ORIGINAL RESEARCH

Piperacillin/Tazobactam Use vs Cefepime May Be Associated With Acute Decompensated Heart Failure

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Background: Piperacillin/tazobactam (PTZ) has been cautiously used or avoided in patients with a history of heart disease due to concern for heart failure (HF) exacerbation given its relatively high sodium content. However, no prior studies have established this association.

Methods: The Antimicrobial Stewardship Team at the James H. Quillen Veterans Affairs Medical Center reviewed the use of PTZ vs the comparator antibiotic, cefepime, in 2 consecutive years to determine whether the use of PTZ was more likely to be associated with acute decompensation of HF. Records of 389 veterans hospitalized in 2018 and 2019 were reviewed and included in this study.

Results: Acute decompensation of HF was significantly associated with the use of PTZ (n = 25; 12.3%) compared with cefepime (n = 4; 2.2%) ($P < .001$). Additionally, hospital readmissions due to HF were higher in the PTZ group compared with the cefepime group (11 vs 1, $P = .02$). There were no significant differences identified in the length of stay or overall mortality between 204 patients who received PTZ compared with 185 patients who received cefepime ($P = .54$ and $P = .63$, respectively).

Conclusions: PTZ use was significantly associated with a higher incidence of acute decompensation of HF and hospital readmission with HF exacerbation compared with cefepime. PTZ use among hospitalized patients with a history of HF should be carefully monitored or avoided.

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Piperacillin/tazobactam (PTZ) is a combination IV antibiotic comprised of the semisynthetic antipseudomonal β-lactam, piperacillin sodium, and the β-lactamase inhibitor, tazobactam sodium.[1] PTZ is extensively prescribed in the hospital setting for a multitude of infections including but not limited to the US Food and Drug Administration–approved indications: intra-abdominal infection, skin and skin structure infection (SSTI), urinary tract infection (UTI), and pneumonia. Given its broad spectrum of activity and relative safety profile, PTZ is a mainstay of many empiric IV antibiotic regimens. The primary elimination pathway for PTZ is renal excretion, and dosage adjustments are recommended with reduced creatinine clearance. Additionally, PTZ use has been associated with acute renal injury and delayed renal recovery.[1-3]

There are various mechanisms through which medications can contribute to acute decomopensated heart failure (ADHF).[4] These mechanisms include direct cardiotoxicity; negative inotropic, lusitropic, or chronotropic effects; exacerbating hypertension; sodium loading; and drug-drug interactions that limit the benefits of heart failure (HF) medications. One potentially overlooked constituent of PTZ is the sodium content, with the standard formulation containing 65 mg of sodium per gram of piperacillin.[1-3] Furthermore, PTZ must be diluted in 50 to 150 mL of diluent, commonly 0.9% sodium chloride, which can contribute an additional 177 to 531 mg of sodium per dose. PTZ prescribing information advises caution for use in patients with decreased renal, hepatic, and/or cardiac function and notes that geriatric patients, particularly with HF, may be at risk of impaired natriuresis in the setting of large sodium doses.

It is estimated that roughly 6.2 million adults in the United States have HF and prevalence continues to rise.[5,6] Mortality rates after hospitalization due to HF are 20% to 25% at 1 year. Health care expenditures for the management of HF surpass $30 billion per year in the US, with most of this cost attributed to hospitalizations. Consequently, it is important to continue to identify and practice preventative strategies when managing patients with HF.

METHODS

This single-center, retrospective, cohort study was conducted at James H. Quillen Veterans Affairs Medical Center (JHQVAMC) in Mountain Home, Tennessee, a 174-bed tertiary medical center. The purpose of this

TABLE 1 Baseline Characteristics

Variable	Piperacillin/tazobactam (n = 204)	Cefepime (n = 185)	*P* value
Age, mean (SD)	75 (10)	75 (9)	.63
Male sex, No. (%)	204 (100)	185 (100)	–
Prior diagnosis of heart failure, No. (%)	165 (80.9)	151 (81.6)	.85
Admission diagnosis, No. (%)			
Pneumonia	105 (51.5)	49 (26.5)	< .001[a]
Urinary tract infection	6 (2.9)	29 (15.7)	< .001[a]
Skin and skin structure infection	48 (23.5)	62 (33.5)	.03[a]
Osteomyelitis	4 (2.0)	9 (4.9)	.11
Other	41 (20.1)	36 (19.5)	.88

[a]Statistically significant.

study was to compare the incidence of ADHF in patients who received PTZ vs cefepime (CFP). This project was reviewed by the JHQVAMC Institutional Review Board and deemed exempt as a clinical process improvement operations activity.

The antimicrobial stewardship team at JHQVAMC reviewed the use of PTZ in veterans between January 1, 2018, to December 31, 2019, and compared baseline demographics, history of HF, and outcomes in patients receiving analogous broad-spectrum empiric antibiotic therapy with CFP. Patients were included if they received at least 24 hours of PTZ or CFP. Patients were excluded if they were diagnosed with ADHF before initiation of antibiotic therapy. Patients with ADHF were identified by clinical diagnosis of ADHF documented by the treating clinician and reaffirmed by the study clinician during retrospective chart review. Clinical information used to determine ADHF included clinical presentation, imaging (ie, chest X-ray, echocardiograms), and laboratory parameters, such as B-type natriuretic peptide. The primary endpoint of this study was the incidence of ADHF during the current hospitalization. Secondary endpoints included the length of hospital stay, hospital readmission, and overall mortality. Patient chart reviews were performed using the JHQVAMC Computerized Patient Record System (CPRS).

Statistical Analysis

Analysis was conducted with R Software. Pearson χ^2 and *t* tests were used to compare baseline demographics, length of stay, readmission, and mortality. Significance used was $\alpha = .05$.

RESULTS

A retrospective chart review was performed on 389 veterans. Of the 389, 204 patients received at least 24 hours of PTZ, and 185 patients received CFP. The mean age in both groups was 75 years. Patients in the PTZ group were more likely to have been admitted with the diagnosis of pneumonia (105 vs 49, $P < .001$). However, 29 patients (15.7%) in the CFP group were admitted with a UTI diagnosis compared with 6 patients (2.9%) in the PTZ group ($P < .001$) and 62 patients (33.5%) in the CFP group were admitted with a SSTI diagnosis compared with 48 patients (23.5%) in the PTZ group ($P = .03$). Otherwise, there were no differences between other admitting diagnoses. Additionally, there was no difference in prior history of HF between groups (Table 1).

Twenty-five patients (12.3%) in the PTZ group and 4 patients (2.2%) in the CFP group were subsequently diagnosed with ADHF ($P < .001$). Hospital readmissions due to HF were higher in the PTZ group compared with the CFP group (11 vs 2, $P = .02$). Hospital readmission due to other causes was not significantly different between groups. Hospital readmission due to infection occurred in 18 patients who received PTZ and 25 who received CFP (8.8% vs 13.5%, $P = .14$). Hospital readmission due to any other indication occurred in 24 patients who received PTZ and 24 who received CFP (11.8% vs 13.0%, $P = .72$). There was no statistically

TABLE 2 Primary and Secondary Outcomes

Variable	Piperacillin/tazobactam (n = 204)	Cefepime (n = 185)	*P* value
Acute decompensated heart failure , No. (%)	25 (12.3)	4 (2.2)	< .001[a]
Length of stay, No. (%)			
< 3 days	28 (13.7)	20 (10.8)	.46
4-6 days	73 (36.3)	76 (41.1)	.28
≥ 7 days	103 (50.5)	89 (48.1)	.78
Readmission reason, No. (%)			
Heart failure	11 (5.4)	2 (1.1)	.02[a]
Infection	18 (8.8)	25 (13.5)	.14
Other indication	24 (11.8)	24 (13.0)	.72
Mortality, No. (%)			
Death during admission	19 (9.3)	14 (7.6)	.54
Death within 6 months of discharge	40 (19.6)	36 (19.5)	.97
Total	59 (28.9)	50 (27.0)	.63

[a]Statistically significant.

significant difference in all-cause mortality during the associated admission or within 6 months of discharge between groups, with 59 total deaths in the PTZ group and 50 in the CFP group (28.9% vs 27.0%, *P* = .63).

There was no difference in length of stay outcomes between patients receiving PTZ compared with CFP. Twenty-eight patients in the PTZ group and 20 in the CFP group had a length of stay duration of < 3 days (13.7% vs 10.8%, *P* = .46). Seventy-three patients in the PTZ group and 76 in the CFP group had a length of stay duration of 4 to 6 days (36.3% vs 41.1%, *P* = .28). One hundred three patients in the PTZ group and 89 in the CFP group had a length of stay duration ≥ 7 days (50.5% vs 48.1%, *P* = .78). Table 2 includes a complete overview of primary and secondary endpoint results.

DISCUSSION

The American Heart Association (AHA) lists PTZ as a medication that may cause or exacerbate HF, though no studies have identified a clear association between PTZ use and ADHF.[4] Sodium restriction is consistently recommended as an important strategy for the prevention of ADHF. Accordingly, PTZ prescribing information and the AHA advise careful consideration with PTZ use in this patient population.[1,4]

The specific mechanism responsible for the association of PTZ with cardiac-related adverse outcomes is unclear. It is easy to presume that the sodium content of PTZ is solely responsible; however, other antibiotic regimens not included as agents of concern by the AHA, such as meropenem, can approach similar overall daily sodium amounts.[4,7] Additionally, total sodium and volume can also be contributed by various IV medications and fluids. This study did not evaluate total sodium intake from all sources, but it is notable that this study identified a possible trend toward the risk of ADHF with PTZ use in a routine practice environment. It is reasonable to postulate additional intrinsic properties of PTZ may be contributing to the development of ADHF, such as its association with renal injury possibly resulting in increased fluid retainment and subsequent fluid volume overload.[1,2,4] Other hypothesized mechanisms may include those previously described, such as direct myocardial toxicity; negative inotropic, lusitropic, or chronotropic effects; exacerbating hypertension; and drug-drug interactions that limit the benefits of HF medications, although these have not been overtly associated with PTZ in the literature to date.[4,8]

ADHF can present similarly to other acute pulmonary conditions, including pneumonia.[9,10] It is important to acknowledge the challenge this creates for diagnosticians to differentiate between these conditions rapidly and precisely. As a result, this patient population is likely at increased risk of IV antibiotic exposure. Other studies have identified worse outcomes in patients who receive potentially unwarranted IV antibiotics in patients with ADHF.[9,10] The

results of this study further emphasize the importance of careful considerate antibiotic selection and overall avoidance of unnecessary antibiotic exposure to limit potential adverse outcomes.

Limitations

There are various limitations to this study. Firstly, no women were included due to the predominantly male population within the Veterans Health Administration system. Secondly, this study was retrospective in design and was therefore limited to the completeness and accuracy of the available data collected. Additionally, this study evaluated any ADHF episode during the associated hospitalization as the primary endpoint. The time to diagnosis of ADHF in relation to PTZ initiation was not evaluated, which may have helped better elucidate this possible association. Furthermore, while a significant statistical difference was identified, the smaller sample size may have limited the ability to accurately identify differences in lower event rate outcomes.

CONCLUSIONS

This study identifies an association between PTZ use and significant cardiac-related adverse outcomes, including increased incidence of ADHF and readmission due to HF exacerbation. While more research is needed to define the exact mechanisms by which PTZ may precipitate acute decompensation in patients with HF, it is judicious to consider close monitoring or the avoidance of PTZ when appropriate antibiotic alternatives are available in patients with a known history of HF.

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Ethics and consent

This quality improvement initiative was performed via routine operational procedure by the Antimicrobial Stewardship Committee, not necessitating patient consent. This project was reviewed by the James H. Quillen Veterans Affairs Medical Center Institutional Review Board and was deemed a clinical process improvement operations activity.

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