We conclude that conjugated tracers gave, overall, good results in the four methods studied, results similar to those obtained with the Sclavo two-step chromatographic technique. They are better than those observed with the one-step analog-based methods, which are still widely used despite their disadvantages. These non-isotopic methods are thus a valid alternative to the isotopic two-step methods currently available.

We acknowledge Professors J. C. Bigorgne and V. Rohmer and Drs. J. F. Supra, C. Fanello, and J. L. Bourrier for helpful collaboration in the clinical part of this work; and all the manufacturers, for supplying their kits and reagents and for their invaluable technical advice.

References

Measurement of Cyclosporine Concentrations in Whole Blood: HPLC and Radioimmunoassay with a Specific Monoclonal Antibody and 3H- or 125I-Labeled Ligand Compared

Bryan A. Wolf, Michael C. Deft, John W. Koenig, M. Wayne Flye, John W. Turk, and Mitchell G. Scott

We compared cyclosporine concentrations in whole blood as measured by HPLC and by RIA with a monoclonal antibody specific for cyclosporine with 3H- or 125I-labeled cyclosporine ligand. The 3H-RIA kit slightly underestimated cyclosporine concentrations (>600 μg/L) in comparison with HPLC. Over a wide range of concentrations, cyclosporine measured with the 125I-RIA kit correlated well with HPLC (slope = 0.99, n = 301, r = 0.98), observed for samples from recipients of kidney, heart, or liver allografts (respective slopes: 1.01, 0.93, and 1.00). The 125I-RIA standard curve was linear to 1000 μg of cyclosporine per liter. Inter- and intra-assay CVs for 125I-RIA measurements of cyclosporine were ≤7%. Evidently, the 125I-RIA kit involving a monoclonal antibody specific for cyclosporine is equivalent to the HPLC assay and can replace it for therapeutic drug monitoring of cyclosporine therapy.

Additional Keyphrases: intermethod comparison \cdot monitoring therapy \cdot organ transplants \cdot "kit" methods

Cyclosporine, a cyclic undeca peptide with strong immunosuppressive properties (1), has been widely used in human transplants of solid organs or bone marrow during the last decade (2). Cyclosporine concentrations in blood are monitored because of the narrow therapeutic range for immunosuppression, the substantial inter- and intra-patient variability in cyclosporine pharmacokinetics, and the frequency of nephrotoxicity during cyclosporine therapy (1–5).

Measurement of cyclosporine concentrations has been complicated by several issues, recently reviewed by the Task Force on Cyclosporin Monitoring (3). HPLC measurement of cyclosporine in whole blood has been recommended because of the analytical specificity of HPLC (3). Many clinical laboratories nonetheless utilize RIA for cyclosporine measurements because of its technical simplicity and its adaptability for use with large numbers of samples. RIA measurements of cyclosporine have been confounded, however, by the nonspecificity of the antisera, which cross-react to various extents with cyclosporine metabolites (7). Because both the immunosuppressive and nephrotoxic properties of cyclosporine metabolites are incompletely characterized and because there is considerable individual variation in cyclosporine metabolism, the clinical utility of these pan-specific RIAs has been questioned (1). To address this problem, Sanoz Ltd., the manufacturer of the drug, has recently developed a monoclonal antibody specific for parent cyclosporine (6, 7), and has incorporated the specific monoclonal antibody into an RIA kit in which [3H]cyclosporine is used as ligand (8). A comparison of cyclosporine concentrations determined with this kit and by HPLC showed that results correlated well, so this specific RIA was proposed to replace HPLC for therapeutic monitoring of cyclosporine concentrations (8). Recently, a technically simpler RIA has been...
introduced in which the same specific monoclonal antibody is used, but with an 125I-labeled cyclosporine ligand. Use of an 125I-labeled RIA would be preferred to 3H-RIA because it obviates the need for liquid scintillation counting.

Here, we report the results of a comparison of cyclosporine measurements in whole blood by HPLC and by RIA with the specific monoclonal antibody and 3H- or 125I-labeled cyclosporine as ligands.

**Materials and Methods**

**Clinical specimens.** Whole-blood samples were collected into tubes containing lithium heparin anticoagulant. In a first phase, using the two RIAs, we assayed, retrospectively, 147 samples that had been received for routine measurement of cyclosporine by HPLC. The samples were mostly from patients who were receiving immunosuppressive therapy with cyclosporine after kidney, heart, liver, or bone marrow transplantation. Whole-blood samples in this first phase were stored at 4°C for as long as one week before assay. During one week, an additional 154 samples were simultaneously analyzed by both the 125I-RIA and HPLC assays for cyclosporine, under routine laboratory conditions.

**HPLC.** Routine HPLC measurements of cyclosporine in whole blood were performed as previously described (9). In brief, the procedure is as follows. Add cyclosporin D to 1 mL of whole blood as an internal standard, acidify with HCl, and extract with diethyl ether. Redissolve the ether extract in acidified methanol, wash with hexane, alkalinate with NaOH, and re-extract with ether. Analyze by isocratic chromatography at 75°C at a flow rate of 2 mL/min on a reversed-phase C-18 column. Acetonitrile/methanol/H2O (50/22.5/27.5 by vol) is the mobile phase. The absorbance of the eluate is monitored at 205 nm. Quantify results by calculating the ratio of the peak heights for cyclosporine and cyclosporin D and interpolating from a standard curve. Values <50 µg/L are routinely reported as <50 µg/L, although for the purpose of the comparison, the precise value was calculated.

**3H-RIA.** For RIA with 3H-cyclosporine as the ligand, we used the Sandimune™ (Mab) RIA kit (Sandoz Pharmaceutical Corp., East Hanover, NJ 07936) according to the manufacturer's procedure, which, in brief, is as follows. Extract 50 µL of whole blood with 950 µL of methanol, vortex-mix, and centrifuge. Assay 50 µL of the methanolic supernate, in duplicate, with the reagents and standards provided in the kit; i.e., incubate the supernate for 2 h at 4°C with the 3H-ligand and the mouse monoclonal specific antibody. Then proceed with charcoal separation and liquid scintillation counting.

**125I-RIA.** For RIA with 125I-labeled cyclosporine as the ligand we used the CYCLO-Trac™ SP-Whole Blood RIA kit (INCSTAR Corp., Stillwater, MN 55082) according to the manufacturer's procedure. This RIA is based on a double-antibody competitive-binding assay. The procedure: Extract whole blood (100 or 200 µL) with methanol (400 or 800 µL), vortex-mix, and centrifuge. Assay the methanolic supernate (50 µL) in duplicate with the reagents and standards provided in the kit; i.e., incubate the supernate for 1 h at room temperature with the 125I-ligand and "anti-CYCLO-Trac SP ImmunoSep" (pre-mixed mouse monoclonal cyclosporine-specific antibody, donkey anti-mouse serum, and normal mouse serum). After centrifuging, decant the ligand from the reaction tubes and determine the amount of radioactivity (1 min counting) in the pellet.

Data were analyzed by logit-log reduction. For the standard curve we used cyclosporine standards of 20, 61, 154, 379, and 1099 µg/L. In one typical standard curve, the following values were generated: nonspecific binding, 5%; binding at 0 concentration, 57%; r² = 0.993; concn50 = 198 µg/L. An average run of 40 samples requires 3–4 h.

**Intra- and inter-assay precision.** Intra-assay CVs were determined with low- and high-cyclosporine pooled specimens of blood with known cyclosporine concentration. Inter-assay CVs were determined from duplicate measurements from eight runs, done during a one-month period, of quality-control material from the INCSTAR kit and commercial material (Cala Diagnostics, Los Osos, CA 93402).

**Statistical analysis.** Data that compared the HPLC and RIA methods were analyzed by unweighted regression analysis or one-way or two-way analysis of covariance.

**Results**

**Comparison of the three assays.** Linear regression analysis of cyclosporine concentrations in whole blood from patients being treated with cyclosporine, as measured with the specific Sandimune 3H-RIA (y-axis) and by HPLC (x-axis) yielded the relationship illustrated in Figure 1 and summarized by the equation 3H-RIA = 0.85 (HPLC) + 58.35 (n = 92, r = 0.947, r² = 0.896, P < 0.001, standard error of estimate = 50.3). When cyclosporine values >600 µg/L (n = 4) were excluded from the data analysis, the following equation was obtained: 3H-RIA = 1.02 (HPLC) + 27.33 (n = 88, r = 0.940, r² = 0.883, P < 0.001, standard error of estimate = 43.1). Thus only at concentrations >600 µg/L does the 3H-RIA underestimate cyclosporine.

Our comparison of the INCSTAR 125I-RIA with HPLC measurements of cyclosporine was performed in two phases. The first phase was a retrospective comparison of whole-blood cyclosporine measurements by the two methods. The second phase was a prospective comparison of the methods. In both phases, correspondence between cyclosporine measurements by HPLC and 125I-RIA was excellent. In phase 1, linear regression analysis yielded a slope near unity (0.96), an intercept near zero (12.78), and a correlation coefficient (r) of 0.978 (n = 147). Similar results were obtained in phase 2 (slope 1.02, intercept 1.67, r = 0.977, n = 154). The minor difference in the slopes of the regression lines from phases 1 and 2 was not statistically significant (P = 0.437).

Because both phases of the study gave identical results, data from the two phases were combined as illustrated in Figure 2A to yield the following equation: 125I-RIA = 0.99
(HPLC) + 7.73 (n = 301, r = 0.977, r² = 0.954, P < 0.001, standard error of estimate = 37.8). Subgroup analyses indicated excellent correspondence between HPLC and 125I-RIA measurements of cyclosporine within groups of patients who were receiving a particular transplanted organ. Values for kidney-transplant recipients are shown in Figure 2B: 125I-RIA = 1.01 (HPLC) − 0.86 (n = 134, r = 0.975, r² = 0.950, P < 0.001, standard error of estimate = 26.3). In the case of heart-transplant recipients, cyclosporine values were correlated as follows: 125I-RIA = 0.93 (HPLC) + 32.07 (n = 84, r = 0.967, r² = 0.953, P < 0.001, standard error of estimate = 38.2, Figure 2C). Finally, data for liver-transplant recipients are shown in Figure 2D: 125I-RIA = 1.00 (HPLC) + 7.76 (n = 51, r = 0.976, r² = 0.963, P < 0.001, standard error of estimate = 55.5). Statistical analysis indicated that the linear relation between 125I-RIA and HPLC was not significantly different in relation to the type of transplant (P = 0.390). Table 1 shows a comparison of the mean values of each assay when samples were categorized by 125I-RIA cyclosporine concentrations.

Figure 3 illustrates the relationship between cyclosporine concentrations as measured by 3H-RIA (y-axis) and 125I-RIA (x-axis). This relationship is summarized by the equation: 

\[
\text{3H-RIA} = 0.91 \times (125\text{I-RIA}) + 58.17 \quad (n = 38, r = 0.975, r^2 = 0.951, P < 0.001, \text{standard error of estimate} = 41.8)
\]

Precision and linearity of 125I-RIA. Intra- and inter-assay CVs for cyclosporine measured by 125I-RIA (Table 2) were found to be ≤7% over a wide range of cyclosporine concentrations. The CV during a one-month period of daily routine use in the clinical chemistry laboratory was 6.5% and 6.7% (cyclosporine concentration = 161 and 916 µg/L, respectively). Linearity of the 125I-RIA was assessed initially by parallel dilutions of a known cyclosporine standard (1035 µg/L) with cyclosporine-free whole blood or the "zero" standard provided by the manufacturer. Under both conditions, the assay curve was found to be linear (data not shown).

A pooled whole-blood cyclosporine sample (of known concentration) was also diluted in parallel with cyclosporine-free whole blood. As shown in Figure 4, the 125I-RIA assay curve was linear at cyclosporine concentrations up to 1000 µg/L (slope = 1.01, intercept = −1.96, r = 0.998). (Samples extracted with blood/methanol ratios between 1:5 and 1:14 gave results similar to those extracted with the 1:4 ratio we used throughout these studies; data not shown.)

The linearity of the 125I-RIA assay curve compared with HPLC was also evaluated with patients' samples by linear regression analyses of data derived from (a) samples with cyclosporine concentrations covering the entire range (0 to 1000 µg/L) and (b) samples with cyclosporine concentrations of <600 µg/L. Table 3 summarizes the equations obtained. Cyclosporine measurements by 125I-RIA and those by HPLC were linearly related over a wide range of cyclosporine concentrations. In the case of cardiac allograft

Table 1. Cyclosporine Determinations In Whole Blood by 125I-RIA and HPLC Compared within Various Concentration Ranges

<table>
<thead>
<tr>
<th>Concentration Range</th>
<th>125I-RIA range</th>
<th>HPLC</th>
<th>125I-RIA</th>
<th>Cyclosporine concn, µg/L, mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–150</td>
<td>106.2 ± 3.9</td>
<td>106.2 ± 3.7</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>151–300</td>
<td>216.5 ± 4.5</td>
<td>219.4 ± 3.7</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>301–450</td>
<td>349.0 ± 6.0</td>
<td>584.3 ± 5.4</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>451–600</td>
<td>482.8 ± 18.5</td>
<td>514.2 ± 11.2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>&gt;600</td>
<td>821.3 ± 55.5</td>
<td>815.2 ± 51.8</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Comparison of cyclosporine (CyA) concentrations measured in whole blood by 125I-RIA and HPLC (A), samples obtained during phases 1 and 2 of the trial (see Materials and Methods); (B), samples from kidney-transplant recipients; (C), samples from heart-transplant recipients; (D), samples from liver-transplant recipients.
In this study, we have compared cyclosporine as measured in whole blood by two different RIA kits and by HPLC. HPLC has been routinely used since 1984 for cyclosporine measurements at our institution. The two RIA kits used in these studies both include the same monoclonal antibody specific for cyclosporine (6, 7, 8, 13). The first RIA kit (Sandimmune™) is manufactured by Sandoz and involves a [3H]-cyclosporine ligand and a charcoal-separation step. Our data indicate that the Sandoz [3H]-RIA kit may slightly underestimate cyclosporine in whole blood as compared with HPLC (slope = 0.85) and with the [125I]-RIA kit (slope = 0.91). The discrepancy between the two methods is confined to cyclosporine concentrations >600 µg/L. When these values are excluded, a slope of 1.02 was obtained (by comparison with HPLC). A previous study with normal volunteers (7) reported a slope of 0.87 in comparing cyclosporine values obtained by [3H]-RIA (with the same specific monoclonal antibody) with those by HPLC. However, a subsequent study on liver-, heart-, bone marrow, and kidney-transplant recipients in which a similar methodology was used reported slopes of 0.98, 1.19, 1.00, and 0.95, respectively (8). Several studies (6, 7, 8, 13) have established that the monoclonal antibody used in the Sandoz [3H]-RIA kit is highly specific for cyclosporine and does not significantly cross-react with cyclosporine metabolites.

The second RIA kit (CYCLO-Trac™ SP-Whole Blood) that we evaluated is manufactured by INCSTAR. In it, [125I]-labeled cyclosporine is used as ligand and the same cyclosporine-specific monoclonal antibody is used as in the Sandoz [3H]-RIA kit. An additional advantage of the [125I]-RIA kit is the technically simpler means of separation as opposed to.

recipients, however, [125I]-RIA measurements of cyclosporine were slightly lower than those by HPLC for cyclosporine >600 µg/L and slightly higher for cyclosporine concentrations <600 µg/L. Further investigation showed that two samples from the same recipient of a heart transplant accounted for the discrepancy between RIA and HPLC measurements. These two samples had values of cyclosporine determined by HPLC of 952 and 1035 µg/L, by [125I]-RIA values of 814 and 878 µg/L, and by [3H]-RIA values of 780 and 834 µg/L, respectively. This phenomenon was not observed with kidney- or liver-transplant recipients.

Linearity of the RIA was also tested by systematically repeating, after threefold dilution, all samples for which cyclosporine concentrations exceeded 600 µg/L (range = 608–1224) that were received during the first two months of routine use of the INCSTAR RIA. Linear regression analysis (n = 50) yielded a slope near unity (0.89) and an intercept close to zero (17.91 µg/L) with a correlation coefficient of 0.913.

**Discussion**

The measurement of cyclosporine concentrations by RIA depends strongly on the specificity of the antibody to cyclosporine. Cyclosporine is extensively metabolized (2), and earlier RIAs with polyclonal, nonspecific antibodies measured both the parent compound and its metabolites (3). It has recently been shown that several cyclosporine metabolites have immunosuppressive properties in some in vitro assays (10, 11), but their immunosuppressive activity in vivo is not yet known. It is also not known whether these or other metabolites are nephrotoxic (12). Thus, present RIAs in which nonspecific polyclonal antibodies are used are not recommended for therapeutic monitoring of cyclosporine (3).

In this study, we have compared cyclosporine as measured in whole blood by two different RIA kits and by HPLC. HPLC has been routinely used since 1984 for cyclosporine measurements at our institution. The two RIA kits used in these studies both include the same monoclonal antibody specific for cyclosporine (6, 7, 8, 13). The first RIA kit (Sandimmune™) is manufactured by Sandoz and involves a [3H]-cyclosporine ligand and a charcoal-separation step. Our data indicate that the Sandoz [3H]-RIA kit may slightly underestimate cyclosporine in whole blood as compared with HPLC (slope = 0.85) and with the [125I]-RIA kit (slope = 0.91). The discrepancy between the two methods is confined to cyclosporine concentrations >600 µg/L. When these values are excluded, a slope of 1.02 was obtained (by comparison with HPLC). A previous study with normal volunteers (7) reported a slope of 0.87 in comparing cyclosporine values obtained by [3H]-RIA (with the same specific monoclonal antibody) with those by HPLC. However, a subsequent study on liver-, heart-, bone marrow, and kidney-transplant recipients in which a similar methodology was used reported slopes of 0.98, 1.19, 1.00, and 0.95, respectively (8). Several studies (6, 7, 8, 13) have established that the monoclonal antibody used in the Sandoz [3H]-RIA kit is highly specific for cyclosporine and does not significantly cross-react with cyclosporine metabolites.

The second RIA kit (CYCLO-Trac™ SP-Whole Blood) that we evaluated is manufactured by INCSTAR. In it, [125I]-labeled cyclosporine is used as ligand and the same cyclosporine-specific monoclonal antibody is used as in the Sandoz [3H]-RIA kit. An additional advantage of the [125I]-RIA kit is the technically simpler means of separation as opposed to.

**Fig. 3.** Cyclosporine (CyA) concentrations as measured in whole blood by [3H]-RIA and [125I]-RIA.

**Table 2.** Intra- and Interassay Precision of Cyclosporine Measurements in Whole Blood by [125I]-RIA

<table>
<thead>
<tr>
<th>Cyclosporine concn, µg/L</th>
<th>CV, %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-assay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101.8</td>
<td>4.1</td>
<td>10</td>
</tr>
<tr>
<td>408.6</td>
<td>5.1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Interassay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100.8</td>
<td>6.8</td>
<td>16</td>
</tr>
<tr>
<td>153.4</td>
<td>7.0</td>
<td>16</td>
</tr>
<tr>
<td>333.1</td>
<td>4.0</td>
<td>16</td>
</tr>
<tr>
<td>886.6</td>
<td>5.7</td>
<td>14</td>
</tr>
</tbody>
</table>

**Fig. 4.** Linearity studies of cyclosporine (CyA) concentrations in whole blood as measured by [125I]-RIA

**Table 3.** Cyclosporine Determinations in Whole Blood by [125I]-RIA and HPLC Compared for Values <600 µg/L

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Conc range, µg/L</th>
<th>Slope</th>
<th>Intercept</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0-&gt;1000</td>
<td>1.00</td>
<td>7.73</td>
<td>301</td>
</tr>
<tr>
<td></td>
<td>&lt;600</td>
<td>1.04</td>
<td>-3.51</td>
<td>288</td>
</tr>
<tr>
<td>Kidney</td>
<td>0-&gt;1000</td>
<td>1.01</td>
<td>-0.86</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>&lt;600</td>
<td>1.03</td>
<td>-2.61</td>
<td>133</td>
</tr>
<tr>
<td>Heart</td>
<td>0-&gt;1000</td>
<td>0.93</td>
<td>32.07</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>&lt;600</td>
<td>1.15</td>
<td>-23.62</td>
<td>80</td>
</tr>
<tr>
<td>Liver</td>
<td>0-&gt;1000</td>
<td>1.00</td>
<td>7.76</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>&lt;600</td>
<td>1.04</td>
<td>-4.10</td>
<td>43</td>
</tr>
</tbody>
</table>

CLINICAL CHEMISTRY, Vol. 35, No. 1, 1989 123
the charcoal-separation step in the Sandoz kit. Overall, an excellent concordance was observed between the INCSTAR 
\(^{125}\)I-RIA kit and HPLC when measuring a large number of 
samples derived from patients receiving therapy with cyclo-
sporine (slope = 0.99, n = 301). This was true for recipients 
of kidney transplants (slope = 1.01), heart transplants 
(slope = 0.93), or liver transplants (slope = 1.00) when these 
subgroups were analyzed separately. Furthermore, the 
\(^{125}\)I- 
RIA kit had satisfactory intra- and inter-assay CVs when 
measured over a large range of cyclosporine concentrations, 
and the assay curve was linear for cyclosporine concentra-
tions between 50 and 1000 µg/L.

One heart-transplant recipient had two cyclosporine sam-
pies (>600 µg/L) for which the RIA underestimated the 
cyclosporine, as compared with HPLC, by about 15%. The 
cause of this discrepancy in this specific patient is not 
known, but conceivably, cyclosporine metabolite(s) present 
in this patient interfered with one of the assays. A recent 
report (14) in which the Sandoz RIA was used has suggested 
a poor correlation (slope = 0.399; intercept = 99, \(r^2 = 0.483, 
n = 73\) between RIA and HPLC in heart-transplant pa-
patients. However, our data demonstrate that there is a good 
correlation (slope = 0.93, intercept = 32.07, \(r^2 = 0.953, n = 
84\) between the INCSTAR \(^{125}\)I-RIA and HPLC in heart-
transplant patients. The differences between these studies 
can be ascribed to the different ligands used—(\(^{3}\)H)cyclo-
sporine in Sandoz RIA, and \(^{125}\)I-labeled cyclosporine in the 
INCSTAR RIA—and to the different precipitation tech-
niques (charcoal vs a double-antibody system).

The utility of RIA kits in which specific monoclonal 
antibodies are used has recently been questioned (15) be-
cause of the relatively poor concordance observed (7) be-
tween cyclosporine as measured by the Sandoz \(^{3}\)H-RIA and 
by HPLC for specimens with cyclosporine concentrations 
<100 µg/L, the former being substantially higher in that 
range (7). Our data indicate a good concordance between 
cyclosporine concentrations determined by \(^{125}\)I-RIA and 
HPLC over a wide range of cyclosporine concentrations: 50–
1000 µg/L.

Our results indicate that the \(^{125}\)I-RIA kit is equivalent to 
the HPLC assay for measuring cyclosporine concentrations 
in patients who are receiving solid-organ allografts. This 
assay has now replaced the HPLC assay for routine clinical 
measurement of cyclosporine at our institution. Advantages 
of the \(^{125}\)I-RIA over HPLC include smaller sample volume 
requirements and the ability to perform batch rather than 
sequential analyses.

We thank Jane Huth and Corinne Greenwald for superb secretarial assistance. We acknowledge the donation of RIA kits for this study from Sandoz Pharmaceuticals Corp. and INCSTAR Corp.

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