A Targeted Review of Vancomycin Use

Rosemary K. Piquette

ABSTRACT

In recent years vancomycin usage at the Ottawa Civic Hospital has been steadily increasing. In an effort to determine the reason for this resurgence, and whether or not it is justified, a prospective assessment of vancomycin utilization was performed. All new orders for vancomycin received in the pharmacy in a two-month period were evaluated against predetermined criteria for appropriate use, which were developed in conjunction with Infectious Diseases and Cardiac Surgery.

Of the 55 orders evaluated during the study period, 32 (58.2%) were considered inappropriate, translating to a cost of approximately $5,500.00 for the seven-week period. Use of vancomycin in penicillin-allergic patients without a confirmed history of IgE-mediated reaction, was responsible for the majority of vancomycin prescribed unnecessarily (~66%).

As a result of the review's findings, the following actions were taken by the Pharmacy and Therapeutics Committee: (1) vancomycin was restricted to specific indications; (2) vancomycin will be prospectively monitored by the Pharmacy Department; (3) physician education on approved indications and dosing of vancomycin; and (4) development of guidelines for assessment and prescribing in penicillin-allergic patients.

Key Words: *vancomycin, drug utilization review, cost containment, penicillin allergy*

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RÉSUMÉ

L'utilisation de vancomycine à l'Hôpital Civique d'Ottawa a augmenté progressivement ces dernières années. Afin de déterminer la raison de cette augmentation, et si elle est justifiée ou non, une évaluation prospective d'utilisation de vancomycine a été effectuée. Toutes les nouvelles ordonnances de vancomycine parvenues à la pharmacie pendant une période de deux mois étaient évaluées selon les critères prédéterminés d'utilisation appropriée, élaborés conjointement avec les départements de Maladies Infectieuses et de Cardiochirurgie.

Sur les 55 ordonnances évaluées pendant la période d'étude, 32 (58.2 pour cent) étaient considérées inappropriées, traduisant un coût à environ 5,500$ pour une période de sept semaines. L'utilisation de vancomycine chez les patients allergiques à la pénicilline n'ayant pas d'antécédants d'une réaction à médiation IgE, était la cause de la plupart des ordonnances de vancomycine prescrites inutilement (~66 pour cent).

Suite aux résultats de la revue d'utilisation, les actions suivantes ont été prises par le Comité de Pharmacologie: (1) Restriction de vancomycine à des indications spécifiques; (2) Monitoring de vancomycine effectué par le département de la pharmacie (3) éducation des médecins sur les indications approuvées et sur la posologie de vancomycine; et (4) élaboration des directives pour évaluation et prescription chez les patients allergiques à la pénicilline.

Mots clés: *vancomycine, maîtrise de coût, allergie à la penicilline, revue d'utilisation de médicament*

INTRODUCTION

The glycopeptide vancomycin is a structurally unique antibiotic which has been available since 1958 for the treatment of gram-positive infections. Used very rarely in the past, this antibiotic has witnessed a resurgence in use in recent years.[1-3] Increased predominance of multi-resistant organisms (e.g. Methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis), increased usage of indwelling catheters and shunts, efficacy of vancomycin in antibiotic associated pseudomembranous colitis (PMC), lack of cross-allergenicity with the

Rosemary K. Piquette, B.Sc.Phm., Staff Pharmacist, Department of Pharmaceutical Services, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9

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Address correspondence to: Rosemary K. Piquette at the above address.

penicillins and the availability of a more purified formulation associated with less adverse reactions are possible reasons reported in the literature to explain this resurgence.[1,3-5]

The drug's new popularity is also evident at this institution. Vancomycin usage figures have steadily and drastically increased since 1983, to the point where it now accounts for 15% of the hospital's total antibiotic budget. We suspected that vancomycin was not being prudently prescribed throughout the hospital, as observed in other institutions.[2,6-9] Despite its excellent activity against gram-positive organisms and relative lack of resistance, vancomycin is not always considered a first line agent due to the availability of other less toxic, less expensive antibiotics.[8] Therefore, a targeted drug review of vancomycin was performed at this 923-bed, acute care, university-affiliated teaching hospital. In order to reduce vancomycin expenditure, we aimed to identify any major areas of inappropriate use in which re-education programs would be beneficial.

METHODS

Indications for rational use and dosing of vancomycin for the purposes of the study were developed from the literature and in consultation with physicians in Infectious Diseases and Cardiac Surgery and were approved by the hospital's Pharmacy and Therapeutics Committee (see Appendix I). All new orders for vancomycin received in the pharmacy department during the study period were prospectively evaluated for compliance with the approved criteria. Upon receipt of a new order, the assigned pharmacist determined patient demographics, antibiotic regimen, indication for vancomycin, and duration of therapy from the active chart. The order was followed until therapy with vancomycin was discontinued. No attempt was made to change these orders when use was considered inappropriate. When necessary, however, the pharmacist questioned the patient as to the type of penicillin allergy reaction when chart documentation was incomplete. This was done in order to accurately assess whether the prescribing of vancomycin to "penicillin-allergic" patients was justified in each case.

Table I: Assessment of Vancomycin Utilization According to Type of Use

	Number of Courses	Number (%) Appropriate	Number (%) Inappropriate
Prophylaxis	20	6 (30.0)	14 (70.0)
Empiric	11	4 (36.4)	7 (63.6)
Treatment	24	13 (54.2)	11 (45.8)
TOTAL	55	23 (41.8)	32 (58.2)

RESULTS

Appropriateness of vancomycin prescribing was prospectively assessed in 55 courses between August 25 and October 16, 1988. Orders were considered "appropriate" if they complied with the predetermined criteria, and "inappropriate" if they did not. Division of orders based on category of use, such as perioperative prophylaxis, empiric therapy, and active treatment, are presented in Table I.

The approximate cost of inappropriate vancomycin orders, based on actual doses administered during the study period, was calculated to be $5,515.70.

Seven of the 32 inappropriate orders (21.9%), which excluded those with a history of penicillin allergy, had inappropriate vancomycin prescribing based on culture and susceptibility results or suspected pathogens. The cost for these orders totalled $1,070.32.

Four cases of suspected or documented PMC were treated with vancomycin during the review period. All were categorized inappropriate, since metronidazole was considered the drug of choice for PMC. One patient was switched to metronidazole after consultation with Infectious Diseases, making the total cost of vancomycin for three patients $1,193.64.

Stated history of penicillin allergy was the single most common reason for prescribing vancomycin in preference to a penicillin or cephalosporin, which accounted for 65.6% of the total number of inappropriate orders. This group includes all patients in whom vancomycin was inappropriately prescribed for prophylaxis. Only 7/25 patients with penicillin allergy documentation had a history consistent with a true IgE-mediated reaction. This type of inappropriate use resulted in a $3,251.74 expenditure.

Based on the recommended optimal doses (Appendix I), the majority of the doses were considered appropriate. All preoperative doses complied with the criteria (17 orders). Eleven orders had dosing considered inappropriate — either excessively high based on renal function parameters such as serum creatinine, creatinine clearance, and BUN, or too low to be considered of therapeutic value. The majority of orders (78.9%) for empiric or active treatment were dosed at an interval of Q6H rather than Q12H. Duration of postoperative prophylaxis exceeded 24 hours in seven cases, accounting

for the high cost of vancomycin prophylaxis.

DISCUSSION

The assessment of vancomycin utilization at this institution was performed to target possible areas of inappropriate prescribing, the existence of which is indicated by the increasingly high usage figures. The results enabled the department to take necessary steps to re-educate pharmacists and physicians, and place more control on vancomycin prescribing to contain costs and promote rational antimicrobial therapy. Our audit was unique in that it was performed prospectively, enabling accurate assessment of penicillin allergy. This is in contrast to the retrospective nature in which vancomycin usage has been reviewed at other hospitals.[6-9]

It is important to note, however, that there may be legitimate needs for vancomycin at our institution which could explain the steady increase. Many patients admitted to this hospital are potential candidates for vancomycin therapy, including those undergoing dialysis, cardiac surgery patients with prosthetic valves, and patients under the orthopaedic service who may have prosthetic implants. We also provide service to a large oncology population who often are immunocompromised or need indwelling central line catheters. We also see a significant number of neutropenic leukemia patients, as there are two admitting haematology physicians on staff. Approximately 50% of identified Staph. epidermidis organisms are resistant to cloxacillin at this hospital. We have not, however, observed any cases of MRSA.

Despite these legitimate needs, the majority (58%) of vancomycin dispensed during the study period was considered unnecessary. In ascending order, the three most predominant inappropriate uses were discovered to be: treatment of PMC with oral vancomycin instead of metronidazole, perceived lack of cost-conscious decision making as evidenced by a disregard for culture and susceptibility results demonstrating in vitro activity of antibiotics other than vancomycin, and the use of this agent in patients labelled as "penicillin allergic".

The latter usage requires further consideration, since it accounted for almost 66% of the total inappropriate orders. Vancomycin was routinely prescribed in those patients with a history of penicillin allergy, even when details as to type of reaction in both nursing and medical histories was lacking. Type I, IgE mediated-immediate onset reactions to penicillin occurs very rarely — 0.04-0.2% of the general population.[19] The number of these individuals who have a cross-allergy to cephalosporins has been quoted at <2% and 5-10%, with an incidence of anaphylaxis of 0.4%.[19,20] Thus, a first generation cephalosporin (or perhaps erythromycin or clindamycin) is a suitable alternative to patients who have not experienced anaphylaxis or urticaria with previous penicillin administration. This audit identified the need for both a more thorough documentation of penicillin allergy reaction type and guidelines for alternate therapy in place of vancomycin. A document with such guidelines has since been developed by the Pharmacy Department and approved by the Division of General Medicine (Infectious Diseases and Allergy). This bulletin highlights incidence and classification of penicillin allergy, discusses skin testing, and provides an algorithmic approach to prescribing.[15]

A similar educational thrust is required to promote metronidazole as the drug of choice for PMC, since the cost difference is several hundred fold, and both metronidazole and vancomycin have been shown to have similar efficacy, relapse, and response rates.[16,17,21]

Most references recommend both vancomycin 500 mg Q6H and 1 g Q12H as empiric starting dose regimens.[5,15,18] For the purposes of this audit, however, we preferred the latter dosing regimen. This was simply because our past experience with the drug had shown that the Q12H interval provided peak and trough measurements in the recommended ranges more often than 500 mg Q6H. Healy et al[22] observed this in their study comparing the two dosage regimens, as we did throughout our audit. Dose adjustment to a Q12H interval based on the patient's pharmacokinetic parameters was frequently necessary when therapy was initiated with the Q6H dosing scheme, especially to reduce trough values to under 10 mg/mL. Considering vancomycin's average half-life of six hours,[4,16] the Q12H dosing is both pharmacokinetically sound and clinically acceptable, in addition to having the benefit of less administration time.[22,23] Although, theoretically, larger doses are reported to be associated with a higher incidence of Red Man's Syndrome,[21] we have not found this to be a problem in our hospital, since the drug is well diluted and infused slowly.

Vancomycin appeared to be inappropriately prescribed according to the predetermined criteria in almost 60% of orders. This inappropriately high usage of the drug translates to thousands of unnecessary dollars spent per year on antimicrobial therapy. Results of the review have led to the recognition of trends in inappropriate prescribing and have

prompted the following recommendations accepted by the Pharmacy and Therapeutics Committee:

1. Vancomycin, as with other high cost antibiotics, should be restricted by criteria for use in the hospital;
2. Vancomycin should be included in the list of high cost antibiotics prospectively monitored by the Pharmacy Department;
3. Increase physician awareness with respect to the proper prescribing of vancomycin.
4. Encourage Q12H dosing when appropriate.
5. Develop guidelines for assessment and prescribing in patients reported as "allergic to penicillin".

The new restrictive policy and attempts to re-educate physicians on approved uses and cost-conscious prescribing strategies is underway. Whether or not these efforts will favourably influence prescribing remains to be seen, but the results of this targeted review of vancomycin utilization have identified the need for ongoing surveillance.

ADDENDUM

Since submission of this paper for publication, vancomycin usage figures for the fiscal year April 1, 1989 to March 31, 1990 have become available. The total vials used for the fiscal year remains high at 8,535. Prescribing of the drug did decline shortly after implementation of those recommendations made by the P&T Committee as a result of the audit. Unfortunately, this effect was short-lived, which may be explained by a change in housestaff, and the issue becoming stale.

Comparing the fiscal years of 1989-90 to that of 1988-89, the total vancomycin dispensed is down by 1,140 vials. This could be extrapolated to a vancomycin cost savings of $21,000.00 over last year, a significant savings, but less than ideally estimated in the audit. Possible explanations for the continued widespread use of the drug at this institution include reasonable fear of methicillin-resistant Staphlococcus epidermidis (incidence ~ 50%), the relatively large number of patients with endocarditis requiring lengthy treatment, and continued physician reluctance to use a cephalosporin in their "penicillin-allergic" patients.

Unfortunately, it is not possible to verify this decrease in vancomycin usage was due solely to the pharmacy department's interventions. The early decrease, however, suggests this may be so. It may also be due, in part, to decreased total daily doses associated with promotion of the Q12H dosing interval in conjunction with pharmacokinetic monitoring.

In summary, vancomycin usage following educational attempts to improve its prescribing showed an initial, albeit short-lived, decline. It appears that continual education is necessary for ongoing success in curbing unnecessary drug use.

Appendix I: Study Criteria for Appropriate Indications of Vancomycin

Prophylaxis:[3,4,10,11]
- surgical (including for bacterial endocarditis) in patients with immediate (Type I) reaction to penicillin, when a first generation cephalosporin, clindamycin, or erythromycin were not suitable alternatives; i.e. due to drug intolerance or need for bactericidal therapy

Empiric:[5,10,12,13]
- in febrile neutropenic patients with leukemia
- patients with prosthetic devices, shunts, and catheters with presumed Staphylococcus epidermidis infection
- adult meningitis associated with trauma

Treatment[1,3-5,10,11,14-17]
- severe gram-positive infections in patients with Type I penicillin allergy, when a first generation cephalosporin, clindamycin, or erythromycin are not acceptable alternatives
- infections caused by organisms reported susceptible only to vancomycin
- weekly dosing in patients undergoing dialysis
- treatment of pseudomembranous colitis (PMC) determined unresponsive to metronidazole therapy

Dosing:[5,15,18]
- pre-operatively, 0.5-1 g; post-operatively, 500 mg Q6H or 1 g Q12H, ⩾24 hours
- treatment, 0.75 — 1 g IV Q12H, or 500 mg IV Q6H in patients with normal renal function
- other empiric regimens with variable dose/intervals if proportional to renal function
- for PMC, 125-500 mg Q6H or QID

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