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High-Dose Daptomycin Is Well Tolerated via 2-Minute IV Push Administration

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Abstract

Background: The purpose of this study was to evaluate the safety of administering high-dose daptomycin (HDD; > 6 mg/kg actual body weight) as a 2-minute intravenous (IV) push (IVP) compared to traditional 30-minute IV piggyback (IVPB) infusion.
Methods: Retrospective cohort study comparing patients receiving HDD as an IVP or IVPB infusion. The primary outcome was the proportion of patients with a documented infusion-related reaction (IRR) to daptomycin.
Results: Three hundred patients were included in the final analysis, 200 patients received IVP, and 100 patients received IVPB representing a total of 1697 administrations. Median (IQR) daptomycin dose was IVP 700 mg (550-900) and IVPB 700 mg (600-900), with mg/kg doses of 8.2 (7.9-10) and 8.3 (8-10), respectively. After adjudication, IRR occurred in 1% of subjects in each treatment group.
Conclusions: This study provides data in more than 1100 administrations of HDD administered via IVP. Infusion-related reactions were documented in 1% of patients regardless of infusion method, suggesting comparable safety to traditional infusion methods. This practice may be useful during fluid shortage and in the outpatient setting.

Keywords

daptomycin, infusion intravenous, medication safety, pharmaceutical preparations

Background

In the setting of drug shortages, hospitals and health systems must adapt to best fulfill patient's health care needs.[1,2] Experts recommend drug shortage response strategies including utilizing therapeutic and administration alternatives.[3] Intravenous fluid shortages are especially problematic because they impact all medications given by intravenous infusion. Changing administration of medications traditionally administered diluted in IV base solutions to IV push (IVP) helps conserve IV base solution for medications that must be administered via a diluted infusion.

Safety data support 2-minute infusions of IV daptomycin up to the labeled dose of 6 mg/kg. The pharmacokinetic exposure and tolerability was similar between patients receiving a 2-minute infusion of daptomycin compared to the traditional 30-minute infusion.[4,5] However, high-dose daptomycin (HDD), defined as doses greater than 6 mg/kg actual body weight, have been associated with improved outcomes in both invasive staphylococcal and enterococcal infections.[6-8] Case reports describe infusion-related reactions (IRR) with administering daptomycin rapid IV infusion using a 6 mg/kg dose.[9] This data raise the question if administering off-label dosing as an IVP carries a different safety profile.

At our institution, daptomycin was transitioned to IVP administration in fall 2017. Intravenous push daptomycin was administered via syringe by nursing staff over at least 2 minutes without an IV syringe pump. The purpose of this study was to evaluate the safety of administering HDD as a 2-minute IV push (IVP) compared to traditional 30-minute IV piggyback (IVPB) infusion.

Methods

The present study was an institutional review board (IRB)-approved, retrospective cohort study in a 5-hospital health system. Patients were identified through the electronic medical record if they received daptomycin doses greater than 6 mg/kg actual body weight and were admitted during January 9, 2017 to January 9, 2018. Patients receiving HDD as an IVP diluted in sterile water for injection were compared to

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Table 1. Baseline Characteristics.

Baseline characteristics	Rapid infusion, n = 200	Traditional infusion, n = 100
Female, n (%)	99 (50)	35 (35)
Age, median (IQR), years	61 (49-71)	63 (52-74)
Actual body weight, median (IQR), kg	83 (68-102)	78 (68-104)
BMI, median (IQR), kg/m^2	28 (23-35)	27 (23-32)
Dialysis, n (%)		
At baseline[a]	25 (13)	22 (22)
During admission	42 (21)	30 (30)
CL_{cr} (non-HD patients), median (IQR), mL/min	94 (54-165)	98 (55-138)

Note. IQR = interquartile range; BMI = body mass index; CL_{cr} = estimated creatinine clearance (Cockcroft-Gault equation); HD = hemodialysis.
[a]$P < .05$.

patients receiving an IVPB diluted in 50 mL of normal saline.[4] Doses were administered in the IVP group by nurses without syringe pumps, while the IVPB were administered using automated IV pumps. All daptomycin IVPB and IVP were prepared in the central pharmacy using sterile compounding techniques. Patients were included if they received at least 2 doses of daptomycin during their inpatient admission. Patients were excluded if they were pregnant, less than 18 years of age, or received amphotericin B or a monoclonal antibody infusion during the index admission.

Characteristics of patient receiving HDD were collected from the electronic medical record using a standardized data collection instrument. The primary endpoint was the proportion of patients with documented infusion-related reactions (IRRs) in the IVP and IVPB groups. Infusion-related reactions were assessed by the investigator based on nursing documentation, medication administration record documentation, and documentation by health care providers in the medical record meeting any of the following symptoms: Skin reaction, shortness of breath, fever, hypotension, hypertension, chills, pain at infusion site, puritis, or flushing. A maximum of 10 administrations per patient were assessed. Any patient with a potential IRR was assessed and scored using the Naranjo algorithm.[10] All identified IRRs were adjudicated blinded to administration method by 2 clinical pharmacy specialists.

The secondary safety outcome was the proportion of patients who had creatinine phosphokinase (CPK) elevations or musculoskeletal-related adverse reactions. Creatinine phosphokinase elevations were defined as follows: if CPK was below the upper limit normal (ULN) on baseline, 2 levels >2 times ULN or 1 level >5 times ULN; if baseline CPK is above ULN, 2 levels >5 times ULN.[11] Musculoskeletal adverse reactions were evaluated through documentation in the medical record.

Baseline characteristics were analyzed using descriptive statistics including median (interquartile range [IQR]) or mean (standard deviation [SD]) for continuous data following non-parametric or parametric distribution as appropriate. Continuous data were compared using the Mann-Whitney *U* test or Student *t* test, as appropriate. Nominal data were described with absolute count (percentage) and compared using the chi-squared test or Fisher exact test.

Given the expected uncommon event rate, a 2-step sample size calculation was used to first evaluate what percent prevalence could be detected with the given data. To estimate a sample size to generate a 95% confidence interval ($Z = 1.96$) for patients experiencing an IRR, with 2% margin of error, a sample size of 700 patients would be necessary. Including 500 patients in each arm would allow the detection of a 5% difference between the 2 infusion strategies with an alpha level of 0.05 and 80% power.

Results

Three hundred patients were included in the final analysis, 200 patients receiving IVP and 100 patients receiving IVPB representing a total of 1697 administrations. Baseline characteristics are reported in Table 1 and were similar between groups, except the IVPB group had significantly more patients on hemodialysis at baseline. Descriptions of daptomycin administration and IRR are reported in Table 2. Median (IQR) daptomycin doses were IVP 700 mg (550-900) and IVPB 700 mg (600-900), with mg/kg doses of 8.2 (7.9-10) and 8.3 (8-10), respectively. Administration site was similar in both groups with the most common being central venous catheters (IVP 99 [50%] subjects vs IVPB 48 [48%] subjects). Peripheral administration occurred in 85 (43%) and 48 (48%) subjects, respectively. Potential IRR occurred in 8 (4%) of the IVP arm and 1 (1%) of IVPB arm ($P = .28$). After blinded adjudication, IRR occurred in 1% of subjects in each treatment group. Infusion-related reactions consisted of the following reactions each in one patient of IVP group: fever and shortness of breath. The IRR in the IVPB group was a skin reaction. One patient from the IVPB group had daptomycin discontinued due to an IRR compared to zero in the IVP group. Creatinine phosphokinase levels were available for 104 (35%) patients. Elevated CPK levels occurred in 6 (5.8%) patients. No patients had documented musculoskeletal adverse reactions.

Table 2. Daptomycin Administration Characteristics and Infusion-Related Reactions.

	Rapid infusion (IVP)	Traditional infusion (IVPB)
Daptomycin dosing and administration		
Daptomycin dose, median (IQR), mg	700 (550-900)	700 (600-900)
Daptomycin dose, median (IQR), mg/kg	8.2 (7.9-10)	8.3 (8-10)
Daptomycin doses evaluated/total doses administered	1176/1547	521/690
Adjudicated infusion-related reactions, n (%)		
Any reaction	2 (1)	1 (1)
Fever	1 (50)	0
SOB	1 (50)	0
Skin reaction	0	1 (100)
Naranjo algorithm, score		
Doubtful, 0	0	0
Possible, 1-4	1 (50)	0
Probable, 5-8	1 (50)	1 (100)
Definite ≥9	0	0
Musculoskeletal reactions, n (%)		
Evaluable CPK levels, n	53	51
CPK elevations, n (%)	4 (8)	2 (4)

Note. IVP = IV push; IVPB = IV piggyback infusion; IQR = interquartile range; SOB = shortness of breath; CPK = creatinine phosphokinase.

Discussion

In our experience with 200 patients who received HDD as an IVP, we identified 2 likely IRRs representing 1% of patients. This safety profile appears to be consistent with the 1% of the population with IRRs in the IVPB group. Elevated CPK levels occurred in 5.8% of the total cohort. We suggest that IVP administration may be a reasonable approach during fluid shortages.[3] Although all patients included were inpatient, our safety evaluation of HDD as an IVP could have implications for outpatient parenteral administration.

IVP administration of daptomycin in adult patients is supported by the U.S. Food and Drug Administration (FDA)-approved package insert.[4] This approval is based on safety and pharmacokinetic data comparing 2-minute vs 30-minute infusion up to the FDA-approved dose of 6 mg/kg.[4] Twenty patients received daptomycin via a 2-minute infusion (12 patients 6 mg/kg, 8 patients 4 mg/kg) and no IRRs were reported.[4] This study was limited by small sample size and only included on-label dosing. A case report previously described erythroderma developing 2 hours after the first 650 mg dose (6 mg/kg) of daptomycin given as a 2-minute infusion.[9] The reaction included redness and warmth around the face next and upper back 2 hours after the infusion. On further administration, erythroderma did not recur.[9] Cervera and colleagues described their experience with outpatient daptomycin therapy in 54 patients across 12 hospitals in Spain. Eighteen patients received daptomycin via a 2-minute bolus with a median administered dose of 4.67 mg/kg. No patients in the 2-minute infusion developed phlebitis during therapy, supporting this administration method.[12] Our study adds pragmatic data in 200 patients receiving daptomycin IVP exclusively using greater than 6 mg/kg doses.

The present study is not without limitations. It was underpowered to evaluate a difference in IRR between IVP and IVPB due to uncommon event rate. A case-control study would be more statistically efficient to evaluate such an uncommon adverse event; however, there was not a reliable method to identify cases from the electronic medical record as most IRRs were documented in free text nursing documentation. Attempts were made to overcome this by including all eligible patients receiving IVP daptomycin during the study timeframe in the final analysis. There may be practice differences in the documentation of IRRs between health care providers that can result in information bias and subjective interpretation. We attempted to minimize this bias by applying a validated adverse effect assessment tool to evaluate the likelihood of causality between administration and adverse event. Additionally, infusion reactions were adjudicated by 2 clinical pharmacy specialists blinded to study group. Our institution does not use syringe infusion pumps for administration. Nurses administered all IVP doses by hand with the administration instructions of more than 2 minutes; however, the actual duration of administration was unable to be measured. Medication safety literature supports that providers who administer IVP medication without a watch or timer are prone to administer medications at a faster rate than recommended.[13]

This study provides data in more than 1100 administrations of HDD administered via IVP. Infusion-related reactions were documented in 1% of patients. These results support the practice of IVP daptomycin as a safe alternative to traditional infusion. This method may be useful during fluid shortage and in the outpatient setting.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Davis has served as a consultant for Spero Therapeutics and Tetraphase Pharmaceuticals. All other authors report no conflict of interest.

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References

1. Mazer-Amirshahi M, Fox ER. Saline shortages: many causes, no simple solution. *N Engl J Med*. 2018;378:1473-1474. doi:10.1056/NEJMp1800347.
2. McLaughlin MM, Skoglund EW. Drug shortages and patient safety: an overview of essential information for the infusion nurse. *J Infus Nurs*. 2015;38:205-208. doi:10.1097/NAN.0000000000000101.
3. Fox ER, Mclaughlin MM. ASHP guidelines on managing drug product shortages. *Am J Health Syst Pharm*. 2018;75(21):1742-1750. doi:10.2146/ajhp180441.
4. Cubicin [Daptomycin] prescribing information. Whitehouse Station, NJ: Merck & CO; 2003.
5. Chakraborty A, Roy S, Loeffler J, Chaves RL. Comparison of the pharmacokinetics, safety and tolerability of daptomycin in healthy adult volunteers following intravenous administration by 30 min infusion or 2 min injection. *J Antimicrob Chemother*. 2009;64:151-158. doi:10.1093/jac/dkp155.
6. Britt NS, Potter EM, Patel N, Steed ME. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among veterans affairs patients. *Clin Infect Dis*. 2017;64:605-613. doi:10.1093/cid/ciw815.
7. Timbrook TT, Caffrey AR, Luther MK, Lopes V, LaPlante KL. Association of higher daptomycin dose (7 mg/kg or greater) with improved survival in patients with methicillin-resistant Staphylococcus aureus bacteremia. *Pharmacotherapy*. 2018;38:189-196. doi:10.1002/phar.2070.
8. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother*. 2004;48:63-68. doi:10.1128/AAC.48.1.63-68.2004.
9. Caulder CR, Sloan A, Yasir A, Bookstaver PB. Infusion-related reaction following daptomycin two-minute rapid intravenous administration. *Hosp Pharm*. 2014;49:644-646.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245. doi:10.1310/hpj4907-644.
11. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50(12):1568-1574. doi:10.1086/652767.
12. Cervera C, Sanroma P, González-Ramallo V, et al. Safety and efficacy of daptomycin in outpatient parenteral antimicrobial therapy: a prospective and multicenter cohort study (DAPTODOM trial). *Infect Dis*. 2017;49(3):200-207.doi:10.1080/23744235.2016.1247292.
13. Institute for Safe Medication Practices. Safe practice guidelines for adult IV push medications. https://www.ismp.org/guidelines/iv-push. Published 2015. Accessed May 25, 2019.