Safety of intravenous push administration of beta-lactams within a healthcare system

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Purpose. A critical shortage of small-volume parenteral solutions in late 2017 led hospitals to develop strategies to ensure availability for critical patients, including administration of antibiotics as intravenous push (IVP). Minimal literature has been published to date that assesses the safety of administration of beta-lactams via this route. Therefore, the purpose of this study was to evaluate the safety of IVP administration of select beta-lactam antibiotics.

Methods. We performed a retrospective review of IVP administrations of aztreonam, ceftriaxone, cefepime, and meropenem at two campuses of the New York University Langone Health system after October 2017. Patients receiving surgical prophylaxis or more than one IVP antibiotic simultaneously were excluded. The primary endpoint was adverse events (ADE) following IVP administration of antibiotics.

Results. We evaluated 1000 patients who received IVP aztreonam (n = 43), ceftriaxone (n = 544), cefepime (n = 368) or meropenem (n = 45). There were 10 (1%) ADE observed, 5 of which were allergic reactions. Four ADE were neurotoxicity related to IVP cefepime. Based on the Naranjo score, 1 adverse event was "probably" and 3 were "possibly" related to cefepime IVP administration. Lastly, only 1 report of phlebitis was observed with the use of IVP ceftriaxone.

Conclusions. The use of IVP as an alternative to intravenous piggyback (IVPB) during times of drug shortage for select beta-lactam antibiotics appears to be safe, and ADE are similar to those previously described for IVPB administration. Future studies evaluating clinical outcomes between IVP and IVPB administration may be of benefit.

Keywords: antibiotics, beta-lactams, drug administration, drug safety, sterile products

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Drug shortages due to manufacturing issues and natural disasters have become an important issue in the delivery of medical care. In 2017, a critical shortage of small-volume parenteral solutions (SVPS) led many hospitals to develop various strategies for rationing these fluids, including the administration of antibiotics as intravenous push (IVP).[1] Given the high concentration and the fast rate of administration when administering an antibiotic as IVP over 5 minutes as compared to intravenous piggyback (IVPB) over 30 minutes, the higher maximum serum concentration poses the risk for an increase in dose-dependent adverse effects.

Although the package insert for some beta-lactam agents provide recommendations for IVP, there is limited published data which assesses the incidence of adverse reactions when using this method and rate of administration.[2-12] Literature describing cephalosporin administration as IVP found overall low rates of phlebitis or infusion reactions, with no differences compared to IVPB.[6,8-11,13] However, these studies were limited to evaluations of phlebitis or injection site reactions,

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without evaluations for cardiac disturbances or neurotoxicity.

New York University Langone Health (NYULH) implemented a health system–wide IVP action plan for select antibiotics as a solution to the shortage of SVPS. Given the limited availability of safety data, the main objective was to evaluate the safety of IVP beta-lactam administration by examining the incidence of reported adverse events.

KEY POINTS

- During times of small-volume parenteral solution shortage, utilization of intravenous push administration of antibiotics across a hospital system is logistically feasible.
- Multidisciplinary teams consisting of pharmacists, nurses, physicians, and information technologists play a vital role in implementation of strategies to combat drug shortages.
- Intravenous push administration over 5 minutes for aztreonam, ceftriaxone, cefepime, and meropenem is safe during shortage of small-volume parenteral solutions.

Methods

Study design, setting, and patient population. The study was a retrospective cohort study conducted at the Tisch and Brooklyn campuses of NYULH, a health-system consisting of approximately 1,500 beds. Due to the retrospective design of this observational project intended for quality assurance purposes, informed consent was not required, and this project was exempt from Institutional Review Board review. The electronic health records (EHR) of unique, consecutively admitted patients 18 years of age or older who received at least two doses of IVP aztreonam, ceftriaxone, cefepime, or meropenem from October to December 2017, the first 3 months after IVP action plan implementation, were evaluated for inclusion. Patients were excluded if they received IVP antibiotics for surgical prophylaxis, were pregnant, or received more than one IVP antibiotic on the same day. For the majority of surgical procedures at NYULH, cefazolin is the first-line agent recommended for prophylaxis, and the safety of cefazolin IVP has been previously established.[6,10,11,13] Patients receiving daptomycin and oxacillin IVP were not included in this analysis given the limited sample size of patients on these agents during this time period. Although meropenem and aztreonam are FDA approved for IVP administration, there is limited guidance on maximum doses that can be administered via this route.

Mandatory antibiotic IVP action plan implementation. A mandatory antibiotic IVP action plan was implemented in October 2017 (Table 1). Medication records in the EHR were modified to the IVP formulation with the appropriate diluent and administration instructions. Only the IVP medication records were available to order in the EHR for all indications via an alternative use alert, however, exceptions to IVP were allowed with approval from a clinical pharmacy manager. Education was provided to all nursing staff prior to implementation of the IVP action plan. The select antibiotics were supplied as vials in the automated dispensing cabinet for nurses to reconstitute, or compounded and dispensed by pharmacy personnel. Administration instructions within the medication orders included directions on reconstitution and manual administration as a slow push over 5 minutes for nursing staff. Monitoring parameters included observing for injection site reactions, changes in mental status, changes in heart rate, palpitations, diaphoresis, restlessness, gastrointestinal disturbances, seizures and seizure-like activity for one hour after administration. Adverse events were required by institutional policy to be documented in the EHR by the bedside nurse, with supplemental information provided by primary provider notes. Nursing documentation per shift includes line flowsheets, nursing shift flowsheets, and nursing notes for significant events requiring medical attention.

Data collection. Electronic health record queries were performed to generate a list of patients who received IVP aztreonam, ceftriaxone, cefepime, or meropenem at NYULH–Tisch or Brooklyn Hospitals during the designated study period. Patient demographics, past medical history, relevant concomitant medications, antibiotic administration including antibiotic agent, dose, frequency, number of doses, indication and line access, and adverse events were collected for each patient meeting inclusion criteria. Adverse events were collected by reviewing provider notes, line flowsheets, vitals graphs, and nursing flowsheets, alongside medication administration records.

Study outcomes. The primary outcome of the study was the incidence of adverse events (ADE), obtained from the nursing documentation in the EHR as well as supplemental provider documentation. Adverse events that were assessed included phlebitis, allergic reactions, infusion-related reactions, gastrointestinal disturbances, cardiac changes, and neurologic disturbances. Phlebitis was graded according to the Visual Infusion Phlebitis Scale.[14] Infusion-related reactions included flushing, alterations in blood pressure or heart rate, diaphoresis, and palpitations. Gastrointestinal disturbances included abdominal discomfort, diarrhea, nausea, and vomiting associated with antibiotic administration in the absence of an alternate explanation. Cardiac changes included alterations in blood pressure or heart rate, and palpitations experienced within 1 hour of IVP administration. Finally, neurologic disturbances included altered mental status, restlessness, peripheral neuropathy or seizures. For each ADE, the type of management was documented and a Naranjo score, which standardizes

Table 1. NYULH Mandatory Antibiotic IVP Action Plan

Drug	Dosage Form	Reconstitution Instructions	Nursing Administration Instructions
Ceftriaxone	1-gram vial 2-gram vial	Reconstitute 1 gram with 10 mL 0.9% sodium chloride Reconstitute 2 grams with 20 mL 0.9% sodium chloride	IVP over 5 minutes **Monitoring**: within 1 hour of administration monitor for the following: • Injection site reactions • Changes in the following: ◦ Mental status ◦ Heart rate • Palpitations • Diaphoresis • Restlessness • Seizures
Cefepime	1-gram vial 2-gram vial	Reconstitute 1 gram with 10 mL 0.9% sodium chloride 2-gram/20 mL syringe will be dispensed by pharmacy	
Meropenem	500-mg vial 1-gram vial	Reconstitute 500 mg with 10 mL sterile water for injection Reconstitute 1 gram with 20 mL sterile water for injection	
Aztreonam	1-gram vial 2-gram vial	Reconstitute 1 gram with 10 mL 0.9% sodium chloride 2-gram/20 mL syringe will be dispensed by pharmacy	
Cefazolin	1-gram vial	Reconstitute 1 gram with 10 mL 0.9% sodium chloride or sterile water for injection	
Daptomycin	500 mg vial	Doses less than 500 mg will be prepared and dispensed by pharmacy	
Oxacillin	1-gram vial 2-gram vial	Reconstitute 1 gram with 10 mL NS or SWFI Reconstitute 2 grams with 20 mL of NS or SWFI	

Abbreviations: IVP, intravenous push; NS, 0.9% sodium chloride; NYULH, New York University Langone Health; SWFI, sterile water for injection.

assessment of causality for adverse drug reactions, was calculated.[15]

Statistical analysis. Descriptive statistics were used to summarize demographic and clinical characteristics. Categorical variables were described as frequencies and proportions, and continuous variables were described as medians with interquartile ranges (IQRs).

Results

A total of 1,134 consecutive patients who received IVP aztreonam, ceftriaxone, cefepime, or meropenem between October 2017 and December 2017 were reviewed. After excluding 134 patients, primarily due to receipt of multiple IVP antibiotics concomitantly (82), missing documentation (19), and receipt of only one dose of the IVP antibiotic (18), we included a total of 1,000 patients. The median age was 70 years (IQR 56, 83) and 55% were female, with a median body mass index of 26 kg/m^2 (IQR 22, 30). The median creatinine clearance at the start of IVP was 57 ml/min (IQR 33, 88), and 34 (3%) patients were receiving dialysis. Sixty-four (6%) patients had a history of seizures and 179 (18%) were on at least 1 antiepileptic medication. There was a median of 2 (1, 3) peripheral lines placed per patient during IVP antibiotic administration. Three hundred seventy-nine (38%) patients had a history of allergic reaction to a medication, 149 (15%) were receiving corticosteroids, and 199 (20%) were receiving antihistamines during IVP antibiotic administration. The majority of patients (82%) were on anticoagulation for either prophylaxis or treatment of thromboembolism. The most common suspected or confirmed indications for receiving antibiotics were pneumonia (31%), urinary tract infections (28%), or intra-abdominal infections (19%). (Table 2)

Five hundred forty-four (54%) patients received a median of 3 (IQR 2, 5) doses of ceftriaxone for a median of 3 days (IQR 2, 5). Three hundred sixty-eight patients (37%) received a median of 8 (IQR 4, 13) doses of cefepime for a median of 4 days (IQR 3, 6). Forty-five patients (5%) received a median of 10 (IQR 6, 16) doses of meropenem for a median of 5 days (IQR 3, 7). Forty-three patients (4%) received a median of 7 (IQR 4, 11) doses of aztreonam IVP for a median of 3 days (IQR 2, 5).

There were a total of 10 (1%) ADE seen among 10/1000 patients. Five of these reactions were attributed to allergic reactions that were not correlated with the IVP administration of antibiotics. Allergic reactions included 1 episode of drug reaction with eosinophilia and systemic symptoms with ceftriaxone, 1 episode of rash with ceftriaxone, 1 episode of hives with ceftriaxone, and two episodes of rash with cefepime. One adverse reaction was an infiltration of a 20-gauge antecubital peripheral venous line after 6 doses of ceftriaxone IVP resulting in a grade 2 phlebitis. The line was changed and ceftriaxone IVP was continued without further ADE. The patient was not receiving any other i.v. medications at the time of the ADE, and the calculated Naranjo score was 1, indicating the ADE was

Table 2. Characteristics of Antibiotic Administration

Variable	Patients (*n* = 1000)
Access	
Central line	125 (13)
Peripheral line	962 (96)
Peripheral venous line	951 (99)
Midline	53 (6)
Number of lines per patient, median (IQR)	2 (1, 3)
Indication for antibiotic therapy[a]	
Pneumonia	310 (31)
Urinary tract infection	275 (28)
Intra-abdominal infection	194 (19)
Skin/soft tissue infection	57 (6)
Febrile neutropenia	31 (3)
Bacteremia	30 (3)
Osteomyelitis	28 (3)
Sepsis	17 (2)
Meningitis	15 (2)
Fever unknown origin	10 (1)
Endocarditis	7 (1)
Spontaneous bacterial peritonitis	6 (1)
Non-meningeal central nervous system infection	2 (0.2)
Other indication[b]	22 (2)
Antibiotic therapy	
Ceftriaxone	544 (54)
Every 12 hours	13 (2)
Every 24 hours	531 (98)
Cefepime	368 (37)
Every 8 hours	282 (77)
Every 12 hours	61 (17)
Every 24 hours	25 (7)
Meropenem	45 (5)
Every 6 hours	12 (27)
Every 8 hours	17 (38)
Every 12 hours	10 (22)
Every 24 hours	6 (13)
Aztreonam	43 (4)
Every 8 hours	38 (88)
Every 12 hours	4 (9)
Every 24 hours	1 (2)

Abbreviations: IQR, interquartile range.
All values are expressed as *n* (%) unless otherwise noted.
[a]Patients may have had more than one indication for antibiotic therapy.
[b]Other indications include: Unknown (4), leukocytosis (3), bronchitis (2), foreign body prophylaxis (2), septic joint (2), kidney transplant (1), catheter infection (1), COPD exacerbation (1), Lemierre's syndrome (1), parotitis (1), proctocolitis (1), cardiac arrest prophylaxis (1), suppurative sialadenitis (1), and surgical site infection (1).

"possibly" related to IVP ceftriaxone. Four (40%) adverse reactions were related to neurotoxicity with the use of cefepime IVP. The neurotoxicity characterized in these elderly patients included altered mental status and myoclonic jerking. Three of these patients had appropriate renal dose adjustment while one patient received a higher dose than recommended. Three cases were graded as "possibly" and one case was graded as "probably" related to IVP administration of cefepime according to the Naranjo score. Details of these patients can be found in Table 3.

Discussion

Aztreonam, ceftriaxone, cefepime, and meropenem were safely administered via IVP during a shortage of SVPS at NYULH. In a total of 10 (1%) ADE, 5 were allergic reactions that were not correlated with IVP administration. Four ADE were neurotoxicity related to IVP cefepime and one report of phlebitis was observed with the use of IVP ceftriaxone.

The existing evidence evaluating IVP beta-lactams has mainly assessed the rates of phlebitis.[8-10,13] Of the many factors that can contribute to phlebitis, osmolarity and rate of administration have been theorized to play significant roles.[16-18] Administration of a medication with an osmolarity greater than 900 mOsm/L through a peripheral line is thought to put the patient at a higher risk for development of phlebitis. The osmolarity of IVP beta-lactams is determined by the individual beta-lactam and the diluent used for its reconstitution.[19] Based on a review of the literature, the osmolarity of aztreonam and meropenem at the concentrations used by NYULH has not been described. However, Gandhi and colleagues conducted osmolarity testing of various beta-lactam antibiotics reconstituted in 10 mL of 0.9% sodium chloride, and found that the osmolarity of ceftriaxone 1 gram in 10 mL 0.9% sodium chloride was 658 mOsm/L, and of cefepime 1 gram in 10 mL 0.9% sodium chloride was 1,040 mOsm/L.[20] Despite the high osmolarity of cefepime

Table 3. Details of Cefepime Neurotoxicity Adverse Reactions (*n* = 4)

IVP Antibiotic	# Doses Prior to Event	Type of i.v. access	Other Concomitant Medications	Naranjo Score	Description of Adverse Event
Cefepime every 8 hours	23	20-, 22-gauge PVL Antecubital, Cephalic, Basilic	Anticoagulant, Antiepileptic drug (seizure history)	3	• 93-year-old M with ICH c/b seizures secondary to hyponatremia. • Patient on cefepime 1 g every 8 hours (CrCl 55 ml/min) and metronidazole for parotitis with continued intermittent myoclonic jerking after correction of hyponatremia. • Primary team concerned for cefepime neurotoxicity so patient was changed to oral ciprofloxacin.
Cefepime every 24 hours	6	20-gauge PVL Cubital, Metatarsal	Anticoagulant	4	• 89-year-old F with acute hypoxic respiratory failure, PNA and UTI on cefepime 1 g every 24 hours (CrCl 8 ml/min, started on dialysis) and vancomycin with encephalopathy. • Team changed cefepime to piperacillin/tazobactam on day 6 of therapy given concern for continued AMS due to cefepime neurotoxicity. • Patient's AMS improved. • Differential included cefepime, toxic-metabolic in setting of infection, hypoxia, uremia, and hypoglycemia.
Cefepime every 8 hours	3	20-, 22-gauge PVL Metacarpal, Basilic	Anticoagulant Corticosteroid	5	• 84-year-old M with increasing SOB, cough, and hypoxia on cefepime 1 g every 8 hours (CrCl 75 ml/min) and azithromycin • Patient also with acute confusion and AMS • ID consult suggested discontinuation of cefepime due to concern for neurotoxicity.
Cefepime every 12 hours → every 24 hours	12	20-, 22-gauge PVL Cephalic, Basilic	Anticoagulant Antihistamine	2	• 81-year-old F with septic/cardiogenic shock and obtunded in setting of uremia, fevers, and sepsis. • Cefepime dose not adjusted (every 12 hours) for declining renal function (CrCl < 10 ml/min) for 3 days until dialysis was initiated, at which point cefepime was changed to every 24 hours. • AMS did not improve with dialysis • ID consult recommended change antibiotics to piperacillin/tazobactam with concern for cefepime neurotoxicity.

Abbreviations: AMS, altered mental status; c/b, complicated by; ICH, intracranial hemorrhage; IVP, intravenous push; IVPB, intravenous piggyback; F, female; M, male; NYULH, New York University Langone Health; PNA, pneumonia; PVL, peripheral venous line; UTI, urinary tract infection.
The patient who experienced phlebitis had a history of tolerating ceftriaxone as IVPB. All other cases of adverse events had not received the same antibiotic as IVPB at NYULH in the past.

at this concentration, we did not observe any infusion site reactions with cefepime administered as IVP via peripheral lines. We hypothesize that this finding was due to the minimal duration (5 minutes or less) of cefepime administration through the line, a finding similar to that of previously published literature evaluating ADE with 3% sodium chloride (1,026 mOsm/L) administered peripherally for a mean duration of 47 minutes.[21]

The rate of administration between each individual beta-lactam has varied throughout the literature. Garrelts and colleagues published a prospective, randomized study comprised of 60 patients who received cefmetazole IVPB over 30 minutes vs IVP over 3 minutes for the purpose of surgical prophylaxis.[8] No statistically significant difference in phlebitis was observed. Another study evaluated cefepime administration over 3-, 5-, 10-, or 15-minute periods, and found no serious ADE, however, the total volume of solution utilized was 50 mL.[9] Additionally, in a prospective, observational study consisting of 240 adult orthopedic surgical patients, there was no observed differences in the rates of phlebitis in candidates who received cefazolin IVPB over 30 minutes compared to IVP over 3 to 5 minutes (3.4% vs 3.3%, P = NS).[13] The authors also conducted a univariate analysis that highlighted that patients with more catheter days (2 vs 1.36) were at a greater risk of phlebitis.[13] For IVP carbapenems, Norrby and colleagues reviewed 2,457 administrations of meropenem i.v. given over 30 minutes vs 5 minutes, and found a phlebitis occurrence rate of 0.7%.[22] The authors reported 165 patients receiving one or more doses of meropenem by bolus injection administered over approximately 5 minutes, with no reports of drug-related ADE specifically attributed to the speed of administration. Overall, the reported rate of phlebitis in prior studies of IVP beta-lactams ranges from 0–3.3%.[8-10,13] In line with previous literature, we found an overall phlebitis rate of 0.4%. Despite the limited patient population and small sample sizes, these studies demonstrate that IVP administration of cephalosporins and carbapenems has similar rates of phlebitis as compared to IVPB.

Our study expands on the existing literature for the safety of IVP administration of beta-lactam antibiotics. In the prior studies, patients received only the first dose of antibiotic administration as IVP, and the indication was mainly limited to surgical prophylaxis.[6,8-12] In comparison, patients at our institution received IVP for the duration of their antibiotic course, regardless of indication. Furthermore, while prior studies limited their evaluation to phlebitis, we included observation for cardiac, neurologic, and gastrointestinal disturbances.[8-10] We found 4/368 (1%) cases of neurotoxicity associated with the use of cefepime IVP, a finding similar or less than that reported in previous literature with IVPB administration.[23-25] Similarly to Appa and colleagues, we found that cefepime neurotoxicity occurred in elderly patients with varying levels of renal function. Only one case in our report was graded as "probably" related to IVP CEF administration according to the Naranjo score.

Administration of beta-lactam antibiotics as IVP over 5 minutes may lead to suboptimal pharmacodynamic target attainment given their time-dependent activity.[7,26] As there was no evaluation of efficacy in our study, further literature comparing IVP to IVPB is necessary to ensure this route of administration is not associated with worse clinical response. Furthermore, the NYULH protocol recommends administration of IVP over 5 minutes, and as administration was completed manually by nursing staff rather than via a syringe pump, there is no documentation of the actual rate of infusion in this cohort. It was possible that administration of these IVP antibiotics occurred over a duration of less than 5 minutes. Given the retrospective nature of this study, collection of ADE relied on documentation in the medical record by either nursing or the provider, and therefore the rate of ADE may have been underestimated. While our sample size for aztreonam and meropenem IVP was small, these antibiotics are FDA approved for administration via this route, and our data supports the safety of this administration strategy. Finally, we did not directly compare IVP to IVPB administration in this study due to its nature as a quality assurance project during the shortage. Despite these limitations, the use of IVP administration was safe in this real-world setting and can be considered as a fluid conservation strategy in times of shortage of SVPS.

Conclusion

The use of IVP as an alternative to IVPB during times of drug shortage for select beta-lactam antibiotics appears to be safe, and ADE are similar to those previously described for IVPB administration. Future studies evaluating clinical outcomes between IVP and IVPB administration may be of benefit.

Disclosures

The authors have declared no potential conflicts of interest.

Additional information

The data have been presented in poster format at the ASHP Midyear Clinical Meeting in Anaheim, CA, in December 2018 and at the Making a Difference in Infectious Diseases (MAD-ID) Annual Meeting in Orlando, FL, in May 2019.

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