Impact of an Antimicrobial Stewardship Program on Patient Safety in Veterans Prescribed Vancomycin

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ABSTRACT

Purpose: This study aimed to determine the safety impact of an antimicrobial stewardship program (ASP) on vancomycin-associated nephrotoxicity and to examine risk factors contributing to the development of toxicity.

Methods: This was a retrospective chart review of data from 453 veterans receiving vancomycin in the VA Western New York Healthcare System between October 2006 and July 2014. *Nephrotoxicity* was defined as an increase in serum creatinine of $\geq$0.5 mg/dL or by 50% of baseline for 2 consecutive days.

Findings: Patients receiving vancomycin after the implementation of the ASP were less likely to develop nephrotoxicity (odds ratio [OR] = 2.06; 95% CI, 1.02–4.28). Nephrotoxicity occurred in 6.84% of patients from the pre-ASP cohort and in 3.75% of patients after the implementation of the ASP. Predictors of nephrotoxicity included hospital service (surgical service, OR = 2.29; 95% CI, 1.13–4.64), elevated maximum trough concentration (unit OR = 1.15; 95% CI, 1.10–1.20), and concurrent piperacillin/tazobactam therapy (OR = 3.21; 95% CI, 1.43–7.96). The number of vancomycin trough concentration measurements per patient did not vary between the pre-ASP and ASP groups.

Implications: ASPs represent an important aspect of a patient-safety initiative in order to reduce vancomycin-associated nephrotoxicity. Concurrent piperacillin/tazobactam therapy, surgical service, and elevated maximum trough concentration were risk factors for nephrotoxicity. (*Clin Ther*. 2016;38:494–502) Published by Elsevier HS Journals, Inc.

Key words: antimicrobial stewardship, nephrotoxicity, patient safety, vancomycin.

INTRODUCTION

The objectives of an antimicrobial stewardship program (ASP) are to prevent the development of antibiotic-resistant organisms by optimizing antimicrobial use while minimizing the undesired consequences of antimicrobial agents, including toxicities and adverse events.[1–3] To date, much of the literature has been focused on the success of ASPs in optimizing antimicrobial use and on the economic benefits of ASP interventions.[4–7] There is limited literature demonstrating the ability of ASPs to decrease the prevalence of *Clostridium difficile* infections or to decrease resistance to antimicrobial agents.[5,6,8] Little has been reported on the larger impact that ASPs may have on overall patient safety.[4–6,9,10]

Vancomycin is an antibiotic targeted for ASPs due to its widespread use, along with the abilities to monitor and adjust doses based on pharmacokinetics. Vancomycin has activity against gram-positive organisms, including resistant organisms such as methicillin-resistant *Staphylococcus aureus*. Monitoring of vancomycin trough concentrations is necessary not only to ensure that therapeutic concentrations are achieved but also to minimize the risk for vancomycin-associated nephrotoxicity (VAN). Available literature has demonstrated that the risk for VAN increases as trough

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concentrations increase.[11–18] The development of VAN can have several implications on patient safety. First, the development of nephrotoxicity may lead to reduced clearance of other medications, resulting in increased drug exposure and the potential for other adverse drug events. Second, renal dysfunction due to nephrotoxicity may necessitate the use of an alternative drug regimen. This alternative regimen may be costly, suboptimal, and/or result in a longer duration of stay.[7,14,16]

The primary objective of this study was to determine the impact of an ASP on the safety of patients prescribed vancomycin in a Veterans Affairs (VA) setting. The secondary objective was to investigate other factors that may affect the prevalence of nephrotoxicity in patients prescribed vancomycin.

MATERIALS AND METHODS

This was a retrospective chart review of data from patients between the ages of 18 to 89 years who received vancomycin in the VA Western New York Healthcare System (VAWNYHS) in 1 of 2 time periods: October 1, 2006, to July 31, 2008 (pre-ASP), and August 1, 2011, to July 30, 2014 (ASP). The institutional review board at VAWNYHS approved the study protocol.

Eligible patients were identified by a data query of those who received IV vancomycin via a VA-developed file manager (FileMan). Patients were included if they received a minimum of 48 hours of IV vancomycin therapy, with at least 1 vancomycin trough concentration obtained within the first 96 hours after starting therapy, and if they had a baseline serum creatinine concentration (SCr) of <2.0 mg/dL. Each patient was included only once. Patients were excluded if they had received an IV contrast agent within 7 days before or during therapy, if they received a concurrent vasopressor, cyclosporine, tacrolimus, or amphotericin; if they had received chemotherapy; if they had a nephrology consultation in the 30 days before the start of vancomycin administration (to omit those patients who may have had preexisting renal impairment); if they were on dialysis at the time of vancomycin initiation; and/or if they received vancomycin between August 1, 2008, and July 31, 2011 (this was a transition period with inconsistent staffing of the ASP program).

Patients' baseline characteristics were extracted from the VA Computerized Patient Record System, with a Charlson Comorbidity Index Score calculated as a measure of severity of illness.[19] In addition, we collected information on the use of concurrent nephrotoxic agents, indication for vancomycin therapy, and microbiology. Duration of IV vancomycin treatment was determined via the electronic medication administration record. Indications were determined by progress notes (from the provider and ASP team) and verified with discharge summary.

The *initial vancomycin trough concentration* was defined as the trough concentration obtained within the first 96 hours of starting vancomycin therapy. The *maximum trough concentration* was defined as the highest vancomycin trough concentration identified during the treatment period. If only 1 trough concentration was obtained during therapy, this served as both the initial and maximum trough concentrations. *Hypotension* was defined as a systolic blood pressure of <80 mm Hg and a reduction of at least 20% from previous values. *Nephrotoxicity* was defined as an increase from baseline in SCr of at least 0.5 mg/dL or by 50% of baseline for 2 consecutive days.[20] *Severity of nephrotoxicity* was defined using the RIFLE (risk, injury, failure, loss, and end-stage renal disease) criteria.[21] Creatinine clearance (CrCl) was calculated via the Cockcroft-Gault equation.[22]

The ASP staff included a board-certified pharmacist with support from an infectious-diseases physician. The pharmacist reviewed all IV antibiotics on a daily basis, including formulary antibiotics such as vancomycin and agents the indications of which are restricted to the treatment of infectious diseases. Prospective and retrospective chart reviews were performed, as well as approvals for restricted antibiotics. Individual charts were reviewed for those patients on IV antibiotics, allowing for patient-centered interventions, including escalation, de-escalation, changes in therapy, and laboratory monitoring/cultures. Patients receiving vancomycin were monitored to determine whether continuation of vancomycin was warranted and whether dosing needed to be altered based on SCr, urine output, or trough concentrations. ASP pharmacists worked within their infectious-diseases scope of practice to order vancomycin levels and to adjust or hold vancomycin doses based on trough concentrations.