Therapeutic drug monitoring status of four common antibiotics: vancomycin, meropenem, linezolid and teicoplanin

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\textbf{ABSTRACT}

Accurate therapeutic drug monitoring (TDM) of vancomycin, meropenem, linezolid and teicoplanin are conducing to develop optimal therapeutic regimes for patients. However, the measurement status of those drugs in different laboratories has not been reported. In this study, four samples including two frozen plasma samples and two lyophilized plasma samples were measured by over 35 laboratories across China. The inter- and intra-laboratory %CV, biases (%) of laboratories and intra- and inter-measurement-system %CV were calculated and analyzed. The short-term stability and homogeneity of those drugs in samples were studied. The results of frozen and lyophilized samples were also compared to determine whether there were significant differences in their matrix effects on various measurement systems. Results showed most laboratories’ intra-laboratory %CVs were less than 9% for all drugs, and the mean inter-laboratory %CVs were 18.4%, 86.4%, 19.1% and 37.1% for vancomycin, meropenem, linezolid and teicoplanin measurements, respectively. For vancomycin, the intra-measurement %CV of commercial measurement systems was found to be smaller than that of other measurement systems. For meropenem, linezolid and teicoplanin, the agreement among laboratories using self-developed methods (Liquid chromatography–mass spectrometry [LC–MS] or high-performance liquid chromatography [HPLC]) was not satisfactory as most intra-measurement system CVs% were over 20%. Drugs in lyophilized samples were found to be more stable than in frozen samples, and no obvious differences in matrix effects were found for those two kinds of processed samples on most measurement systems. In conclusion, this study depicted the measurement status of those drugs in clinical laboratories, and found the lyophilized samples were more suitable EQA material for those drugs.

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\textbf{Introduction}

Vancomycin, meropenem, teicoplanin and linezolid have been widely used in infection-related diseases since they were discovered [1,2]. However, since their therapeutic ranges (the minimal effective level to minimal toxic level) are remarkably narrow, and metabolism heterogeneity among patients is significant, inappropriate use of them in clinic would lead to toxic effects and drug-resistances [3–6]. Therefore, it is essential to optimize their use not only to maximize the therapeutic efficacy but also to prolong their clinical lifespan by limiting the emergence of resistance. Therapeutic drug monitoring (TDM) is the management of drugs or their active metabolite levels in biological samples (usually plasma), which aims to improve efficacy and/or reduce toxicity and achieve individualized treatment by adapting drug doses based on their measured concentrations [7,8]. TDM has been used as a powerful tool to avoid the side effects and antimicrobial resistance of antibiotics since 1956 [9].

In 2021, a national survey was conducted by the Chinese National Center for Clinical Laboratories and the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society to study the TDM status in China. This study included 405 laboratories across China, results showed that among the 14 commonly used antimicrobial drugs, vancomycin, meropenem, teicoplanin and linezolid were the most common antibiotics for TDM in China as 172/405, 44/405 and 41/405 participating laboratories were detecting them, respectively.

Despite the TDM of vancomycin, meropenem, teicoplanin and linezolid having been carried out in an increasing number of clinical laboratories, the measurement status
of those drugs in clinical laboratories have not been reported in detail. In this study, to assess the current measurement status of vancomycin, meropenem, teicoplanin and linezolid in China, four processed plasma samples including two-levels frozen plasma samples and 2-levels lyophilized plasma samples were measured by different laboratories across China and the results from different laboratories were compared and analyzed. At the same time, to explore the suitable EQA materials for the TDM of those four drugs, the stability, homogeneity and differences in matrix effects of those two kinds of processed plasma samples were studied and compared.

Materials and methods

Specimens

The vancomycin, meropenem and teicoplanin used in this study were purchased from the Chinese National Institutes for Food and Drug Control (Beijing, China), and their Art. No were 130360-201302; 130506-201403 and 130374-202103, respectively. The linezolid was purchased from Solarbio (Beijing, China) with Art. No 122A021.

Two levels of frozen pooled plasma samples and two levels of lyophilized pooled plasma samples used in this study were prepared by spiking the drugs in the collected pooled plasma. For the sample preparation, two bottles (500 mL) of pooled plasma were first prepared via pooling fresh leftover patient plasma samples that were collected from Beijing Hospital. The two bottles of pooled plasma were then filtered (first with 0.45 μm filter membrane and then 0.22 μm filter membrane) and spiked with those drugs to prepare two pooled plasma samples with low and high drug concentrations. After that, the two pooled plasma was mixed for 2 h at 4 °C on the magnetic stirring apparatus and was aliquoted into 1 mL vials. At last, half of the aliquots of each pooled plasma sample were frozen at −80 °C until analysis (202111- low level, 202112- high level, abbreviated as frozen samples) and another half of the aliquots were processed to lyophilized powder and were also stored at −80 °C (202113- low level, 202114-high level, abbreviated as lyophilized samples).

It needs to be mentioned that frozen sample 202111 and lyophilized sample 202113 were processed from the same spiked pooled plasma and frozen sample 202112 and lyophilized sample 202114 were processed from another bottle of spiked plasma. Therefore, 202111 and 202113 had the same concentrations for those drugs, and 202112 and 202114 had the same concentrations for those drugs.

Stability and homogeneity experiments

Before the shipment to laboratories, the homogeneity of aliquots and the short-term stability of samples at various temperatures (−20, 4 °C and room temperature) were studied. To study the homogeneity between the aliquots of processed samples, 20 aliquots of each processed plasma sample were randomly selected and each of them was measured in duplicate and the homogeneity was determined depending on the ISO 13528 standard (https://www.iso.org/standard/56125.html).

For the stability study, three aliquots of each frozen sample were stored at room temperature and 4 °C for 2, 4, 24 h, 3 and 7 d, respectively, and at −20 °C for 14 d. Three aliquots of each lyophilized sample were stored at 4 °C for 7 and 14 d, respectively, and at −20 °C for 20 d. Then, each aliquot was measured two times along with samples that were always stored at −80 °C. The measurement results of samples with and without storage condition alternation were compared to define the stability.

Measurement protocol

Each sample with two aliquots (a total of eight vials) were distributed on dry ice to laboratories and stored at −80 °C until measurement. Along with the samples, a registration form requesting information about their measurement systems including the principle, reagents, calibrators and instruments was also provided for laboratories. Aliquots were measured like clinical samples by laboratories on two separate days; the interval between the two days should not exceed 7 d. After converting units into μg/mL, laboratories were requested to submit two values for each sample before the given deadline (a total of eight values were collected for four samples).

Statistical analysis

The intra-laboratory imprecision (intra-laboratory %CV) was calculated using the laboratory’s two repeated values for each laboratory. The means of two repeated values were used to calculate the inter-laboratory imprecision (inter-laboratory %CV), and the relative differences (%) between frozen sample 202111 and lyophilized sample 202113, frozen sample 202112 and lyophilized sample 202114. The means of two repeated values of laboratories using the same measurement systems were used to calculate the intra-measurement-system imprecision (intra-measurement-system %CV).

The spiked concentrations of those drugs were determined as the target values of each sample (Supplementary material Table S2). The bias% of results from laboratories was calculated by comparing the mean of two repeated values with the target values and the means of bias% of laboratories using the same measurement systems were used to evaluate the accuracy of relevant measurement systems.

The total allowable error (Tea) limits for those drugs (±30% of the target value) recommended by the Chinese National Center of Clinical Laboratories was used to calculate the check values and evaluate the homogeneity based on the ISO 13528 standard. 1/3 of the Tea (10%) was used to evaluate the short-term stability of lyophilized samples and frozen samples. Samples were considered to be stable if the results of samples with storage conditions alternations were within 100 ± 10% of the results of samples that were always stored at −80 °C.
All calculations were completed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) and MedCalc statistical software 18.11.6-64-bit (Mariakerke, Belgium).

Results

Measurement systems used by laboratories

Vancomycin, meropenem, teicoplanin and linezolid were detected by 86, 50, 35 and 48 laboratories across China, respectively. Various measurement systems, such as laboratory-developed methods (Liquid chromatography–mass spectrometry (LC–MS), high-performance liquid chromatography (HPLC)) and commercial measurement system (Abbott, Siemens and Demeter) were used by laboratories to measure those drugs. For vancomycin, both laboratory-developed methods and commercial measurement systems were used by laboratories. For meropenem, teicoplanin and linezolid, notably, commercial immunoassays, such as Siemens and Abbott measurement systems, were not widely used by laboratories. Instead, the self-developed LC–MS methods were widely used as 66%, 66% and 71% of laboratories were using it to detect meropenem, teicoplanin and linezolid, respectively (Supplementary material Table S1).

The stability, homogeneity and differences in matrix effects of processed samples

Results showed that aliquots of all processed samples were homogeneous as all between-samples standard deviation values (S_s) were smaller than the check values (Supplementary material, Table S2).

For the stability of frozen samples, results showed that vancomycin and teicoplanin could be stably stored at room temperature and 4℃ for no more than 24 h. Linezolid could be stably stored at 4℃ for 72 h. Meropenem could be stably stored at 4℃ for 24 h, but only 4 h at room temperature (Supplementary material Table S3, Figure 1). At −20℃, all of those four drugs could be stably stored for at least 20 d (Supplementary material Table S3). In lyophilized samples (202113, 202114), all drugs could be stably stored at 4℃ for at least 20 d and at 0℃ for at least 20 d (Supplementary material Table S4).

The relative differences (%) between the results of frozen samples and lyophilized samples on various measurement systems were concluded in Table 1. The mean relative differences (%) between frozen samples and lyophilized samples on most measurement systems were within ±10% for vancomycin (Table 1). However, for meropenem, an obvious difference (%) was observed between lyophilized samples.
Table 1. The relative differences (% between the results of frozen samples and lyophilized samples on various measurement systems.

| Measurement System | Vancomycin | Linezolid | Teicoplanin |
|--------------------|------------|-----------|-------------|
| Mean (Low) | 11.1 | 9.2 | 8.3 |
| Mean (High) | 11.6 | 9.2 | 9.2 |
| Mean (LC-MS) | 11.1 | 9.2 | 9.2 |
| Mean (HPLC) | 11.1 | 9.2 | 9.2 |
| Mean (Demeter) | 11.1 | 9.2 | 9.2 |
| Mean (Simens) | 11.1 | 9.2 | 9.2 |
| Mean (Abbott) | 11.1 | 9.2 | 9.2 |
| Mean (Supplementary material) | 11.1 | 9.2 | 9.2 |

The measurement results from different laboratories for those drugs were presented in Supplementary material Figure S1. The upper quartiles of intra-laboratory %CVs of laboratories ranged from 3.9% to 8.7% for drugs in processed samples (Table 2) indicating the intra-laboratory imprecision of most laboratories was acceptable for the measurements of those drugs. The inter-laboratory %CVs among laboratories ranged from 15.8% to 19.7% and from 14.8% to 25.9% for vancomycin and linezolid, respectively. Notably, the inter-laboratory imprecision of meropenem and teicoplanin was unacceptable as the mean inter-laboratory %CV ranged from 67.3% to 118.6% and 33.3% to 39.2%, respectively (Table 2). Therefore, the agreement between different laboratories for meropenem and teicoplanin measurements was much worse than that of vancomycin and linezolid.

The intra-measurement-system %CVs and accuracy of measurement systems

For vancomycin, the intra-measurement-system %CVs of commercial measurement systems (Abbott, Siemens and Demeter) were found to be much smaller than that of laboratory-developed LC–MS and HPLC methods (Table 3). For meropenem, intra- and inter-measurement-system imprecisions were unacceptable as most intra- and inter-measurement-system %CV were over 60% indicating that despite being based on the same principles, the agreement between results from different laboratories still varies greatly (Table 3). For linezolid, the intra-measurement-system CV% of LC–MS methods was better than that of HPLC methods. However, for teicoplanin, intra-measurement-system CV% of HPLC methods was better than that of LC–MS methods (Table 3).

For vancomycin, the mean biases of commercial methods Abbott and laboratory-developed HPLC methods were less than other measurement systems. For meropenem, the accuracy of most laboratories was unacceptable as the mean biases ranged from −56.0% to −86.8%. Compared with meropenem, the mean biases of linezolid were much better as the mean biases of most processed samples ranged from −19.3% to 4.5%. And the mean biases of the LC–MS method were slightly smaller than
that of HPLC and Demeter. Instead, the mean biases of the HPLC method were slightly smaller than that of the LC–MS method for teicoplanin (Table 3).

**Discussion**

In this study, over three-quarters of laboratories’ intra-laboratory CV% for the measurements of those four drugs were less than 9%. Therefore, the intra-laboratory imprecision for vancomycin, meropenem, linezolid and teicoplanin measurements in clinical laboratories was acceptable for most laboratories. However, measurement results of vancomycin, linezolid and teicoplanin from different laboratories were not comparable as the inter-laboratory %CVs ranged from 15.8% to 19.7% for vancomycin, from 14.8% to 25.9% for linezolid and from 33.3% to 39.2% for teicoplanin (Table 2). Notably, the agreement of meropenem measurement results between laboratories was even much worse as its inter-laboratory %CV ranged from 67.3% to 118.6% (Table 2). The incomparable results from different medical settings would impact the development of effective therapeutic regimes as well as require unnecessarily repeated measurements especially when patients transfer between hospitals. Therefore, there is an urgent need to improve the comparability of the results from different laboratories for vancomycin, meropenem, linezolid and teicoplanin measurements.

In this study, we found that meropenem, linezolid and teicoplanin were mainly measured by laboratory-developed LC–MS and HPLC methods and vancomycin was measured by both laboratory-developed methods and commercial immunoassays. For vancomycin, commercial measurement systems Abbott, Siemens and Demeter were found to show smaller intra-measurement-system %CVs than laboratory-developed LC–MS and HPLC methods. One possible explanation was that commercial measurement systems usually use the same calibrators, reagents and measurement procedures, in this case, good agreement among different laboratories was easy to achieve. Instead, the laboratory-developed methods often used different homemade reagents and calibrators. Consequently, the difference between the calibrators and reagents would lead to variations in measurement results from different laboratories.

For linezolid and teicoplanin measurements, the laboratory-developed LC–MS methods were widely used in clinical laboratories. The mean biases of linezolid measurement were better than that of the other three drugs indicating the measurement of linezolid was more accurate than other three drugs in clinical laboratories. For meropenem, both the accuracy of laboratories and the agreement among laboratories were unacceptable and activities including the improvement of the performance of measurement systems, EQA program and methods comparison need to be conducted to promote the measurement status of meropenem.

Despite laboratory-developed LC–MS and HPLC methods being widely used to measure those drugs, however, the agreement among laboratories using them was dissatisfactory, one possible explanation for the disagreement and inaccuracy of results from laboratories using self-developed LC–MS methods is that there might be some metabolites and interferences in patients’ plasma samples which would lead to different levels of interference response to the response of analyte. Consequently, the measurement results of different measurement systems vary a lot. For example, some metabolites and interferences in patients might be hard to be separated from the analyte in liquid chromatography separation which would result in fake responses in mass spectrometry and inconsistent measurement results. Therefore, to improve the agreement among laboratories, those laboratory-developed methods are encouraged to employ similar measurement procedures and calibrators that can be traced to the same standard. To improve the accuracy of the measurements of those drugs in clinical laboratories, manufacturers and laboratories should trace their calibrators to higher orders reference materials, which is known as standardization or harmonization.

In addition to the improvement of measurement systems, the EQA programs are also effective tools to optimize the comparability among different laboratories [10]. Suitable EQA materials are essential for the success of EQA programs [11]. In this study, vancomycin, meropenem, linezolid and teicoplanin were found to be more stable in lyophilized samples than in frozen samples. On the other hand, the lyophilized samples and frozen samples did not show obvious differences in matrix effect on various measurement systems except for the meropenem. Notably, the obvious differences (%) between frozen samples and lyophilized samples for meropenem might be induced by its poor stability in frozen samples as it could only be stably stored at room temperature for 4 h in frozen samples and some laboratories might leave samples at room temperature for over 4 h when they measure the sample. Therefore, for most measurement systems, the matrix effects of those two kinds of processed samples were similar and their measurement results did not show obvious differences (%) for three of four drugs (vancomycin, teicoplanin and linezolid). As a
Table 3. The intra-measurement-systems %CV and bias (%) of vancomycin, meropenem, linezolid and teicoplanin measurement results from different measurement systems.

| Intra-measurement-systems %CV | 202111 | 202112 | 202113 | 202114 |
|-------------------------------|--------|--------|--------|--------|
| Vancomycin | | | | |
| LC-MS (31) | 17.8 | –54.1 to 6.3 | –23.4 | 22.3 | –83.8 to 19.0 | –25.3 | 21.9 | –65.9 to 28.9 | –14.1 | 21.0 | –59.8 to 48.4 | –12.9 |
| Demeter (14) | 10.9 | –40.9 to 15.2 | –27.2 | 16.7 | –46.2 to 16.1 | –29.9 | 12.0 | –33.4 to 1.6 | –19.9 | 19.3 | –40.5 to 11.3 | –19.7 |
| Siemens Viva (21) | 11.6 | –32.7 to 12.0 | –22.6 | 17.3 | –39.2 to 19.3 | –28.3 | 11.9 | –36.0 to 3.3 | –21.3 | 18.1 | –38.8 to 9.6 | –24.7 |
| Abbott (13) | 6.3 | –7.7 to 25.4 | –6.5 | 12.1 | –25.0 to 14.3 | –13.9 | 10.8 | –27.7 to 12.9 | –10.9 | 9.8 | –28 to 2.46 | –15.5 |
| HPLC (6) | 13.8 | –40.9 to 37.7 | –8.0 | 22.2 | –39.4 to 33.3 | –7.0 | 15.6 | –35.6 to 47.3 | 4.6 | 25.3 | –33.7 to 58.5 | 5.6 |
| Others (7) | 12.0 | –33.1 to 2.0 | –19.3 | 19.1 | –33.3 to –5.4 | –20.0 | 11.3 | –32.9 to –1.5 | –4.2 | 18.7 | –33.8 to 1.6 | –21.1 |
| Inter-measurement-system %CV | 8.4 | 11.1 | | | | | | | | 11.9 | | 12.7 |
| Meropenem | | | | | | | | | | | | |
| LC-MS (33) | 80.3 | –87.4 to 20.0 | –67.3 | 80.0 | –89.4 to 8.3 | –73.1 | 62.2 | –78.8 to 63.8 | –57.8 | 65.0 | –82.1 to 77.3 | –56.0 |
| Demeter (6) | 49.0 | –96 to –71.6 | –83.8 | 59.8 | –97.4 to –78.2 | –86.8 | 39.3 | –94.2 to –62.6 | –74.8 | 52.3 | –97.4 to –78.2 | –86.8 |
| HPLC (9) | 68.2 | –91.4 to –37.0 | –76.8 | 38.1 | –92.0 to –70.5 | –84.2 | 163.0 | –83.8 to –40.8 | –69.9 | 28.5 | –50.7 to –83.4 | –71.2 |
| Others (2) | 4.5 | –80.0 to –76.6 | –78.1 | 4.7 | –83.0 to –80.0 | –82.2 | 16.4 | –79.0 to –70.8 | –75.5 | 9.8 | –82.3 to –79.4 | –81.3 |
| Inter-measurement-system %CV | 121.8 | 82.5 | 213.5 | 80.3 |
| Linezolid | | | | | | | | | | | | |
| LC-MS (34) | 18.8 | –60.3 to 38.7 | –7.1 | 14.4 | –58.7 to 12.5 | –11.1 | 16.4 | –59.0 to 31.7 | –4.9 | 15.9 | –54.3 to 26.9 | –7.2 |
| Demeter (10) | 44.6 | –33.0 to 123.0 | 4.5 | 17.4 | –31.1 to 21.6 | –14.6 | 29.5 | –37.3 to 70.3 | –6.9 | 21.3 | –28.3 to 34.2 | –11.1 |
| Others (2) | 6.1 | –16.3 to –6.7 | –11.8 | 11.6 | –24.3 to –10.2 | –19.3 | 12.0 | –19.7 to –23 | –12.6 | 14.1 | –23.0 to –5.4 | –16.8 |
| Inter-measurement-system %CV | 22.1 | 34.0 to 360.4 | 158.5 | 17.1 | –47.2 to 163.0 | 23.4 | 12.3 | –61.6 to 207.8 | 78.9 | 12.4 | –49.4 to 163.8 | 31.9 |
| 7.3 | 8.5 | 8.0 | 8.8 |
| Teicoplanin | | | | | | | | | | | | |
| LC-MS (23) | 42.9 | –74.0 to 60.2 | –19.2 | 43.0 | –77.0 to 47.5 | –23.9 | 40.3 | –78.0 to 74.4 | –19.2 | 37.1 | –70.0 to 47.8 | –18.3 |
| Demeter (8) | 36.1 | –46.4 to 34.6 | –8.2 | 22.3 | –51.2 to 0.5 | –26.4 | 32.4 | –45.4 to 40.2 | –2.74 | 24.4 | –46.8 to 10.2 | –19.3 |
| Others (4) | 20.0 | –16.4 to 11.2 | –2.6 | 1.8 | –40.4 to –38.8 | –39.6 | 34.6 | –62.0 to 54.6 | 24.2 | 9.8 | –39.35 to 30.35 | –34.9 |
| Inter-measurement-system %CV | 22.2 | –2.2 to 46.0 | 21.2 | 18.7 | –3.8 to –2.3 | –3.1 | 20.8 | –7.2 to –5.6 | –6.4 | 21.8 | –2.5 to –1.7 | –2.1 |
| 18.9 | 14.0 | 7.9 | 10.4 |

The numbers in the brackets are the number of laboratories using the relevant measurement system. %CV refers to the intra-measurement-systems %CV.
result, three key attributes make the lyophilized sample a better EQA material for vancomycin, meropenem, teicoplanin, and linezolid measurements: (1) lyophilized samples were more stable than frozen samples, (2) the transport and storage of lyophilized samples were more convenient and cost-effective, (3) no obvious differences were observed between the results of lyophilized samples and frozen samples measured by different measurement systems.

Notably, in our study, each laboratory measured each processed plasma sample one time per day on two specific days and the intra-laboratory %CV was calculated using the two results, which might not be fully representative as two repeated results might be insufficient to reflect the full random error.

Conclusion

In conclusion, currently, an increasing number of laboratories are providing the TDM measurements for various antibiotics using self-developed methods, however, the comparability and agreement among results from different laboratories have not been reported. This study provided reliable data about laboratory performances as well as the current measurement status of vancomycin, meropenem, linezolid, and teicoplanin measurements, which may provide data support for laboratories to choose measurement systems, manufacturers to elevate performance, and clinicians to better interpret measurement results of the TDM results. This study also demonstrated that the lyophilized samples were the suitable EQA material for vancomycin, meropenem, linezolid, and teicoplanin measurements.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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