug concentrations at the site of infection, namely, the CSF. Importantly, use of standard doses that demonstrate “therapeutic” antibacterial concentrations in plasma may not necessarily ensure sufficient CSF concentrations.29

Complicating this scenario are the significant changes encountered in patient physiology with critical illness,7 which can have a profound influence on antibacterial drug handling. Specifically, neurosurgical patients have been identified as a cohort predisposed to ARC,27,30 a phenomenon describing enhanced renal elimination of circulating solute, such as pharmaceuticals.29 Enhanced antibacterial elimination in this setting will then predispose to subtherapeutic drug concentrations,31 treatment failure, or the selection of drug-resistant bacterial strains.18

Current antibacterial dosing regimens rarely consider such issues in clinical practice, as the majority of schedules are derived from studies in healthy volunteers. In addition, a lack of reliable clinical end points to titrate therapy against makes dosage adjustment complicated. Therapeutic drug monitoring of antibacterial agents offers a useful objective measure that clinicians can use to optimize doses, when standard prescriptions may be insufficient.20

In this report, we present a case of SAH requiring EVD insertion, which was subsequently complicated by ventriculitis. In a unique fashion, TDM of both plasma and CSF were used to tailor antibacterial therapy in a patient with ARC, promoting clinical success. We highlight the difficulty in achieving therapeutic drug concentrations in such patients, review the relevant physiological disturbances impacting on pharmacokinetics, and we demonstrate the utility of TDM in optimizing antibacterial concentrations in this setting.

Our institution operates a 30-bed tertiary-level ICU that acts as a major referral center for neurosurgical patients. Specialist intensive care physicians are supported by an active neurosurgical service, with expertise in EVD insertion and management of SAH. From early 2009, TDM for a range of antibacterial agents (including β-lactams) has been available to optimize drug prescription, with utilization of this service at the discretion of the treating physician and/or clinical pharmacist.32

For intermittent dosing regimens, this involves drawing a blood sample (immediately prior to redosing) to determine a trough plasma drug concentration. This is typically performed after at least 4–5 doses have been administered, to ensure steady-state pharmacokinetics. In cases in which continuous infusions are used, a random blood sample is obtained after at least 4–5 half-lives. In this particular case, CSF samples were also obtained concurrently via the EVD. Antibacterial concentrations were then determined in both plasma and CSF by high performance liquid chromatography, as has been previously described in detail.15

Antibacterial doses were subsequently altered on the basis of these data, to ensure optimal bacterial eradication. For β-lactam dosing, a trough plasma concentration greater than the MIC of the causative pathogen was targeted,12 typically involving an increase in dose frequency. For vancomycin, plasma concentrations of 20–25 μg/ml were considered necessary to achieve effective CSF concentrations.17

In patients in whom plasma creatinine concentrations alone are considered a poor index of renal function, a measured CL_cr is also obtained at the time of TDM. This involves an 8-hour urine collection via an indwelling catheter, with determination of the plasma creatinine concentration at a point midway. This service (including TDM) is provided as a part of routine clinical care, and as such, informed consent was not considered necessary by our institutional review board (Royal Brisbane and Women’s Hospital, Human Research Ethics Committee). However, for the purposes of publication, written informed consent was obtained from the patient’s surrogate decision maker.

Case Report

History and Presentation. This 44-year-old alcoholic man (weight 95 kg, height 180 cm) with a history of withdrawal seizures, obstructive airway disease, hypertension, and depression was brought into his local emergency department following a seizure. A CT scan of the brain revealed a large volume of intraparenchymal hemorrhage predominantly in the left frontal lobe, intraventricular hemorrhage with concomitant obstructive hydrocephalus, and diffuse subarachnoid blood. This was associated with rupture of an anterior communicating artery aneurysm (Fisher Grade 4).

The patient was intubated for airway protection as his initial GCS score23 of 11 (E4, M6, V1) had deteriorated to 6 (E1, M4, V1). He was then transferred to our institution, the closest regional neurosurgical center. On arrival, he was assessed by the neurosurgical and neurointerventional service. An EVD was placed in the setting of hydrocephalus and worsening neurological status, and the patient underwent successful endovascular coiling of the aneurysm. A craniotomy was subsequently performed to evacuate the left frontal hematoma as it was noted to have expanded at angiography, causing significant mass effect. The patient was successfully extubated on Day 16 of the admission, at which point his GCS score was 13 (E3, M6, V4).

Treatment. The EVD was removed on Day 18 after isolation of Staphylococcus epidermidis in a CSF sample obtained according to routine departmental practice (sampling on alternate days). With no clinical signs of infection, no further treatment commenced. The following day, however, the patient’s condition deteriorated, with a decrease in GCS score to 8 (E3, M4, V1), new fevers (up to 40.2°C), and an increase in the peripheral white blood cell count (20.1 × 10^9/L, neutrophil count 18.0 × 10^9/L). The patient was therefore reintubated for airway protection, and he commenced taking vancomycin (2 g loading and 3.5 g/24 hrs continuous infusion) as empirical therapy for the susceptible Staphylococcus epidermidis (MIC 2 μg/ml) and meropenem (2 g 3 times per day) as treatment for a susceptible Klebsiella pneumoniae (MIC 2 μg/ml) that had, by this point, also been isolated from the same CSF sample.
Therapeutic drug monitoring in CSF

Vancomycin TDM was instituted immediately, but despite dose increases to 4.5 g/24 hrs (47 mg/kg/day) continuous infusion, plasma concentrations were still at subtherapeutic levels on Day 5 (Table 1). Concurrent with the low plasma vancomycin concentration, a measured CLCR was found to be markedly elevated at 375 ml/min/1.73 m² (reported reference range 74–126 ml/min/1.73 m²), consistent with ARC. Of note, the patient was not receiving vasopressor therapy or large-volume intravenous fluid therapy as this time. Subsequently, a further loading dose of vancomycin (500 mg) was given and the infusion increased to 6 g/24 hrs.

Therapeutic plasma vancomycin concentrations (23 μg/ml) were subsequently achieved, although a dose approximately 2–3 fold higher than generally recommended was needed (63 mg/kg/day). At this point, owing to worsening CT evidence of hydrocephalus and no clinical improvement, a new EVD was inserted (Day 23 of admission), thereby allowing CSF sampling. Despite therapeutic concentrations in plasma, CSF vancomycin concentrations were relatively low (3–6 μg/ml) with a CSF penetration ratio of 13%–17%, and remained low despite continuation of this dose.

With persistent growth of K. pneumoniae in the CSF, TDM of meropenem was also commenced using both plasma and CSF sampling. Meropenem plasma concentrations were undetectable (< 0.1 μg/ml) with empirical 2-g intravenous dosing 3 times daily (Table 2), and dosing was subsequently increased to 4 times daily, achieving plasma trough concentrations of 2.0–2.4 mg/L. As these concentrations achieved our predefined target (> MIC), the dosing regimen was not further altered. Of note, CSF concentrations of meropenem were similar to those seen in plasma, illustrating the significant difference in tissue penetration between the 2 antibacterial agents.

Posttreatment Course. Klebsiella pneumoniae continued to be isolated until Day 27 of admission (9 days after meropenem therapy was started), and meropenem was continued for 10 days after this (total 19 days of therapy). Vancomycin was discontinued after 14 days of therapy. A tracheostomy was inserted on Day 27 of admission, and the patient was successfully weaned from mechanical ventilation. Neurologically at this point he had made gradual improvement to a GCS score of 11 (E4, M6, V1 [due to tracheostomy]). With resolving hydrocephalus and sterile CSF samples, the EVD was removed on Day 30 of admission. The patient was subsequently discharged from the ICU for further rehabilitation.

**Discussion**

In this case, we report the difficulty in achieving adequate plasma and CSF drug concentrations when using standard antibacterial dosing regimens, reminding the prescriber that a one-size-fits-all approach is grossly flawed in the critically ill (doses up to 2–3 times those usually recommended were required for each antibacterial agent). Furthermore, we illustrate the value of TDM in allowing the clinician to escalate dosing to achieve optimal drug exposure, thereby improving the chances of clinical success. In addition, this was achieved without exposing the patient to undue toxicity and side effects.

Antibacterial agents vary considerably in both their pharmacokinetics characteristics (how the body deals with the drug), and their bacterial “kill” characteristics, or pharmacodynamics. An understanding of this relationship is essential to providing optimal therapy. In the case of β-lactams, maintaining a drug concentration greater than the pathogen’s MIC for a substantial period (T) of the dosing interval (T₅₀₀) is essential for bacterial eradication. For glycopeptides (such as vancomycin) this relationship is more complex, with the concentration time AUC over the course of 24 hours (AUC₀–₂₄) to MIC ratio (AUC₀–₂₄/MIC) being the pharmacokinetics/pharmacodynamics characteristic best associated with clinical cure.

As an example, a plasma AUC₀–₂₄/MIC ≥ 400 has been advocated to ensure optimal outcomes in methicillin-resistant Staphylococcus aureus pneumonia and was only achieved when plasma concentrations exceeded 30 μg/ml in our case, although how such a target translates to CNS infection remains uncertain. Typically, as AUC₀–₂₄/MIC values are infrequently measured, using TDM to manipulate intermittent dosing schedules on the basis of plasma trough concentrations provides the most readily available and reliable method to optimize vancomycin exposure.

However, our case highlights a key limitation in using TDM (particularly in the neurosurgical population), which is the use of plasma drug concentrations as a surrogate of those at the site of infection. In this scenario, vancomycin CSF concentrations were significantly lower (13%–17%) than those obtained in plasma, reinforcing CNS penetration as a major consideration in accurate dose selection. This is primarily a reflection of the differing pharmacokinetics properties of the drugs used, as

**TABLE 1: Vancomycin infusion doses and corresponding concentrations**

<table>
<thead>
<tr>
<th>Day of therapy</th>
<th>Infusion rate (g/24 hrs)</th>
<th>Plasma Concentration (μg/ml)</th>
<th>Plasma AUC₀–₂₄ (μg/ml × hr)</th>
<th>CSF Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.5</td>
<td>13</td>
<td>156</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>16</td>
<td>192</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>4.5</td>
<td>15</td>
<td>180</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>23</td>
<td>276</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>35</td>
<td>420</td>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE 2: Meropenem doses and corresponding concentrations**

<table>
<thead>
<tr>
<th>Day of Therapy</th>
<th>Dose</th>
<th>Serum Concentration (mg/L)</th>
<th>CSF Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2 g TDS</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>2 g QID</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>7</td>
<td>2 g QID</td>
<td>2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* QID = four times daily; TDS = three times daily.*
illustrated by the disparate CSF/plasma ratio for vancomycin and that for meropenem.

A previous review of CNS drug penetration has described the ratio of AUC in CSF to plasma for common antibacterial agents and identified AUC \(_{CSF}/AUC_{plasma}\) values of 0.39 for meropenem and 0.30 for vancomycin. While this is not directly comparable to our data (as only trough measurements were available for meropenem), the requirement for significantly higher doses of vancomycin to achieve therapeutic concentrations in this specific subset of patients is consistent with that of previous literature.

As CSF TDM is not widely available, our findings remind the clinician that higher plasma concentrations (necessitating higher empirical dosing) may be required when utilizing antibacterial agents with poor tissue penetration, such as glycopeptides. Previous guidelines have suggested targeting vancomycin plasma trough concentrations of 15–20 \(\mu\)g/ml, although no controlled trial data exist that directly assess the clinical outcome benefit of such an approach. Unfortunately, large-scale randomized studies are currently unfeasible, and in the absence of such, dosing should continue to use a sound pharmacokinetics/pharmacodynamics rationale. In this respect, a key area for further investigation is an improved understanding of the relationship between neurotoxicity (particularly for \(\beta\)-lactams) and drug concentrations, both in plasma and CSF, such that an upper limit can be defined. In combination with local susceptibility data, such information would enable dose adjustment that will ensure antibacterial efficacy while minimizing the potential for toxicity.

Altered patient physiology in critical illness, in particular ARC, will also complicate antibacterial prescription in this setting. While research is ongoing, a measured \(CL_{CR}\) of at least 130 ml/min/1.73 m\(^2\) has been used to define ARC in terms of subtherapeutic antibacterial plasma concentrations, although further validation of this cutoff is needed. These changes are principally a consequence of the underlying systemic inflammatory response, which results in a hyperdynamic, vasodilated state and increased organ blood flow.

In addition, the application of vasopressors and aggressive fluid replacement, as often used in suspected cerebral vasospasm, is also likely to promote ARC. Specifically, this phenomenon has been previously demonstrated in traumatic brain injured patients receiving directed therapy for intracranial hypertension, although data for SAH are currently lacking. The net result is the greater delivery of solute to the kidney and associated augmented elimination.

As both the glycopeptides and \(\beta\)-lactams are principally renally eliminated, ARC is likely to significantly alter the pharmacokinetic parameters of these agents. In this respect, plasma vancomycin concentrations have previously been shown to correlate well with measured creatinine clearance, and, in a prospective single-center observational study of septic ICU patients \((n = 93)\), vancomycin concentrations were significantly lower in the group of patients with ARC, leading to subtherapeutic exposure to the drug. Recent data exploring the relationship between ARC and \(\beta\)-lactam trough drug concentrations has also confirmed a robust relationship between elevated \(CL_{CR}\) values and subtherapeutic drug concentrations.

This case also illustrates the value of and need for early and regular antibacterial TDM in critically ill patients, where sufficient drug exposure is often difficult to appreciate. Neurosurgical patients in particular represent an at-risk ICU population, where, due to the lack of easily discernible clinical end points (such as the use of blood pressure when titrating antihypertensive medications), antibacterial underdosing may be common.

This is partially a reflection of the predominance of literature focusing on the identification of acute kidney injury and the subsequent need for dose reduction, rather than the converse scenario, where doses may in fact need to be increased. This is further compounded by the lack of sensitivity of mathematical estimates of renal function to identify ARC, limiting the recognition of this phenomenon. As such, in the absence of TDM, a measured \(CL_{CR}\) may provide a useful future clinical tool to identify such patients, although until additional safety and efficacy data are available, empirical dose escalation cannot be recommended.

Conclusions

This case emphasizes the difficulty in achieving therapeutic antibacterial concentrations in neurosurgical critically ill patients, both as a reflection of varying CNS penetration and enhanced drug elimination. As such, these considerations support the hypothesis that the standard antibacterial prescription is potentially flawed in this setting, although substantial additional research is required prior to advocating empirical dose adjustment. In this respect, the implications of altered physiology, such as ARC, on antibacterial dosing clearly requires further work, particularly in defining the incidence, investigating alternative dosing strategies, and assessing the likely clinical outcome impacts.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lipman, Udy. Acquisition of data: Lonsdale. Analysis and interpretation of data: Lonsdale, Udy, Roberts. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lipman. Statistical analysis: Lonsdale, Udy. Administrative/technical/material support: Lipman.

References

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