Measuring Plasma Concentrations of Ribavirin

Smolders, Elise Joelle; Kan, Rodney; de Kanter, Clara Tresia Marcus Maria; van Luin, Matthijs; Aarnoutse, Rob Edward; Touw, Daan Johannes; Burger, David Marinus

Published in:
Therapeutic Drug Monitoring

DOI:
10.1097/FTD.0000000000000319

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 17-09-2023
To the Editors:

A chronic hepatitis C virus (HCV) infection is nowadays treated with combination therapy of novel direct-acting antivirals. These drugs are very effective, and high sustained virological response rates are achieved in patients without cirrhosis (>90%). Cirrhotic patients are more difficult to treat, which could be due to physiological changes caused by scarring of the liver. Therefore, ribavirin is added to direct-acting antiviral therapy, which improves HCV treatment response and gives an opportunity to shorten treatment duration from 24 to 12 weeks. Ribavirin has a strong concentration–effect relationship, and therapeutic drug monitoring (TDM) can be used to individualize the dose of ribavirin.

Therefore, several laboratories developed ribavirin assays. These methods are generally validated internally for validation parameters such as accuracy, precision, selectivity, sensitivity, reproducibility, and stability according to international guidelines. To ensure the accuracy of these bioanalytical methods and to alert laboratories to previously undetected problems, we developed an international external quality control program (QC) or proficiency testing (PT) program for measurement of ribavirin.

The aim of this report was to describe the results of the first year of this ribavirin PT program.

In 2015, we dispatched 2 samples per round (2 rounds in total) to the participating laboratories. For these samples, bovine serum was spiked with low and high concentrations of ribavirin. These samples were freeze dried and were shipped by regular mail. For 2 participants, the samples were shipped on dry ice because they participated in another program requiring shipment on dry ice. The concentrations chosen resembled the range of concentrations measured in patients treated with a normal dose of ribavirin (patient weight <75 kg = 1000 mg/d and ≥75 kg = 1200 mg/d). The target range for ribavirin plasma concentrations at steady state is 2.2–3.6 mg/L.

Details of similar programs have been described previously. Participants were informed about their performance in measuring ribavirin concentrations. Accuracy was considered to be acceptable if measurements were within the 80%–120% limits of the spiked (weighed-in) concentrations. This 20% threshold was based on guidelines for method validation for bioanalysis of drugs with 20% deviations used as fixed criterion for inaccuracy at the lowest level of quantification and on maximum allowable error specifications for drug measurements according to the US Clinical Laboratory Improvement Amendments (CLIA) of 1988.

Eight laboratories participated in the program, of which 2 participants completed one round. Most participants (n = 7) used liquid chromatography with mass spectrometry detection to determine ribavirin concentrations. One center used high-performance liquid chromatography with an ultraviolet detector.

In round 1, 81% of the samples (ie, 13 of 16 samples) were determined accurately, and the variation in accuracy of samples with low concentrations was 86%–336%. The samples spiked with high ribavirin concentrations varied from 55% to 160% in accuracy (Table 1 and Fig. 1).

In round 2, a total of 75% samples (ie, 9 of 12) were determined accurately within 80%–120% of the weighed-in concentrations. Accuracy for samples with low and high concentrations varied from 97% to 303% and from 97% to 148%, respectively.

The median inaccuracy for all measurements was 6.1% (range: 0.8%–236.2%). It was 6.7% (range: 1.6%–236.2%) and 6.1% (range: 0.8%–60.4%) for low and high ribavirin concentrations, respectively.

Of the 8 participating laboratories, 5 had all samples analyzed within 80%–120% limits of the weighed-in concentrations, 3 reported at least one inaccurate result, of which one participant reported all 4 samples inaccurately (>120%).

The aim of a PT program is to provide external validation of bioanalytical assays to assure and improve quality. Participating laboratories were informed about their performance and their ability to measure the correct analyte concentrations. This may help them to improve their laboratory performance. The analysis of this small sample set showed that 6/28 of the ribavirin samples were measured inaccurately, which was in line with first rounds of

D. J. Touw is on the advisory board of Sanquin and received a research grant from ZONMW. D. M. Burger is on advisory boards of Abbvie, BMS, Gilead, Janssen, ViV Healthcare, and Merck. He received sponsorship and research grants from BMS, Janssen, ViV Healthcare, and Merck. The remaining authors declare no conflict of interest.

Participating laboratories pay a subscribing fee for their participation in the program.

<p>| TABLE 1. Overall Performance of the 8 Laboratories |</p>
<table>
<thead>
<tr>
<th>Round, Concentration</th>
<th>No. Samples</th>
<th>Expert Concentration, mg/L</th>
<th>Measured Concentration, Median mg/L (Range mg/L)</th>
<th>Median Inaccuracy, Median % (Range %)</th>
<th>Number and Percentage of Measurements With Acceptable Accuracy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, High</td>
<td>8</td>
<td>3.64</td>
<td>3.66 (2.00–5.84)</td>
<td>8.2 (0.8–60.4)</td>
<td>6/8 (75)</td>
</tr>
<tr>
<td>2, High</td>
<td>6</td>
<td>2.18</td>
<td>2.25 (2.12–3.22)</td>
<td>4.1 (0.9–47.7)</td>
<td>4/6 (67)</td>
</tr>
<tr>
<td>1, Low</td>
<td>8</td>
<td>0.82</td>
<td>0.80 (0.70–2.74)</td>
<td>6.4 (1.8–236.2)</td>
<td>7/8 (88)</td>
</tr>
<tr>
<td>2, Low</td>
<td>6</td>
<td>0.51</td>
<td>0.55 (0.49–1.54)</td>
<td>7.5 (1.6–203.2)</td>
<td>5/6 (83)</td>
</tr>
</tbody>
</table>

*Inaccuracy is percentage bias from the true concentration. Measured/expert concentration >100%: inaccuracy = (100 × measured concentration/true concentration) – 100. Measured/expert concentration <100%: inaccuracy = 100 – (100 × measured concentration/true concentration).*
similar QC programs.\textsuperscript{6–8} The laboratories with a poor performance should improve their analyses. In the specific case of the laboratory that inaccurately reported all 4 concentrations, intralaboratory validation was possibly incorrect, or other errors might have been involved, such as methodological, clerical, or technical errors.

The impact of reporting inaccurate high ribavirin plasma concentrations is that dosage might be reduced unnecessarily, possibly leading to subtherapeutic ribavirin concentrations and potentially causing virologic failure. For concentrations reported with an accuracy <80\%, this might lead to increased dosages, causing unnecessary adverse events such as anemia.

Ribavirin is important for HCV treatment in cirrhotic patients. To ensure safety and efficacy, TDM may be used in daily practice. TDM is especially relevant in specific patient populations such as patients with renal failure or patients receiving hemodialysis. Thus, for treatment of patients with HCV, it is critical that laboratories are able to measure the correct plasma concentrations, which is ensured by our external QC program. Laboratories measuring ribavirin are encouraged to participate in our PT program (www.kkgt.nl).

Elise Joëlle Smolders, MSc\textsuperscript{*}
Roderick Kan, MSc\textsuperscript{†}
Clara Tresia Marcus Maria de Kanter, PharmD, PhD\textsuperscript{‡}
Matthijs van Luin, PharmD, PhD\textsuperscript{§}

Rob Edward Aarnoutse, PharmD, PhD\textsuperscript{++}
Daan Johannes Touw, PharmD, PhD\textsuperscript{++}
David Marinus Burger, PharmD, PhD\textsuperscript{++}

*Department of Pharmacy, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands
†Department of Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
‡Department of Clinical Pharmacy, Rijnstate Hospital, Arnhem, the Netherlands
¶Department for Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands

ACKNOWLEDGMENTS
We express gratitude to the KKG/T/SMML for the preparation of the quality control samples. We thank all the participating laboratories for their cooperation.

REFERENCES


