What Proportion of Vancomycin Trough Levels Are Drawn Too Early?

**Frequency and Impact on Clinical Actions**

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**Abstract**

Vancomycin trough levels are recommended to predict vancomycin efficacy, and inaccurate levels may lead to inappropriate clinical actions. However, the frequency of timing errors and associated clinical impact is unknown. We retrospectively analyzed vancomycin levels (n = 2,597) measured during 13 months at a large academic medical center. Of the specimens, 41.3% were drawn too early. These samples yielded significantly higher average ± SD vancomycin concentrations than correctly timed samples (22.1 ± 11.7 mg/L vs 15.5 mg/L ± 8.6 mg/L; P < .001), and, consequently, clinicians were more likely to decrease, discontinue, or hold a patient’s vancomycin dose (25.6% vs 21.4%; P < .02) or repeat the vancomycin level (29.2% vs 20.0%; P < .001). A substantial proportion of specimens collected to assess vancomycin efficacy were drawn too early, leading to overestimation of patients’ true trough level and possible underdosing of vancomycin or a high rate of repeat tests for vancomycin.

Vancomycin is a glycopeptide antibiotic, first introduced in the 1950s, that rose to prominence in the 1980s as a first-line treatment for methicillin-resistant Staphylococcus aureus.1 When monitoring vancomycin therapy is clinically indicated, serum or plasma trough concentrations are recommended as a surrogate marker of pharmacodynamic target attainment to predict vancomycin efficacy.2 Peak levels, previously used to assess toxicity, are currently thought to have little clinical usefulness owing to the improvement in vancomycin formulations over time and evidence indicating a low risk of toxicity using standard doses.3-5

Vancomycin is typically administered by regular intermittent intravenous infusions. A standard dosing regimen is 30 mg/kg per day divided into intervals of 12 hours, with adjustment for renal function. A correctly timed trough level must be drawn shortly before a dose is given and after the drug has reached steady state. A sample drawn too early should not be used to predict vancomycin efficacy because it would likely be an overestimate of the patient’s true trough. Consequently, a clinician may unnecessarily decrease a vancomycin dose or fail to appropriately increase it, leading to underdosing and possibly contributing to a therapeutic failure. Underdosing of vancomycin is also a concern owing to the increased risk of the development of vancomycin-resistant species.5

A number of studies have concluded that many tests for therapeutic drug monitoring may be inappropriate owing to lack of indication, redundancy, improper collection, and improper interpretation,2-15 with 1 study reporting inaccurate specimen timing as a primary cause of inappropriate vancomycin levels.16 However, to our knowledge, the frequency of
specimen timing errors in vancomycin monitoring and associated clinical impact have not been assessed. Thus, we designed this study to determine how often specimen collections for vancomycin trough levels are incorrectly timed, to compare vancomycin concentrations between levels drawn too early and those correctly timed, and to examine differences between the 2 groups in the frequency that clinicians adjusted dosing and obtained repeat laboratory tests.

Materials and Methods

Study Site

Brigham and Women’s Hospital (BWH; Boston, MA) is a 777-bed academic medical center with approximately 46,000 admissions per year. The BWH clinical chemistry laboratory performs approximately 800 vancomycin assays every month. Our institution’s therapeutic range for vancomycin is 15 to 20 mg/L.17 This study was approved by the Partners Human Research Committee.

Study Design

We performed a retrospective analysis of the clinical practice of vancomycin monitoring. As outlined in Figure 1, we evaluated all vancomycin level determinations performed during the 13-month study period of April 1, 2009, to April 30, 2010, that met inclusion criteria. The first criterion required that levels have a documented collection time. Second, we only included levels for patients receiving vancomycin every 12 hours (Q12H), the most common dosing interval at our institution. Since our focus was on the effects of drawing a level too early vs timing it correctly, we excluded “late” levels, ie, those drawn longer than 14 hours after the last dose. Finally, to select for timed trough levels, in contradistinction to “random” levels, we excluded levels obtained after vancomycin had been held or discontinued, indicating clinical concern of toxicity.

Data Sources

Laboratory Test Results and Collection Times

Our institution has an internally developed laboratory information system (LIS) that we accessed to obtain a record of all vancomycin measurements performed by the BWH clinical chemistry laboratory during the study period. The sample collection time was manually entered into the LIS at the time of laboratory receipt from specimen labels printed by the positive patient identification device used by phlebotomists (approximately 50% of samples)18 or from the paper requisition accompanying the sample if not obtained by a phlebotomist.

Medication Administration Data

We accessed our institution’s internally developed electronic medication administration record (eMAR) to obtain a record of vancomycin administrations for our study population.19 Before administering a drug, nurses scan bar codes on the medication, the patient’s wristband, and their employee badge. The time the employee badge is scanned is recorded as the drug administration time, which we used to assess level timing as described subsequently.

Data Analysis

Assessment of Level Timing

We evaluated each vancomycin level as follows, with \( x \) equal to the time elapsed between administration of the last dose and sample collection for the level:

\[
\begin{align*}
& x < 10 \text{ hours} \quad \text{Drawn Too Early} \\
& 10 \text{ hours} \leq x \leq 14 \text{ hours} \quad \text{Correctly Timed}
\end{align*}
\]

For a patient receiving vancomycin Q12H, a trough level would optimally be obtained around 12 hours after the last dose; however, we considered an error of \( \pm 2 \) hours to be acceptable. In most cases, we considered the last dose to be the dose given before sample collection. However, in cases with a very short sampling time relative to the last dose (ie, \( \leq 30 \) minutes), which we determined was likely due to imprecise documentation of drug administration and/or blood collection times, we used the time of the next previous dose (ie, 1 dose prior). After determining each level’s sampling time relative to last dose, we assessed the distribution of sampling times and determined the proportion drawn too early vs correctly timed.

Comparison of Levels Drawn Too Early and Correctly Timed Levels

We compared the plasma vancomycin concentrations and subsequent clinician actions in the 2 groups (drawn too early
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vs correctly timed) to investigate the possible adverse effects of drawing a sample too early. We also determined whether the 2 groups had similar baseline characteristics (age, sex, most recent creatinine level, estimated glomerular filtration rate, and previous vancomycin test result) to verify that these characteristics were not contributing to any differences in the 2 populations. For calculation purposes, all test results below the lower limit of detection of the assay (0.5 mg/L) were converted to 0.0 mg/L.

Clinical Actions

Clinical actions taken in response to levels were grouped into 3 types: (1) dose held, decreased, or discontinued; (2) dose increased; and (3) repeat vancomycin level. Only clinical actions performed within 12 hours of reporting the vancomycin level, but before another level was reported, were included in the study. If the physician’s order for vancomycin was discontinued and no new order was placed for 6 hours, we counted this as discontinuing vancomycin. If a new order with an altered dose amount or frequency was placed within 6 hours of discontinuing vancomycin, we counted this as an increase or decrease to the patient’s dose. The 6-hour threshold was determined based on clinical experience and confirmed by chart review (n = 40). A held dose was considered to have occurred if the following reasons were provided (selected from a drop-down menu in the eMAR): “held per MD,” “parameters exceeded” (used when a vancomycin level exceeds parameters set by a clinician, typically 20 mg/L), or “other, see comments” with a comment referring to the measured vancomycin level. Doses documented as held for other reasons, such as “IV,” “Med Not Available,” “Off Floor,” were not included in our analysis of clinical actions. For cases in which no dosing adjustment was found, we determined whether a repeat vancomycin level, ie, an additional test reported within 24 hours of the original, had been performed.

Statistics

The $\chi^2$ test was used to compare categorical variables, and a 2-tailed Student $t$ test was used for continuous variables. A $P$ value less than .05 was considered significant.

Results

Selection of Levels for Analysis

Of 10,386 plasma vancomycin concentrations measured in the study period, we excluded 2,016 (19.4%) lacking a documented specimen collection time, 4,733 (45.6%) obtained for a patient not on a Q12H schedule, 884 (8.5%) collected more than 14 hours after the last dose, and 156 (1.5%) in which vancomycin was held or discontinued between the last vancomycin administration and specimen collection (Figure 1). Of the 45.6% that were excluded based on dosing interval, 1,634 patients (34.5%) were on a Q24H schedule, 1,004 (21.2%) were on a Q8H schedule, and the remainder were on other schedules (eg, Q48H) or did not have a dosing regimen documented in the eMAR. In total, 2,597 (25.0%) of plasma vancomycin concentrations measured during the study period met the inclusion criteria.

Patient Characteristics

Data for a total of 1,242 different patients were included in the study, of whom 585 patients had multiple vancomycin levels included and 390 had occasion to fall into both the correctly and incorrectly timed groups. There was no significant difference in age, sex, renal function, or previous vancomycin level between the 2 groups Table 1.

Outcomes

Of the evaluated levels, 41.3% (1,075/2,597) were drawn too early Figure 2. The median sampling time relative to the last dose was 7.6 hours for levels drawn too early and 11.5

Table 1

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Early Levels* (n = 1,075)</th>
<th>Correctly Timed Levels* (n = 1,522)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of unique patients</td>
<td>674</td>
<td>958</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>626 (58.2)</td>
<td>919 (60.4)</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>638/1,026 (81.7)</td>
<td>1,194/1,472 (81.1)</td>
<td></td>
</tr>
<tr>
<td>30–60</td>
<td>178/1,026 (17.3)</td>
<td>250/1,472 (17.4)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>101/1,026 (10.0)</td>
<td>220/1,472 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>59 ± 17</td>
<td>59 ± 16</td>
<td></td>
</tr>
<tr>
<td>Creatinine level (mg/dL)</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Previous vancomycin level (mg/L)</td>
<td>16.5 ± 9.2</td>
<td>17.1 ± 10.7</td>
<td></td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; NS, not significant.

* The unit of analysis is each level determination, so patients with multiple levels were counted more than once. In addition, some levels did not have information available for 1 or more of the categories, so the sample may be smaller than 1,075 and 1,522 for early and correctly timed levels, respectively. Data are given as number (percentage), number/total (percentage), or mean ± SD. Creatinine values are given in conventional units; to convert to Système International units (µmol/L), multiply by 88.4.
hours for correctly timed levels. Samples drawn too early had a higher average ± SD vancomycin concentration than those that were correctly timed (22.1 mg/L ± 11.7 mg/L vs 15.5 mg/L ± 8.6 mg/L; *P < .001*). Table 2. Figure 3 shows the average vancomycin concentration for samples drawn at each hour after the last dose. The average concentration peaked at 2 to 3 hours at 35.1 mg/L, which is consistent with an intravenous infusion given during a 1- to 2-hour period, and decreased at each additional hour after the last dose.

Levels drawn too early were twice as likely as correctly timed levels to be supratherapeutic (53.8% vs 26.0%; *P < .001*) and half as likely to be subtherapeutic (26.3% vs 52.1%; *P < .001*; Table 2). Early levels accounted for 59.4% (583/982) of levels of more than 20 mg/L, 72.9% (210/288) of levels of more than 30 mg/L, and 80% (66/83) of levels of more than 40 mg/L.

**Clinical Actions**

While the frequency that clinicians made some alteration to dosing was similar between levels drawn too early and correctly timed levels (~33% vs ~35%; *P > .10*), the type of adjustments made differed significantly depending on how soon after the last dose the specimen was drawn (Table 2). Figure 4. When levels were drawn too early, clinicians more frequently held, decreased, or discontinued a patient’s vancomycin dose (25.6% vs 21.4%; *P < .02*) and less often increased a patient’s vancomycin dose (7.1% vs 13.5%; *P < .001*; Table 2). Clinicians also more frequently obtained a repeat vancomycin level, as opposed to adjusting the dose when a level drawn too early was reported (29.0% vs 20.0%; *P < .001*; Table 2). Levels drawn at 8 to 10 hours, just missing the cutoff for correct timing, were the most likely to be followed by a decision to hold, decrease, or discontinue

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**Table 2**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early Levels (n = 1,075)</th>
<th>Correctly Timed Levels (n = 1,522)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma vancomycin concentration (mg/L)†</td>
<td>22.1 ± 11.7</td>
<td>15.5 ± 8.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vancomycin levels (mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>578 (53.8)</td>
<td>395 (26.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>15-20</td>
<td>214 (19.9)</td>
<td>334 (21.9)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;15</td>
<td>253 (23.3)</td>
<td>795 (52.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical action taken in response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Held, decreased, or discontinued dose</td>
<td>275 (25.6)</td>
<td>326 (21.4)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Dose increase</td>
<td>76 (7.1)</td>
<td>206 (13.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Repeat vancomycin level only; no dosing adjustment</td>
<td>312 (29.0)</td>
<td>304 (20.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NS, not significant.

† The therapeutic range for vancomycin is 15-20 mg/L, with levels >20 mg/L considered supratherapeutic, levels 15-20 mg/L therapeutic, and levels <15 mg/L considered subtherapeutic.
vancomycin compared with correctly timed levels (30% vs 21%; *P* < .001; Figure 4A). Clinicians were least likely to increase the patient’s dosing regimen when responding to levels drawn 2 to 6 hours after the last dose (2% vs 14% for correctly timed levels; *P* < .001; Figure 4B). Repeat levels with no other clinical action were most frequently obtained for levels drawn 2 to 6 hours after the last dose (44% vs 20% for correctly timed levels; *P* <.001; Figure 4C).

**Discussion**

We found that the samples for about 4 in 10 vancomycin levels intended to predict vancomycin efficacy in patients receiving Q12H dosing were collected too early and, thus, did not represent true trough levels. When compared with correctly timed levels, samples drawn too early had significantly higher plasma vancomycin concentrations and were twice as likely to be supratherapeutic. In some cases, clinicians may have realized that levels were not drawn at the appropriate time, as suggested by a high number of repeat levels obtained, particularly for collections drawn 2 to 6 hours after the last dose. However, in many cases, it seems that clinicians may have not have realized that elevated concentrations were due to inaccurate timing. This is suggested by the increased rate that clinicians held, decreased, or discontinued vancomycin in response to early levels and the lower rate at which they increased the patient’s vancomycin regimen. In these cases, the inappropriate use of levels drawn too early to predict efficacy could have led to undertreatment and therapeutic failure. Once the root cause of inaccurate sample timing is established, a more robust infrastructure is required to increase the accuracy of collections for vancomycin levels.

Clinicians often adjusted dosing after obtaining an incorrectly timed level (Table 2 and Figure 4), even though these levels did not represent true trough levels and, therefore, should not be used as a basis for clinical decisions. Moreover, clinicians held, decreased, and discontinued vancomycin at a higher frequency when responding to early levels, particularly when levels were drawn at 8 to 10 hours after the last dose (Figure 4A). These levels, comprising 43.8% (471/1,075) of all early levels, missed the cutoff for correct timing by only a couple of hours, suggesting that clinicians may have attempted to obtain the level at the right time but were unsuccessful (Figure 2). While only a couple of hours off, these samples were still 1.6 times as likely to be supratherapeutic, as compared with levels drawn at the correct time. Clinicians may have considered these levels to be drawn “close enough”
to the right time or failed altogether to realize that levels were obtained too early, leading to the higher rate of held, decreased, or discontinued doses.

In comparison, levels drawn less than 8 hours after the last dose, which were typically higher (Figure 3), were not as likely to be followed by dosing adjustments and more likely to be repeated (Figure 4), suggesting that clinicians sometimes questioned the accuracy of these results. The pharmacists at our institution often intervene when levels are high, and they carefully consider pharmacokinetics, which may have contributed to awareness that these levels did not represent true troughs and which may explain the higher rate of repeats. At institutions with less active clinical pharmacy programs, such recoveries would be expected to be less frequent. However, even if clinicians are realizing the levels are inaccurate timed and thus refraining from inappropriate use of the levels, repeating laboratory tests contributes to delays in patient management and waste in the system.

We observed a low percentage of levels within the therapeutic range and a higher than expected percentage below the therapeutic range, even within the group of early levels (Table 2), which may explain the relatively high rates of dosing increases in both groups (Figure 4B). These findings are consistent with previous findings at our institution, and a quality improvement project is currently underway in the pharmacy department to improve vancomycin dosing. Our pilot study showed an increase in levels within the therapeutic range from 50% to 90% (data not shown) after intervention.

The root cause for the high percentage of inappropriately timed levels is currently under investigation, but we suspect the cause is multifactorial. While clinicians are prompted at the time of placing an electronic order for a vancomycin level with ordering instructions and recommendations, the menu option does not default to a trough level. After a clinician places an order, the nurse must schedule for the level to be drawn, sometimes requiring coordination with the phlebotomy team, which may further complicate the process of getting a correctly timed sample. Finally, neither the sample collection time nor any dosing information is displayed with the vancomycin result in our LIS, making it difficult for clinicians to be cognizant of sample timing relative to dose administration and providing 1 explanation why inappropriate clinical actions were observed for early levels.

The increased adoption of clinical information systems presents new opportunities to address the issue of correct timing of monitoring for vancomycin and other therapeutic drugs through real-time display of dose administration, specimen collection, and test result data, as well as automated guidance to help clinicians time samples correctly. Of note, the method we used to gather data and evaluate the timing of specimen collection was automated and used data recorded by our LIS and eMAR. Our ongoing efforts are aimed at linking the LIS, positive patient identification system, and eMAR such that we can display the time relative to last administration along with each drug level.

Limitations

It is possible that some of the levels we evaluated were intended as peaks or random levels, although peaks are rarely clinically indicated, and we carefully designed criteria to exclude random levels. In addition, about 46% of results were excluded because patients were not on a Q12H schedule; however, a preliminary analysis showed that the rate of incorrect timing was similar for patients with other dosing regimens. We also did not evaluate whether trough levels were clinically appropriate (eg, had the patient reached steady state). Furthermore, it is possible that clinical factors beyond timing of vancomycin levels contributed to some of our findings, although we did not observe any significant baseline differences in age, sex, renal function, or previous vancomycin levels between the 2 groups. Finally, our study has the limitation of being conducted only at 1 institution, and the findings may vary depending on each institution’s standard practices of vancomycin administration and therapeutic drug monitoring.

Conclusion

Samples for vancomycin trough levels were frequently drawn too early, resulting in higher vancomycin concentrations that may have contributed to a high rate of repeat vancomycin levels and possibly inadvertent underdosing. Further effort is needed to identify the root causes of incorrect sample timing and to implement solutions to improve the accuracy of vancomycin monitoring.

References

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