Propylene Glycol Interference in Gas-Chromatographic Assay of Ethylene Glycol

To the Editor:

We wish to substantiate the important observations of LeGatt and Tisdell (1) cautioning against the use of propylene glycol as an internal standard for quantifying ethylene glycol. A 32-year-old woman presented to our emergency department in an agitated state after the ingestion of multiple drugs in an attempted suicide. Gastric lavage and charcoal were administered as well as intravenous diazepam (Valium) and lorazepam (Ativan) for sedation. While attempting to quantify ethylene glycol in her serum by gas chromatography, we observed that the specimen contained a compound that was eluted with a retention time similar to that of propylene glycol, the internal standard. Although ethylene glycol was undetectable, concentrations of propylene glycol at admission as well as in subsequent serum specimens obtained over the next 35 h were substantial (Table 1). Propylene glycol concentrations peaked 10–15 h after admission to the hospital. Subsequently it was determined that Ativan and Valium contained propylene glycol, 80% and 40%, by weight, respectively. Calculations based on the administered doses of these two benzo-diazepines revealed that 18 g of propylene glycol had been given. In addition, lactic acidosis (Table 1) was observed, presumably as a consequence of propylene glycol toxicity (2). Thus, as previously described in another patient for whom measurement of ethylene glycol was requested, we found propylene glycol in serum after treatment with intravenous formulations that contained propylene glycol. Therefore, in measurements of ethylene glycol by gas chromatography, 1,3-propanediol (e.g.) should be used as an internal standard (1) to avoid interference from propylene glycol.

<table>
<thead>
<tr>
<th>Time after admission, h</th>
<th>Propylene glycol, mg/L (mmol/L)</th>
<th>Lactate, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>210 (2.76)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>490 (6.32)</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>1220 (16.05)</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>1240 (16.32)</td>
<td>5.2</td>
</tr>
<tr>
<td>20</td>
<td>680 (8.95)</td>
<td>2.7</td>
</tr>
<tr>
<td>30</td>
<td>160 (2.11)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

References


Fred S. Apple
MaryKay Googins
David Resen

Hennepin County Med. Ctr.
Clin. Labs., #812
701 Park Ave.
Minneapolis, MN 55415

Misleading Use of Correlation and Regression in Method-Comparison Studies of Cyclosporine

To the Editor:

Measurement of cyclosporine (CsA) concentrations in blood is an invaluable aid in adjusting dosage with the aim of ensuring adequate immunosuppression while minimizing toxicity. In addition to the established specific methods for the measurement of CsA, RIA and HPLC, several new immunoassays using specific monoclonal antibodies have been introduced recently to the therapeutic monitoring of CsA. Because the RIAs with the specific monoclonal antibody manufactured by Sandoz tend to slightly overestimate blood CsA concentrations, it is of great importance to determine how closely results obtained with the new immunoassays correspond to those obtained with HPLC, the standard comparison procedure for CsA determinations. However, investigators do not always reach correct conclusions as to the degree of agreement between the methods studied.

Moyer et al. (1) recently evaluated the fluorescence polarization immunoassay (FPIA) with a specific monoclonal antibody from Abbott Laboratories. In addition to stating that measurement of CsA by FPIA "correlated well" ($r = 0.97$) with HPLC results, they reported a "positive bias of 19%" for the FPIA results compared with those from HPLC in 224 whole-blood samples from liver-transplant recipients. However, this conclusion is erroneous, because it is based on the slope of the regression equation FPIA = 1.19 (HPLC) + 79, and ignores the effect of the large y-intercept. This equation suggests that the average extent of overestimation by the FPIA was at least 50% in the therapeutic range of CsA.

Dasgupta et al. (2) recently examined the analytical performance of another immunoassay allegedly specific for parent CsA, the EMIT™ cyclosporine assay (Syva Co., Palo Alto, CA). These investigators also measured CsA concentrations in 196 whole-blood samples from transplant patients by this assay, by HPLC, and by RIA (InoStar Cyclo-Trac SP). They reported "a small positive bias between the EMIT assay ($y$) and HPLC ($x$) as reflected by the slope of 1.27 ($y$-intercept = 16.4), and emphasized the good correlation ($r = 0.96$) between the methods (the standard error of the estimate, $S_{y|x}$, was 34.9 μg/L). Actually, the degree of agreement between these methods was poor. For example, for a CsA value of 100 μg/L by HPLC, the EMIT method would on the average give a result of 143 μg/L, and we are 95% sure that the value would be between 73 and 213 μg/L (3).

Correlation coefficients have been widely misused as an indicator of between-method agreement in studies comparing different methods for CsA measurement. This statistic does nothing useful. A correlation coefficient measures the strength of the relation between the results by two methods, not the agreement between them. A set of measurements that cluster closely around any straight line, not necessarily around the line of identity, will result in a high correlation coefficient (4).

In addition to the slope and y-intercept, the standard error of the estimate is essential information in the interpretation of linear-regression analysis. The standard deviations of the slope and y-intercept should also be reported. These issues were discussed in the recent Canadian consensus meeting on CsA monitoring (5). Moreover, spurious data may be a major source of error in linear-regression analysis; this may have been the case in the study of Moyer et al. (1). It is therefore important always to plot the data.

A properly performed linear-regression analysis can yield a great deal of useful information about how well two methods compare. The microcomputer revolution has made it easy to perform regression analysis of large quantities of measured data, and some caution is needed to avoid pitfalls in the interpretation of the results.

References


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