Use of a Clinical Decision Support System Alert to Prevent Supratherapeutic Vancomycin Concentrations

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Abstract

Background: Alerts issued by clinical decision support systems (CDSS) may be useful to identify and prevent the occurrence of acute kidney injury among patients on nephrotoxic drugs, particularly vancomycin. **Objective:** The purpose of this instructive study was to determine the effectiveness of using a pharmacist-run CDSS alert of early serum creatinine increases in patients receiving intravenous vancomycin to decrease the proportion of severely elevated vancomycin concentrations. **Methods:** This was a retrospective study of a prospectively reviewed CDSS alert that triggered in patients with an increase in serum creatinine by 25% from baseline within 24 hours. Severely elevated vancomycin concentrations were divided into a control group (before alert implementation) and a study group (after alert implementation) and considered for study inclusion. The proportion of severely elevated vancomycin concentrations (ie, >30 mg/L) were collected in the control and study groups. **Results:** There were 1290 and 1501 vancomycin concentrations in the control group and the study group, respectively. A total of 696 CDSS alerts triggered during the study period. The proportion of severely elevated vancomycin troughs decreased from 5.3% (n = 68, median = 36.6 mg/L, interquartile range = 33.75–43.2 mg/L) in the control group to 3.7% (n = 55, median = 34.7 mg/L, interquartile range = 31.3–39.3 mg/L) in the study group. This reflects a statistically significant decrease in the proportion of severely elevated vancomycin concentrations ($P = .04$). **Conclusion:** Overall, this instructive analysis on a novel use of CDSS software suggests that the implementation of an alert based on early detection of serum creatinine changes led to a significant decrease in the proportion of severely elevated serum vancomycin concentrations.

Keywords

clinical decision support system, vancomycin, acute kidney injury, alert

Background

Vancomycin is one of the most commonly used antibiotics to treat known or suspected invasive Gram-positive infections, including methicillin-resistant *Staphylococcus aureus*, and it is responsible for 5% to 7% of all cases of acute kidney injury (AKI).^{1,2} While the side effects of vancomycin were historically attributed to impurities in formulation,^{3–5} higher vancomycin trough concentrations have also been associated with an increased incidence of nephrotoxicity.^{6,7} Elevated serum vancomycin trough concentrations between 30 mg/L and 65 mg/L are a risk factor for AKI in hospitalized patients.⁸

Alerts issued by clinical decision support systems (CDSS) may be useful to identify and prevent the occurrence of AKI among patients on nephrotoxic drugs, particularly vancomycin.⁹ In a previous study concerning the effect

of alerts for rising creatinine on treatment outcomes in patients on nephrotoxic drugs, it was found that the relative risk of serious renal impairment was almost half of the risk as compared to without the use of alerts.¹⁰ Another prior study found a stronger benefit in alerts involving laboratory value–drug combination alerts than drug laboratory values alone.¹¹ Furthermore, vancomycin-related alerts were among the most frequently triggered alerts of all preset

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alerts.¹² Renal function, particularly glomerular filtration rate, is the strongest indicator of AKI, but serum creatinine is more practical and available to clinicians.⁹ As trough concentrations are not drawn daily for vancomycin, an increasing serum creatinine concentration may predict a rising vancomycin concentration before vancomycin trough concentrations are available.

CDSS alerts may function to support further monitoring of patients after the initial computerized medication order. In 2011, Northwestern Memorial Hospital (NMH) implemented a pharmacist-run CDSS alert to identify patients who have an increase in serum creatinine concentrations and are also receiving vancomycin therapy. The goal of the CDSS alert is early adjustment of the vancomycin order (change in dose or interval or discontinuation if appropriate), thus reducing the incidence of severely elevated trough concentrations that may result in or act as a surrogate marker of nephrotoxicity. The purpose of this instructive study was to determine the effectiveness of using a pharmacist-run CDSS alert of serum creatinine increases in patients receiving intravenous vancomycin to decrease the proportion of severely elevated vancomycin concentrations.

Methods

This was a retrospective study conducted at NMH, an 897-bed academic tertiary medical center in Chicago, IL. The CDSS alert was implemented using the electronic clinical surveillance system, TheraDoc (Hospira, Inc; Lake Forest, IL). TheraDoc is used at NMH for various clinical alerts and communication between pharmacists. The CDSS alert was set to meet 2 criteria: a text match for the word “creatinine” (but not “urine creatinine”) with a result change by 25% or greater from baseline within 24 hours, and an active order for vancomycin. As part of their daily clinical activities, unit-based clinical pharmacists prospectively reviewed the alerts daily for potential intervention. Any alerts that were triggered after this daily review were reviewed the next day. Vancomycin trough concentrations were ordered based on clinical judgment. Any trough data were reviewed in real time as available. The CDSS alert prompted pharmacists to assess the patient’s renal function, vancomycin dose, and vancomycin interval. If a prospective change in vancomycin dose or interval was warranted, the pharmacist contacted the primary medical team for intervention as appropriate. Interventions were defined as a vancomycin dose decrease or interval increase, holding a dose of vancomycin, or discontinuation of vancomycin. The pharmacist may also have concluded that no intervention was necessary based on patient factors. Pharmacists documented these interventions in TheraDoc under the alert. This study was approved by the Northwestern University and Midwestern University Institutional Review Boards.

Severely elevated vancomycin concentrations were considered for inclusion from patients who were >18 years of age; hospitalized at NMH between December 15, 2010, and December 31, 2011; and received intravenous vancomycin therapy. Severely elevated vancomycin concentrations were excluded if they had received renal replacement therapy at the time of the vancomycin trough. Renal replacement therapy included hemodialysis, peritoneal dialysis, and continuous veno-venous hemofiltration. Severely elevated concentrations were also excluded if the concentration was not drawn at an appropriate time to be considered a true trough.¹³ True trough concentrations were defined as concentrations collected within 1 hour prior to the end of a dosing interval or concentrations collected after the dosing interval provided a subsequent dose of vancomycin was not administered.¹³ Severely elevated serum trough concentrations were defined as 30 mg/L or higher.¹³ Only the first severely elevated vancomycin concentration per patient per admission was considered for study inclusion.

Severely elevated vancomycin concentrations were divided into a control group and a study group. The control group was evaluated from December 15, 2010, to June 15, 2011, and represents the 6 months prior to CDSS alert implementation. During the control period, patients were monitored daily by unit-based pharmacists as part of standard clinical practice at NMH. Any vancomycin dose or interval adjustments were made based on the clinical judgment of the pharmacist. Interventions were documented; however, they were classified under differing categories based on the intervention made (eg, pharmacokinetic, adverse event avoided, etc). While there was a daily pharmacy presence on medical rounds, there was no system in place to alert pharmacists to decreasing renal function, and despite a patient having a serum creatinine “in range,” the absolute number may have increased significantly.

The severely elevated vancomycin concentrations in the study group were evaluated from July 1, 2011, to December 31, 2011, and represents the 6 months post CDSS alert implementation. Data from the initial 2-week period (June 16, 2011, to June 30, 2011) were excluded to allow sufficient time for full implementation of the alert and targeted education. After implementation of the alert, the pharmacy process for monitoring vancomycin therapy did not change. The number of alerts that triggered during the study period as well as the total number of vancomycin concentrations were collected.

Statistical Analysis

The proportion of severely elevated serum vancomycin trough concentrations per total number of vancomycin trough concentrations was compared between control and study populations. Additionally, alert documentation was evaluated to determine the proportion of alerts that resulted in a pharmacist intervention. Statistical analysis was

performed using Intercooled Stata, version 13 (Statacorp, College Station, TX). Categorical variables were evaluated with the χ^2 test. All tests were 2 tailed, with $P < .05$ considered significant.

Results

There were 1290 vancomycin concentrations in the control group and 1501 in the study group. A total of 696 CDSS alerts triggered during the study period. The proportion of severely elevated vancomycin trough concentrations decreased from 5.3% ($n = 68$, median = 36.6 mg/L, interquartile range = 33.75-43.2 mg/L) in the control group to 3.7% ($n = 55$, median = 34.7 mg/L, interquartile range = 31.3-39.3 mg/L) in the study group. This reflects a statistically significant decrease in proportion of severely elevated vancomycin trough concentrations after CDSS alert implementation ($P = .04$). Additionally, of the 696 alerts that triggered during the study period, 280 (40%) resulted in pharmacist intervention.

Discussion

This study showed a significant decrease in the proportion of severely elevated vancomycin concentrations following the implementation of a CDSS alert. These alerts successfully prompted pharmacist intervention to modify drug therapy to avoid severely elevated vancomycin concentrations. Many systems provide guidance for the initial medication order but renal function frequently changes in hospitalized patients. By using an increase in serum creatinine over the previous 24 hours from baseline, the issue of patients with low serum creatinine levels that may increase significantly but still appear within normal limits is eliminated. The results suggest the use of pharmacist-run CDSS alerts as a "safety net" measuring physiologic parameters to warrant adjustments in drug therapy.

The findings are consistent with success in previous studies that monitored renal function to avoid nephrotoxicity.^{10,12,14-17} One study did not show a benefit in alerts triggered at the time of ordering a drug that should be renally adjusted in a patient with reduced renal function.¹⁸ However, the CDSS alert in this study would trigger with changing serum creatinine, which may indicate changing renal function and not at the time of ordering. The current study supports the use of CDSS alerts to decrease the proportion of severely elevated vancomycin concentrations; however, other studies varied in their results depending on type of alerts, number of alerts, and health care setting. As in this analysis, a previous study using changes in laboratory values to detect adverse drug reactions did show a benefit.¹⁹ Another study similar to ours, analyzing drug-induced thrombocytopenia alerted by CDSS with pharmacist intervention, also reported positive results.¹¹

This study is unique because it is a pharmacy-run, interactive alert that cannot be deferred or overridden. These alerts were integrated into the pharmacist's workflow and assisted the pharmacist in identifying patients at highest risk of medication dose-related problems. As pharmacists round with the medical team at our institution, they were able to suggest therapy changes in a timely manner. Overall, the available literature on pharmacist-run alerts has shown beneficial outcomes. One pharmacist-run alert study found that patients receiving excessive antibiotics had significantly reduced renal function.¹⁶ Three other pharmacist-run alert studies showed benefit to alerts used to detect adverse drug events.^{11,12,20} Pharmacists are often involved in the monitoring of patient laboratory results and may have more success using an alert system, especially when the alert is not firing at the time of ordering when a physician is most likely to see it.

Limitations

Limitations to this study must be considered. First, this alert was studied at one hospital with a particular electronic medical record system. As this study was conducted at a large, academic hospital with pharmacists that round daily with the medical team, there was a low baseline rate for severely elevated vancomycin concentrations and it may be difficult to show clinical significance. However, this study has shown a decrease the proportion of severely elevated concentrations, and this alert should be validated in other settings with limited pharmacy resources. This alert would likely better benefit from study at large community institutions with limited pharmacy resources. Future directions may also include an alert that notifies pharmacists of a specific increase in renal function at which point doses may need to be adjusted to standard dosing. Second, the alerts were evaluated only once per day; however, this evaluation would occur after morning blood work had been drawn and blood work is often drawn only once per day for inpatients. Third, the potential for unfavorable workflow issues was not evaluated in this study as this alert is not the only active alert to which pharmacists must respond at our institution.²¹ Fourth, this study did not assess the type of patient population as it was an instructive analysis. Future studies of this type of information may help other institutions streamline implementation of a similar alert and better understand which patient care areas may experience a higher number of alerts. Future studies should also assess the needed time for pharmacists to respond to alerts.

Conclusion

Overall, this instructive analysis on a novel use of CDSS software suggests that the implementation of an alert based on early detection of serum creatinine changes led to a

significant decrease in the proportion of severely elevated serum vancomycin trough concentrations. Preventing severely elevated vancomycin trough concentrations can potentially decrease the incidence of renal toxicity and improve outcomes; however, this is more difficult to measure. Additionally, it was demonstrated that pharmacists effectively managed the CDSS alert and made interventions in nearly half of the alerts.

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Authors' Note

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Moellering RC Jr. Vancomycin: a 50-year reassessment. *Clin Infect Dis*. 2006;42(suppl 1):S3-S4.
2. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis*. 1994;18:533-543.
3. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity. A review. *Med Toxicol Adverse Drug Exp*. 1988;3:376-386.
4. Darko W, Medicis JJ, Smith A, Guharoy R, Lehmann DE. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. *Pharmacotherapy*. 2003;23:643-650.
5. Elting LS, Rubenstein EB, Kurtin D, et al. Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. *Cancer*. 1998;83:2597-2607.
6. Lee-Such SC, Overholser BR, Munoz-Price LS. Nephrotoxicity associated with aggressive vancomycin therapy. Paper presented at: 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco, CA; September 2006.
7. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. *Clin Ther*. 2007;29:1107-1115.
8. Farber BF, Moellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother*. 1983;23:138-141.
9. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol*. 2009;20:672-679.
10. Rind DM, Safran C, Phillips RS, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med*. 1994;154:1511-1517.
11. Harinstein LM, Kane-Gill SL, Smithburger PL, Culley CM, Reddy VK, Seybert AL. Use of an abnormal laboratory value-drug combination alert to detect drug-induced thrombocytopenia in critically ill patients. *J Crit Care*. 2012;27:242-249.
12. Kilbridge PM, Welebob EM, Classen DC. Development of the Leapfrog methodology for evaluating hospital implemented inpatient computerized physician order entry systems. *Qual Saf Health Care*. 2006;15:81-84.
13. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis*. 2009;49:325-327.
14. Cho A, Lee JE, Yoon JY, et al. Effect of an electronic alert on risk of contrast-induced acute kidney injury in hospitalized patients undergoing computed tomography. *Am J Kidney Dis*. 2012;60:74-81.
15. Colpaert K, Hoste EA, Steurbaut K, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. *Crit Care Med*. 2012;40:1164-1170.
16. Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Ann Pharmacother*. 1999;33:1026-1031.
17. Selby NM, Crowley L, Fluck RJ, et al. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. *Clin J Am Soc Nephrol*. 2012;7:533-540.
18. Sellier E, Colombet I, Sabatier B, et al. Effect of alerts for drug dosage adjustment in inpatients with renal insufficiency. *J Am Med Inform Assoc*. 2009;16:203-210.
19. Moore C, Li J, Hung CC, Downs J, Nebeker JR. Predictive value of alert triggers for identification of developing adverse drug events. *J Patient Saf*. 2009;5:223-228.
20. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA*. 1998;280:1311-1316.
21. Campbell EM, Sittig DF, Ash JS, Guappone KP, Dykstra RH. Types of unintended consequences related to computerized provider order entry. *J Am Med Inform Assoc*. 2006;13:547-556.