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Success With Extended-Infusion Meropenem After Recurrence of Baclofen Pump-Related Achromobacter Xylosoxidans Meningitis in an Adolescent

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Abstract:

A 13-year-old female experienced a recurrence of baclofen pump-related central nervous system (CNS) infection caused by Achromobacter, despite absence of retained foreign material. Due to the failure of meropenem (120 mg/kg/d in divided doses every 8 hours and infused over 30 minutes) in the initial infection, the dose was infused over 4 hours during the recurrence. Meropenem is an antibiotic for which efficacy is time dependent, and 4-hour versus 30-minute infusions have been shown to prolong the time the concentration of the antibiotic exceeds the minimum inhibitory concentration (MIC) of the organism at the site of infection (T>MIC). Meropenem serum concentrations were obtained and indicated that T>MIC was at least 75% of the dosing interval. Our patient improved with no noted recurrences or adverse effects on the extended-infusion meropenem regimen. Utilization of extended-infusion beta-lactam dosing whenever possible in the treatment of serious infections caused by gram-negative organisms should be considered, as this dosing appears to be safe and improves the probability of achieving pharmacokinetic/pharmacodynamic goals.

Background

Intrathecal baclofen pump devices allow for relief from spasticity due to achievement of optimal baclofen concentrations in the spinal cord without the adverse effects often observed with oral administration.[1] However, these devices can be associated with serious complications including infections at the pump implantation site and associated organ space infections such as meningitis.[2] Retrospective evaluations have suggested infection rates of these devices ranging from <5% up to 20%.[2-4] Commonly reported pathogens include *Staphylococcus aureus* (both methicillin susceptible and resistant) and coagulase-negative *Staphylococcus*, but *Enterococcus* species and gram-negative pathogens have been reported as well.[2-3,5] Depending on the extent of the infection, therapy may include systemic antibiotics and/or device removal.[6]

Achromobacter xylosoxidans is an aerobic gram-negative bacillus found in the environment, particularly in water.[7,8] It is a known human pathogen, mostly causing infection in patients with compromised immune systems, including bacteremia and pneumonia, but its status as a colonizer is unclear.[7,8] Meningitis cases caused by *A. xylosoxidans* have been reported in children and adults, with one known report of meningitis associated with an epidural catheter.[8,9] Although treatment failure or infection recurrence have been reported in device-related infections, particularly when the device is not removed, we found no reports in the literature of baclofen pump device infections that recurred after device removal.[2,5,10,11] We report a case of a patient with recurrent *A xylosoxidans* meningitis associated with an intrathecal baclofen pump device.

Case

A 13-year-old, 27.4-kg caucasian female receiving intrathecal baclofen therapy for cerebral palsy-associated spasticity was admitted for baclofen pump revision when part of the catheter was visualized exteriorly with breakdown at the site of catheter insertion into the spine. Cerebrospinal fluid (CSF) and fluid from the baclofen pump device insertion site were sent for culture during replacement of the malfunctioning catheter. Empiric therapy with gentamicin (192 mg [7 mg/kg] intravenously [IV] every 24 hours] and cefepime (1370 mg [50 mg/kg] IV every 8 hours, infused over 4 hours) was initiated when the cerebrospinal fluid (CSF) Gram stain indicated the presence of gram-negative rods. Culture and susceptibilities are illustrated in Table 1, and in consideration with clinical findings confirmed *A xylosoxidans*-associated baclofen pump device pocket infection and meningitis.

The device and all catheters were subsequently removed, and the antimicrobial therapy was changed based on the susceptibility findings to meropenem 1100 mg (40 mg/kg) IV every 8 hours, infused over 30 minutes. The patient completed 21 days of meropenem therapy at home via a peripherally inserted central catheter (PICC). At a follow-up appointment 7 days after completion of therapy, the patient was noted to be well and exhibiting no signs of infection.

Approximately 5 months later, the patient presented to the emergency department (ED) with complaints of progressive sleepiness over the previous month, with acute unresponsiveness and altered mental status. Computed tomography demonstrated hydrocephalus, an external ventricular drain (EVD) was inserted, and blood and CSF cultures were sent for analysis and culture. The CSF had 183 mg/dL protein and glucose <10 mg/dL. *Achromobacter xylosoxidans* was again isolated

from the CSF. Ceftazidime 2720 mg (100 mg/kg) IV every 8 hours and gentamicin 204 mg (7.5 mg/kg) IV every 24 hours were empirically initiated due to concern for meropenem resistance. Gentamicin was adjusted to 15 mg/kg IV every 24 hours following therapeutic drug monitoring in an effort to optimize achieved peak concentrations. Extrapolated gentamicin peak concentration following a dose of 10 mg/kg was 21 µg/mL, which was likely suboptimal due to the previous gentamicin minimum inhibitory concentration (MIC) of 16 µg/mL. Unfortunately an MIC taking into account the synergy of the dual agents was unavailable, so the optimal peak concentration for the synergistic gentamicin remained unclear. The patient's estimated volume of distribution based on this peak was 0.5 L/kg. Over the following 5 days, the patient showed signs of clinical improvement with negative CSF cultures but without return to baseline mentation. Upon demonstration of meropenem susceptibility (Table 2), therapy was changed to meropenem 1080 mg (40 mg/kg) IV every 8 hours, infused over 4 hours, and gentamicin was discontinued. Ceftazidime was avoided due to risk of infection with multidrug-resistant organisms following its use.[12] Given recurrence despite previous therapy with meropenem, serum meropenem concentrations were evaluated to ensure pharmacacodynamic target achievement. Blood samples were collected in red-top tubes and frozen for transport to ARUP Laboratories in Salt Lake City, Utah. Blood samples were to be obtained just prior to 10th meropenem dose, at the end of the 4-hour meropenem infusion, 2 hours after the end of the infusion, and 4 hours after the end of the infusion/just prior to the 11th dose. Cerebrospinal fluid sample was to be ideally obtained at end of 4-hour meropenem infusion, but neurosurgery workflow necessitated obtaining the sample from the EVD prior to administration of the 10th dose. Blood samples were obtained as planned, but the 11th dose was accidentally initiated early and the final sample was reflective of mid-infusion rather than the intended trough. Concentration determination occurred via quantitative bioassay in accordance with previous reports.[13,14]

Serum concentration results are available in Table 3. Using standard pharmacokinetic calculations to manipulate the obtained serum concentrations, the patient's volume of distribution was approximately 0.21 L/kg which is similar to the 0.3 to 0.4 L/kg that has been reported previously.15,16 The patient's estimated elimination constant (ke), calculated from the 2 values collected after cessation of the infusion, was 0.77 h^{-1} which correlates with an elimination half-life (t1/2) of 54 minutes, which is consistent with what is reported in individuals >2 years of age.17 The patient's estimated meropenem trough concentration was 2.5 µg/mL, which correlates with a trough concentration in the CSF of 0.05 to 0.15 µg/mL using 2% to 6% CSF–blood penetration ratio as has been reported.9,17,18 The meropenem concentration at the end of the infusion was 50 µg/mL, indicating that the concentration throughout the 4-hour infusion most likely remained above the MIC during that time. The correlating CSF meropenem concentration using previously reported CSF penetration ratios would be 1 to 3 µg/mL, which is consistent with the reported value of <5 µg/mL. Using the calculated half-life, this would represent a meropenem concentration in the CSF that exceeded the MIC of the organism for 75% to 95% of the dosing interval, which exceeds the 40% needed for bactericidal activity with carbapenems.19 It was therefore assumed that pharmacodynamic target attainment for meropenem was achieved.

The patient continued to improve clinically and returned to baseline mental status by day 10 of meropenem therapy. Six weeks of meropenem was completed via PICC at home with no further recurrences to date.

Discussion

Although *Achromobacter* has been reported as a cause of health care-associated infections, we did not find reports of this organism causing infections related specifically to the presence of a baclofen pump device. Due to the limited antimicrobial susceptibilities displayed by this organism, broad-spectrum therapy with a carbapenem was required.

This patient's organisms were not specifically genetically typed, but it was assumed that the second *Achromobacter* meningitis represented relapse or primary treatment failure, rather than a completely new infection. While it may not be unusual for a course of antibiotics to essentially fail in the presence of retained foreign material, in this case there were no remaining foreign materials.[3] It is possible that some infected tissue remained after the initial meropenem therapy, which could be attributed potentially to inadequate dosing, inadequate duration, or inadequate surgical management. It could also be that this patient remained colonized with *A xylosoxidans* post meropenem therapy which lead to reinfection.

Meropenem serum concentrations are not generally obtained as part of routine practice, but serum concentrations were monitored to ensure pharmacokinetic/pharmacodynamic goals were met due to the recent therapeutic failure of meropenem. It is believed that the desired pharmacodynamic exposure was achieved based on the meropenem serum concentrations obtained. The efficacy of beta-lactam antibiotics is dependent upon the time the concentration of the antibiotic exceeds the MIC of the organism at the site of infection (T>MIC).[19] In our case, administration time was extended from the usual 30 minutes to 4 hours as this has been shown to prolong T>MIC.[20,21] In our institution, extended-infusion times for antipseudomonal beta-lactams are commonly used in order to improve pharmacodynamic target attainment.[22] Extending infusion times of antipseudomonal beta-lactams has been shown to improve pharmacodynamic target attainment in both adults and children and has been associated with reduced mortality in critically ill adults with serious gram-negative bacterial infections.[21,23-26] This is especially important when treating infections where the site of infection may be difficult to penetrate with antibiotics or infections caused by organisms with higher MICs, such as *Pseudomonas aeruginosa.* Failed initial treatment with a 30-minute interval could have been related to lack of achievement of 40% T>MIC which could lead to suboptimal or incomplete killing and potential organism regrowth. Through use of Monte Carlo simulations, Courter and colleagues determined that infusion of meropenem over 3 hours as opposed to 30 minutes significantly improved the probability of target attainment (40% free T>MIC), such that 97% of patients would experience achieved target attainment for isolates with MICs as high as 8 µg/mL. Although the MIC for the *A xylosoxidans* was 0.25 µg/mL in our case, the aforementioned probabilities of target attainment assume an infection site in the blood. As it is more difficult for antibiotics to reach the CSF when compared to the blood, it is anticipated that target attainment would be more difficult to achieve for the same MIC in the CSF when compared to the blood. The longer infusion time for meropenem in our case is certainly not a new concept; use of extended-infusion meropenem has been reported in at least 3 previous adult

patients (aged 38, 54, and 61 years) for treatment of gram-negative meningitis.[13,14] All patients recovered, experienced no adverse effects, and experienced CSF meropenem concentrations that exceeded the MIC of the organisms nearly 100% of the time. Unfortunately, we did not have as many optimally timed CSF or serum concentrations as in previously reported cases, but we were still able to document optimized therapy. The lack of 100% T>MIC in our case may be explained by the fact that children may clear beta-lactam antibiotics more quickly than adults or by the minimal inflammation experienced by our patient.

Conclusion

Although the reason for the recurrence following removal of all foreign material is unclear, the patient was treated successfully using meropenem infused over 4 hours for a total duration of 6 weeks. The patient did not experience toxicity due to the meropenem, as determined by no change in weekly complete blood count and basic metabolic panel, and no signs and symptoms of infection have been detected at 6 months of follow-up. These authors would recommend utilization of extended-infusion beta-lactam dosing whenever possible in the treatment of serious infections caused by gram-negative organisms, as it appears to be safe and improves the probability of achieving pharmacokinetic/pharmacodynamic goals.

Article Notes

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Table 1. Culture Results During First Admission.

Achromobacter xylosoxidans

	CSF		Wound (device insertion site)	
Antibiotic	MIC, μg/mL	Interpretation	MIC, μg/mL	Interpretation
Amikacin	≥64	R	≥64	R
Ampicillin/sulbactam	≥32	R	16	I
Cefepime	16	I	16	I
Ceftazidime	4	S	4	S
Ceftriaxone	≥64	R	≥64	R
Ciprofloxacin	NR	NR	2	I
Gentamicin	≥16	R	≥16	R
Levofloxacin	NR	NR	4	I
Meropenem	0.25	S	NR	NR
Sulfamethoxazole/ trimethoprim	NR	NR	≤20	S
Tobramycin	8	I	≥16	R

Abbreviations: CSF, cerebrospinal fluid; I, intermediate; NR, not reported; R, resistant; S, susceptible.

Table 2. CSF Culture Results During Second Admission.

Achromobacter xylosoxidans

Drug	MIC, μg/mL	Interpretation
Amikacin	≥64	R
Ampicillin/sulbactam	16	I
Cefepime	16	I
Ceftazidime	4	S
Ceftriaxone	≥64	R
Colistin	1	S
Gentamicin	≥16	R
Levofloxacin	3	I
Meropenem	0.25	S
Tobramycin	8	I

Abbreviations: CSF, cerebrospinal fluid; I, intermediate; NR, not reported; R, resistant; S, susceptible.

Table 3. Timeline of Meropenem Doses and Obtained Concentrations.

Time	Dose	Concentration (site)	Relation to dose
0613	1080 mg		
1400		<5 μg/mL (CSF)	7.75 hours after previous dose start
1425		5 μg/mL (blood)	8.2 hours after previous dose start
1454	1080 mg		
1900		50 μg/mL (blood)	End of 4-hour dose infusion
2123		8 μg/mL (blood)	2.4 hours after end of dose infusion
2211	1080 mg		
2230		49 μg/mL (blood)	20 minutes after beginning of new dose

Abbreviation: CSF, cerebrospinal fluid.