REVIEW ARTICLE

Development of Acute Kidney Injury with Concomitant Use of Vancomycin and Piperacillin-Tazobactam. A Review of Recent Literature

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This article explores the potential association between co-administration of vancomycin and piperacillin-tazobactam with the development of acute kidney injury (AKI) when compared with vancomycin and other beta lactam antibiotics or vancomycin monotherapy. Based upon available evidence, the combination of vancomycin and piperacillin-tazobactam at therapeutic dosages correlates with increased incidence of AKI when compared to vancomycin and cefepime, vancomycin and meropenem, and vancomycin monotherapy. The majority of these trials are retrospective and most do not evaluate patient outcomes. There remains a need for large, prospective, randomized, controlled trials to determine a causative relationship and assess clinical ramifications with the concomitant use of vancomycin and piperacillin-tazobactam and development of AKI.

Keywords: Acute kidney injury, cefepime, piperacillin-tazobactam, vancomycin

INTRODUCTION

The combination of antipseudomonal β-lactams and an agent active against methicillin-resistant *Staphylococcus aureus* (MRSA) is often indicated for the empiric treatment of severe infections, such as diabetic foot infections, sepsis, and the treatment of hospital acquired pneumonia/ventilator acquired pneumonia. An antibiotic regimen that consists of these agents provides extensive coverage of both Gram-positive and Gram-negative organisms. Two of the most commonly utilized agents in these situations are vancomycin and piperacillin-tazobactam. Recently, there has been concern that this combination of antimicrobials contributes to an elevated risk for development of acute kidney injury (AKI). Vancomycin has been shown to cause acute tubular necrosis and piperacillin-tazobactam has been shown to cause acute interstitial nephritis[1], but determining the true incidence is difficult due to the necessity of renal biopsy for confirmation of diagnosis[2]. This article seeks to review the reported association between co-administration of vancomycin and piperacillin-tazobactam and the development of AKI.

Description of available literature

A prospective, open-label, cohort study conducted by Peyko *et al*.[3] was performed at a single medical center over a span of three months. It compared the occurrence of AKI

in patients receiving vancomycin and piperacillin-tazobactam versus vancomycin in combination with either cefepime or meropenem. The primary outcome of this study was the development of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) AKI work-group criteria[4]. Patients included in this trial had to be greater than 18 years old with an order for either piperacillin-tazobactam, cefepime, or meropenem for at least seventy-two hours and have a steady state trough level for vancomycin while receiving therapy with a beta lactam. During the 3 months, 210 patients were identified as candidates for the study. Of those patients, 85 met criteria for inclusion to the study; 59 were randomized to the vancomycin and piperacillin-tazobactam group while 26 were randomized to the vancomycin and either cefepime or meropenem group. AKI developed in 37.3% of the vancomycin and piperacillin-tazobactam group compared to 7.7% of the vancomycin and cefepime or meropenem group ($p = 0.005$), according to the KDIGO criteria. Although this study demonstrated a correlation of increased AKI with vancomycin and piperacillin-tazobactam, there are notable limitations. The sample size in this study was small and power was not met, which could limit external validity. Patients were not stratified according to KDIGO stages, making it difficult to quantify the potential impact.

A meta-analysis performed by Giuliano *et al.*[5] analyzed fifteen observational studies and assessed the incidence of AKI in patients receiving vancomycin in combination with piperacillin-tazobactam compared to vancomycin monotherapy or in combination with cefepime or meropenem. Ten of the fifteen studies compared vancomycin and piperacillin-tazobactam versus vancomycin monotherapy. Four of the fifteen studies compared vancomycin and piperacillin-tazobactam to vancomycin and other β-lactams. Only one study included in the analysis compared vancomycin and piperacillin-tazobactam with vancomycin monotherapy or vancomycin plus other antibiotics (mainly cefepime). A total of 3258 patients comprised the fifteen studies that were included in the final analysis. The authors found an association with the development of AKI and vancomycin and piperacillin-tazobactam compared to vancomycin alone (OR 3.98; 95% CI 2.749-5.763; $I^2 = 31.4\%$; and $p < 0.001$). The authors performed a secondary analysis that removed lesser quality studies and found a significantly higher incidence of AKI in patients receiving vancomycin and piperacillin-tazobactam versus vancomycin monotherapy or combined with a different β-lactam (OR 4.596; 95% CI 2.929-7.212; $I^2 = 0\%$; $p < 0.001$). However, when the authors compared vancomycin and piperacillin/tazobactam versus vancomycin and a different beta-lactam (excluding vancomycin monotherapy), they found no significant difference. Unfortunately, most of the data was from trials that compared vancomycin monotherapy versus the combination of vancomycin and piperacillin-tazobactam, leading to potential bias with regards to severity of illness. Furthermore, a number of the trials included in the meta-analysis failed to report information such as severity of illness scores, vancomycin trough levels, and the definition of AKI varied between the trials. Despite the limitations of the analysis, the results suggest a correlation between vancomycin and piperacillin-tazobactam combination therapy and AKI incidence.

Navalkele *et al.*[6] performed a retrospective, matched, cohort study that compared the incidence of AKI in patients taking both vancomycin and piperacillin-tazobactam compared to patients taking vancomycin and cefepime. This study

defined AKI based on three definitions: the RIFLE (Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria[7], the Acute Kidney Injury Network (AKIN) classification[8], and the Vancomycin Consensus Guideline definition[9]. Patients had to have been taking the combination antibiotic therapy for greater than forty-eight hours in order to be included in this trial. Patients were excluded from this trial if they had a baseline serum creatinine greater than 1.2 mg/dL or if they required renal replacement therapy at the time combination therapy was initiated. There were 329 patients who received vancomycin and piperacillin-tazobactam versus 803 patients that received vancomycin and cefepime. Of the 803 patients that received vancomycin and cefepime, 279 were matched with someone from the other treatment group and included in the trial. The rate of AKI development, based on the RIFLE criteria, was greater in the vancomycin and piperacillin-tazobactam group (81 patients, 29%) than the vancomycin and cefepime group (31, 11.1%) (HR = 4.0, 95% CI, 2.6-6.2, $p < 0.0001$). Per the AKIN criteria (stage 1: 48 patients vs. 20 patients, stage 2: 21 patients vs. 8 patients, and stage 3: 20 patients vs. 11 patients), rates of AKI were higher in the vancomycin and piperacillin-tazobactam group (32%) than the vancomycin and cefepime group (14%) (HR 3.5; 95% CI, 2.3-5.2; $p < 0.0001$). And finally, per Vancomycin Consensus Guidelines, rates of AKIwere also higher in the vancomycin and piperacillin-tazobactam group versus the vancomycin and cefepime group (24% versus 8.2%, respectively) (HR 4.4; 95% CI, 2.7-7.3; $p < 0.0001$). The median length of stay after initiation of combination therapy was longer for vancomycin and piperacillin-tazobactam patients compared to vancomycin and cefepime patients (8 days vs. 6 days; $p = 0.01$). There was no significant difference in mortality rates between the groups (16 deaths versus 24 deaths). This trial demonstrated that concomitant vancomycin and piperacillin-tazobactam correlated with a higher incidence of AKI development when compared to vancomycin and cefepime. The authors should be commended for stratifying AKI and utilizing different criteria for diagnosis. Additionally, the evaluation of mortality and length of stay provides insight into the overall impact on patient outcomes.

CONCLUSION

Based upon available evidence, the combination of vancomycin and piperacillin-tazobactam at therapeutic dosages has shown a correlation with increased incidence of AKI when compared to vancomycin and cefepime, vancomycin and meropenem, or vancomycin monotherapy. However, these trials were not without limitations. It is important to note the largest study and the studies included in the meta-analysis were observational, and therefore conclusions should be drawn accordingly.

The results of these studies should also be evaluated in the context of their varying threshold of AKI categorization. As to lend generalizability, future results should be stratified for the severity of AKI and patient progression to hemodialysis should be assessed. Furthermore, due to the low threshold of AKI, there may have been patients identified as having an AKI that did not have clinically significant implications on outcomes.

In current practice, there is a role for empiric broad-spectrum antibiotics and the use of vancomycin and piperacillin-tazobactam should not be avoided when clinically indicated, especially in patients with adequate baseline kidney function. Practicing sound stewardship by only using

the combination vancomycin and piperacillin-tazobactam when clinically indicated could lessen potential harm from the combination. Practitioners should consider if the expanded anaerobic and enterococcal coverage with piperacillin-tazobactam, when compared to cefepime, is warranted.

It is also important to make health care providers aware of this potential outcome and consideration should be given to patients identified as high risk for kidney problems. Furthermore, this correlation should be considered when developing a hospital formulary, as often the empiric use of vancomycin and piperacillin-tazobactam is recommended for broad-spectrum coverage.

As a result, there remains a need for large, prospective, randomized, controlled trials to determine a causative relationship and evaluate patient outcomes with the concomitant use of vancomycin and piperacillin-tazobactam and development of AKI. Exploring the additive nephrotoxic effects may elucidate the mechanism through which vancomycin and piperacillin-tazobactam interact and lead to better identification of at-risk patients.

Notes

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