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Vancomycin therapeutic drug monitoring: is there a consensus view? The results of a UK National External Quality Assessment Scheme (UK NEQAS) for Antibiotic Assays questionnaire

C. M. Tobin[1]*, J. M. Darville[1], A. H. Thomson[2], G. Sweeney[3], J. F. Wilson[4], A. P. MacGowan[1] and L. O. White[1]†

[1]Bristol Centre for Antimicrobial Research and Evaluation, Department of Microbiology, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB; [2]Pharmacy Department and Department of Medicine and Therapeutics, Western Infirmary, North Glasgow Hospitals Trust and [3]Microbiology Department, Southern General Hospital, Glasgow; [4]Department of Pharmacology, Therapeutics and Toxicology, University of Wales College of Medicine, Cardiff, UK

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This study investigated vancomycin therapeutic drug monitoring (TDM) and issues related to patient management. Questionnaires were distributed to 310 participants in the UK National External Quality Assessment Scheme (NEQAS) for Antibiotic Assays. The response rate was 57.4%. The majority (76%) had an 'in-house' assay service based, almost exclusively, in the microbiology department, and a fluorescence polarization immunoassay (FPIA) was used by 97%. Almost half (48.7%) had an assay service available for 24 h/day, 7 days/week and 92.7% expected same-day results. The majority (80%) had issued guidelines for vancomycin use. A 12 hourly initial dosing regimen was used by 89%. Trough assay samples were taken <10 min before the dose by 91.5%. For post-dose assay samples, 44% took a sample at 1 h, 28% at 2 h and the remainder at 'other' times. For trough target ranges, 93% quoted <10 mg/L or 5–10 mg/L. There was no consensus with regard to post-dose assay sample times and 23 ranges were quoted. The majority (74.4%) regarded a trough level of ≥10 mg/L as 'toxic' but 13 concentrations were quoted as toxic post-dose measurements. In conclusion, there was a wide variability and poor consensus with regard to post-dose vancomycin assay sampling times, target ranges and what constituted a toxic level.

Keywords: vancomycin, therapeutic drug monitoring, questionnaire

Introduction

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has led to a resurgence in vancomycin use.[1] When it was first released in the 1950s, impure drug formulations resulted in a high incidence of renal dysfunction and ototoxicity.[2] It was believed that drug toxicities could be avoided if serum concentrations were kept below 40 mg/L and therapeutic drug monitoring (TDM) was recommended.[2,3]

As the MIC for susceptible organisms was ≤4 mg/L, and the free fraction of vancomycin ~50%, target ranges of 5–10 mg/L[4–8] or 5–15 mg/L[8] have been recommended for trough concentrations. Pharmacokinetically, vancomycin has a relatively slow distribution phase with a half-life ranging from 1.6 to 3.6 h, according to renal function.[9] Consequently, enough time must elapse for distribution into the body compartments before post-dose sample collection; at least 1 h, and preferably 2 h after the end of an infusion of at least 100 min.[7] After a standard dosage regimen of 1 g 12 hourly, target ranges of 20–40 mg/L[7,8] for samples taken 1 h, or 18–26 mg/L[5,7,8] for samples taken 2 h, after the infusion have been proposed.[5,7,8] However, these ranges were derived from small-scale, healthy volunteer studies.

*Corresponding author. Tel: +44-117-959-5654; Fax: +44-117-959-3217; E-mail: tobin_c@southmead.swest.nhs.uk
†Deceased.

With the pure drug formulation used today, vancomycin toxicity is not as common, or as severe, as reported originally. When vancomycin monotherapy is used, a low rate (~5%) of reversible renal dysfunction has been found[10–12] and a correlation between serum concentration and reversible ototoxicity has not been established.[13–15] The association between vancomycin and renal dysfunction should be considered weak. There may be many other underlying causes of renal dysfunction in the patient group likely to be treated with vancomycin. It has been reported that vancomycin augments renal dysfunction[10,11,14,16–19] and, to a lesser extent, ototoxicity caused by other agents.[14,15] However, these findings are from uncontrolled observational studies. Once again, there may be other underlying causes for toxicity, as these patients would have been severely ill.

Few data exist to correlate vancomycin serum concentration with clinical efficacy.[20–22] However, de Gatta *et al.*[23] reported a lower incidence of renal dysfunction in patients with haematological malignancies who received TDM and had a mean trough concentration of 8.9 mg/L, compared with patients who had received no monitoring and achieved a mean trough concentration of 16.9 mg/L. Zimmerman *et al.*[24] also found a greater incidence of renal dysfunction in patients with higher trough concentrations, but observed that patients were more likely to be afebrile at 72 h if their trough concentrations were >10 mg/L, and proposed that the upper limit for trough concentrations should be 20 mg/L.

Despite these limited and conflicting data, most patients receiving vancomycin are still monitored. It is recommended, for non-renal patients, that serum concentrations are monitored after 4–5 days of therapy and after 2 days if the patient is receiving other nephrotoxic agents.[7,8] The *British National Formulary* (BNF[25]) recommends that peak plasma concentrations 2 h after the infusion should not exceed 30 mg/L and a trough range of 5–10 mg/L.

By distributing this questionnaire, we aimed to investigate the current practice of vancomycin TDM. In addition to general questions about the type of service provided, we aimed to investigate matters related to patient care, such as how dosages are selected, what sampling times and target ranges are used, and how avoidance of vancomycin toxicity is managed.

Materials and methods

A pilot vancomycin TDM questionnaire was sent to 50 UK National External Quality Assessment Scheme (NEQAS) members. This was then revised, expanded and sent to 310 subscribers to the UK NEQAS for Antibiotic Assays. There were 32 questions split into three sections: methodology; dosage regimen and interpretation; and toxicity. Most answers were in a tick-box format. For questions relating to sampling times and concentration ranges, laboratories were requested to enter their own values.

The questionnaires were returned over a 6 month period and the responses entered into a Microsoft Access database. For the majority of questions, the percentage in each category was calculated after importing the questionnaire data into a Microsoft Excel spreadsheet.

Results

Response rate and laboratory type

The overall response rate was 57.4% (125 UK, 21 European, seven non-European laboratories and 25 where the location was not specified). The majority (71%) were from UK NHS hospitals. Other respondents were from UK public health laboratories (19%), UK private hospitals (7%) and the remainder from European and non-European hospitals.

Vancomycin assay service and requests received

Most hospitals (76%) offered an on-site vancomycin assay service, usually in the microbiology (77%) or a biochemistry department (19%). The majority (97%), used a fluorescence polarization immunoassay (FPIA), and the remainder an enzyme-multiplied immunoassay technique, bio-assay or chemiluminescence techniques. In 28% of hospitals, samples were assayed immediately, with 65% offering a same-day results service. Almost half (48.7%) had a 24 h/day, 7 days/week service or offered, alternatively, a service on a stat basis (12.7%). The remainder had a weekday (09.00–17.00 h) plus weekend service, or offered a service outside normal working hours but not 24 h/day.

The number of assay requests made per year ranged from 5 to 7500. A quarter of laboratories received <100 assay requests. Most laboratories (37.7%) received between 100 and 500, 12.6% between 500 and 1000, and 23.8% received >1000 per year.

Dosage regimen

The majority (80.3%) had guidelines for vancomycin use. When selecting the initial dosage, 52.1% stated that manufacturer's guidelines or the BNF were used. A quarter relied on other methods, such as discussion between consultants, microbiologists and pharmacists, or the use of pharmacokinetic software. A further 20% decided on the initial dosage regimen after reviewing serum creatinine concentrations or creatinine clearances. Twelve-hourly dosage regimens were used as standard by 88.9% of respondents. The remainder used once-daily (2.6%), 8 hourly (2.6%), 6 hourly (3.3%) or other (2.6%) dosing regimens.

Drug analysis and target ranges

The majority (70.9%) recommended vancomycin assays after 2–3 days of therapy, although some would analyse within the first 24–48 h (21.7%). The majority (91.5%) would take a trough sample for vancomycin <10 min before the next dose was due. For post-dose samples, few (11%) stated that their sample time referred to after the end of the infusion. Less than half (44%) would take a post-dose sample at 1 h, 28% at 2 h and 13.5% did not quote a sample time (despite quoting a target range). Ten post-dose sampling times were quoted.

Nine trough ranges were cited, with most quoting ≤10 mg/L (48.7%) or a range of 5–10 mg/L (44.4%). A small number (5.1%), accepted higher trough concentrations of up to 15 mg/L. Twenty-three post-dose ranges were quoted. The ranges and the number of respondents for each are shown in Figure 1. Fourteen ranges were quoted for assay samples taken 1 h post-dose and 10 for 2 h post-dose samples. One respondent quoted a lower post-dose range of 10–14 mg/L for dialysis patients.

Vancomycin toxicity

Almost half (44%) did not know what proportion of their pre-dose results were above normal range. Of those who responded, a third claimed that ≤5% of their trough results were above the normal range each year (range 0.1–40%). For post-dose samples, 48.1% responded and 66.6% again quoted <5% to be toxic (range 0.1–20%).

The majority (74.4%) thought that a toxic trough concentration was ≥10 mg/L. Others (12.8%) thought that a trough vancomycin of ≥15 mg/L was toxic and the remainder quoted eight other concentrations (ranging from ≥8 mg/L to ≥60 mg/L). There was less agreement about what represented a toxic post-dose concentration. A vancomycin concentration of ≥40 mg/L was quoted by 40%, ≥30 mg/L by 19.7% and ≥50 mg/L by 12.8% of respondents. The remainder quoted 10 other concentrations, ranging from ≥25 to ≥80 mg/L.

Vancomycin concentrations above the normal range were dealt with in a number of ways. A dose reduction would be advised by 34.8%, omission of the next dose by 29.6% and 24.7% would extend the dosing interval. Vancomycin would be re-analysed by 51.4% during the first 24–48 h after a dosage alteration or 'as soon as possible' by 21.1%. In addition, 21.1% of respondents cited that a number of clinical factors would have to be considered before re-analysis. When re-analysing vancomycin, 27.7% would request a random sample, 25.7% a trough sample, 16.7% pre- and post-dose specimens. For patients with previous above-normal range concentration, re-analysis would be performed daily by 40%, every 2–3 days by 35.9%, every 5–7 days by 2.1% and 20% reported that they would re-analyse at other intervals (every 2 days, every 3 days or daily until the patient is stabilized followed by assay on alternate days).

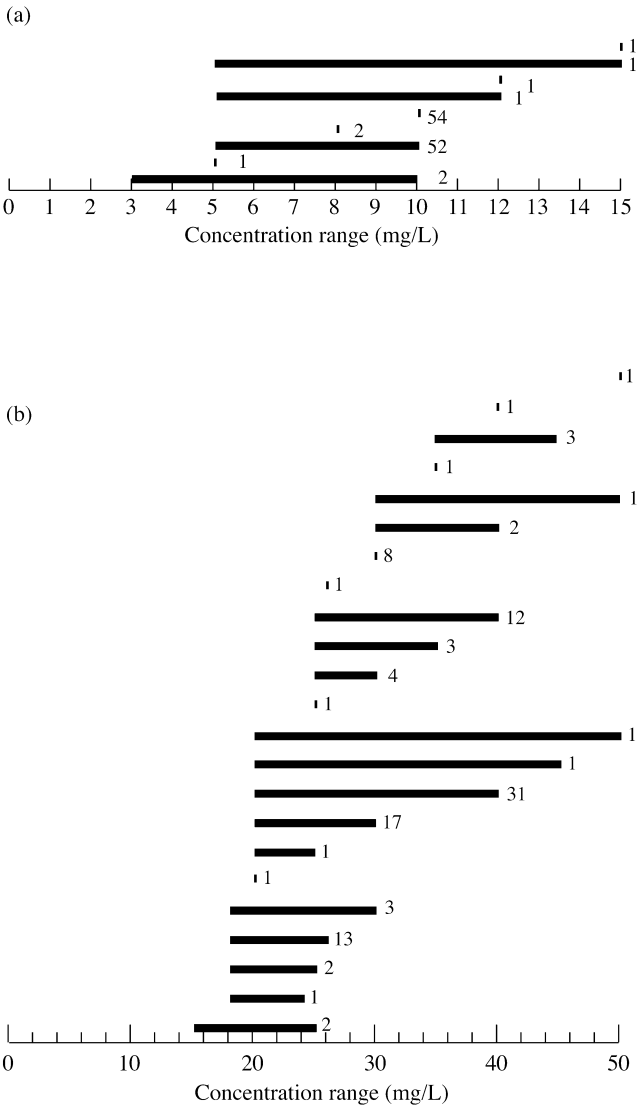

Figure 1. (a) Vancomycin trough target ranges. The left side of the bar represents the lower range and the right side, the upper range quoted. The number of laboratories responding for each range is indicated at the end of each bar. (b) Vancomycin post-dose target ranges. The left side of the bar represents the lower range and the right side, the upper range quoted. The number of laboratories responding for each range is indicated at the start of each bar.

Vancomycin subtherapeutic concentrations

Eight 'subtherapeutic' concentrations were quoted for a trough (from ≤1 to ≤15 mg/L), but 80.3% stated that a subtherapeutic trough was ≤5 mg/L. There was less agreement about a subtherapeutic post-dose concentration, with 50% of respondents quoting ≤20 mg/L. Nine post-dose concentrations were quoted (from ≤4 to ≤30 mg/L).

Reporting and result interpretation

Results were reported by microbiologists (46.8%) and biomedical scientists (45.7%). Pharmacists and biochemists

(6.4%) reported results in some hospitals. Results were initially telephoned (79.3%) or reported via a computer linkage (16.5%). Paper copies were issued by 68.4% for their final report or a computer linkage was used (26.9%).

Results were interpreted by comparison with target ranges by 77.1% of respondents, or by using other methods (14.0%) including 'experience' or discussion with clinical colleagues. Few (six respondents) used pharmacokinetic computer programs.

Are vancomycin assays useful?

A quarter of respondents stated that they found assays useful and another 25% that trough and post-dose samples were the most useful. A further 25% reported that assays were essential in the management of dialysis patients, although we do not know what proportion of these respondents dealt with this group of patients directly. Only 4.6% of respondents thought that they were inappropriate for most patients, and 0.3% thought that they were inappropriate for all. Trough-only assay samples were thought to be the most useful by 14.3%.

Discussion

A limitation of this type of survey is that there may be some bias even though the response rate was good. Vancomycin monitoring is still regarded as important for patient care. A quarter of laboratories received more than 1000 assay requests each year and only one respondent thought that vancomycin TDM was inappropriate. All offered some type of vancomycin TDM service every day, with at least a same-day turnaround for results. Most hospitals had policies for vancomycin use. Despite many hospital and laboratory mergers in the UK, microbiology departments were still the main providers of the service and of clinical advice.

Half of the respondents relied on the BNF (or similar) for determining the initial dosage. The remainder decided on a regimen after discussion with colleagues, or after using a pharmacokinetic computer program. Despite employing a range of techniques, almost all (90%) selected a 1 g 12 hourly initial dosing regimen. The use of this standard dosage may be inappropriate. We were surprised to find that, for a renally cleared drug, only 18.6% of respondents stated they had selected a dose based on a serum creatinine measurement. In selecting the initial vancomycin dose, the use of a dosing nomogram, based on population pharmacokinetics, which takes into account creatinine clearance, should be considered. Many have been cited and evaluated in the literature.[6,26–30]

The majority followed guidelines that advise vancomycin analysis after 2–3 days of therapy. Although there is now much evidence to support the assay of trough samples from certain patient groups,[31–36] just 16% of respondents were ordering trough-only samples. A quarter of our respondents were still ordering trough and post-dose samples.

All respondents had a clear understanding of dealing with trough vancomycin samples. However, there was much confusion with regard to post-dose assay sample times and concentration ranges. Few (eight) stated that their post-dose samples were taken after the end of the infusion and a variety of sampling times were quoted. Unfortunately, the advice of the BNF is that post-dose samples should be taken '2 h after an iv infusion', which could be misinterpreted as 2 h after the start of an infusion. Many concentrations and ranges were quoted for post-dose samples. Despite respondents stating that they were following the BNF guidelines, very few (7.2%) respondents quoted '<30 mg/L' as a target post-dose concentration. The current BNF (September 2001) only recommends trough monitoring with a target of 5–10 mg/L. This is of concern, as 77% of respondents interpreted results by direct comparison with a target range that appears to be different from that published in the BNF. These findings are similar to the results of earlier surveys in Australasia and the USA, where there was no consensus with regard to post-dose assay sampling times and post-dose ranges.[37,38]

Most respondents (75%) still regard vancomycin as a toxic drug. Although respondents were confident about defining a toxic trough concentration, many concentrations were also quoted for a toxic post-dose measurement. It is of concern that almost 50% of respondents did not know what percentage of their samples were above the normal range and there was a relatively low reported incidence of above normal range trough and post-dose concentrations occurring each year. However, a review of trough concentrations from non-renal patients at Southmead Hospital, between April 1997 and March 1998, revealed that 33% of these samples were above the accepted target range i.e. >10 mg/L (C. M. Tobin, unpublished observation).

Conclusions

The results of this survey support the case for the urgent development of evidence-based practice guidelines for vancomycin TDM. We suggest that the following topics should be evaluated: is there any benefit to be derived from the regular, retrospective review of assay results to assess the proportion of concentrations that are outside target range? What is the most appropriate method for vancomycin dosing? Should a nomogram, which takes into account the patient's age, weight and renal function, be used? What is the added value from measuring post-dose concentrations in comparison with trough concentrations only? Should a higher trough concentration range be adopted? What are the benefits of using continuous-infusion vancomycin? Should all patient groups have vancomycin monitored?

Finally, with the almost exclusive use of FPIA (FLx/TDx; Abbott Diagnostics), we would like to highlight the issue of

cross-reactivity of the assay with the crystalline degradation product that accumulates in patients with renal failure. Cross-reactivity may result in falsely elevated serum concentrations of up to 40% and the correlation between the serum concentration and renal function for this assay has yet to be established.[39,40] As vancomycin monitoring is regarded as essential for this patient group, we suggest that the use of an assay technique where cross-reactivity does not occur (such as the Axysym; Abbott Diagnostics, Maidenhead, UK) should be investigated.

We believe, along with many others, that there should be a complete reappraisal of the dosage and monitoring of vancomycin. The basic cost of a single vancomycin assay is ~£4. Our hospital performs in excess of 2000 assays each year. But, if the costs of blood collection, transport to the laboratory, time spent processing paperwork, running the assay, result reporting and interpretation are taken into consideration, the true costs are very high and probably exceed the drug costs for twice-daily 1 g iv dosing (£35). Clear guidelines are required urgently, not based on anecdotal evidence. If better practices are adopted, there are benefits for all.

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