Letters to the Editor

Improve the precision of the International Sensitivity Index (ISI) estimation. Since human brain can no longer be used, placental thromboplastin is the only remaining reagent extracted from human tissues that needs to be calibrated against rTF/95. This might raise concerns because of the apparent dissimilarity of the two preparations. To address this issue a placental reagent obtained from Behringwerke (Marburg, Germany) was included in the collaborative study organized to calibrate rTF/95 at 19 laboratories (2). Here we present results on the calibration of that preparation against different IRPs. The design of the study and the statistical analysis have been described elsewhere (2).

The criteria used to judge the calibration were as follows: (i) the within-laboratory precision of the calibration, expressed as the coefficient of variation (CV) of the slope of relationship of PT values (placental reagent vs. IRPs); (ii) the between-laboratory precision of the calibration, expressed as the CV of the ISI and (iii) the conformity of the calibration model, tested as the assumption that the mean log-PT of normals lies on the orthogonal regression line drawn through patients data points.

<table>
<thead>
<tr>
<th>IRP</th>
<th>N. of labs</th>
<th>Mean ISI CV (Median range)</th>
<th>Between-laboratory CV</th>
<th>Conformity to the calibration model</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCT/253</td>
<td>18*</td>
<td>1.149 2.1 (1.1-2.8)</td>
<td>4.4</td>
<td>89.7%</td>
</tr>
<tr>
<td>RBT/90</td>
<td>18*</td>
<td>1.165 2.4 (1.5-3.8)</td>
<td>3.8</td>
<td>100%</td>
</tr>
<tr>
<td>OBT/79</td>
<td>18*</td>
<td>1.181 2.0 (1.4-2.8)</td>
<td>4.0</td>
<td>100%</td>
</tr>
<tr>
<td>rTF/95</td>
<td>18*</td>
<td>1.156 1.6 (1.2-2.5)</td>
<td>3.2</td>
<td>94.7%</td>
</tr>
</tbody>
</table>

* one laboratory excluded because it was identified as an outlier (2)
** one laboratory excluded because of poor performance (2)
§ percentage of laboratories with non-significant deviations from the assumption that the log-PT of normals lies on the orthogonal regression line drawn through patients data points.

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References

1. WHO Expert Committee on Biological Standardization. Guidelines for the use of other thromboplastin reagents less sensitive to LA that manufacturers might develop.

The conclusions of Moll and Ortel (1) and others on the validity of the traditional PT test (both with conventional and recombinant thrombo-


dear Sir,

Recently, monitoring warfarin therapy in patients with LA has received much attention in the scientific literature (1-3) and the use of the time honored prothrombin time (PT) has been questioned. There are a few points on this issue which we wish to point out.

It has been stated that the International Normalized Ratio (INR) is not valid in patients with LA taking warfarin (1, 3). This is confusing. If subsequent studies will confirm what has been shown in some of the studies, it is the test (i.e., the PT) which would be affected by LA, not the INR which is only a scale for reporting results. Therefore, it would be more appropriate to search for thromboplastins less sensitive to the LAs and retain the expression of results as INR, rather than searching for alternate tests to monitor warfarin in those patients. Moll and Ortel (1) state that the prothrombin-proconvertin time test is less affected by LA. Although no clear evidence was provided, one may reasonably assume that the prothrombin-proconvertin time would be less sensitive to LA because in this test the plasma is diluted and hence the effect of LA is weakened. If this is true, this test could be used for patients with LA on warfarin and the results expressed as INR, not as percentage activity. In fact the reagent used by Moll and Ortel (1) like many others of this type which are available on the market (i.e., Hepato Quick, Thrombotest, Pro-IL-complex, just to mention a few) are so called “combined” thromboplastin reagents (i.e., rabbit or ox brain/lung tissue extracts) to which optimal amounts of factor V and fibrinogen have been added. These reagents can be conveniently calibrated to determine the International Sensitivity Index (ISI) against the International Standard for “combined” thromboplastin, coded OBT/79 and following the procedures recommended by WHO (4). This would have the distinct advantage of retaining the large experience gained over the years in establishing therapeutic ranges with the INR scale. Furthermore, it would permit the use of other thromboplastin reagents less sensitive to LA that manufacturers might develop.

The conclusions of Moll and Ortel (1) and others on the validity of the traditional PT test (both with conventional and recombinant thrombo-
Letters to the Editor

The recent study by Arroyo et al. (1) is valid (4). The small number of patients and controls investigated and the fact that thromboplastin reagents have not been properly calibrated to assign them an ISI value. This may be due to a variety of effects, such as (i) the influence of non vitamin K dependent clotting factors on the PT with different reagents; (ii) whether or not the stable phase of the therapy has been attained and (iii) whether or not the INR is outside the range from 1.5 to 4.5 for which this scale is valid (4). The small number of patients and controls so far investigated and the lack of information on the stability of therapy do not permit us to draw definite conclusions. Furthermore, Lawrie et al. (2) in their recent report on the same topic conclude that the INR values in patients with LA are concordant provided that the reagents are calibrated to assign them an instrument-specific ISI. Their opinion is that the discrepancies so far reported are mainly due to the incorrect application of the ISI rather than to the influence of LAs on the PT (2). These conflicting findings leave room for further investigation. Important limitations of previous studies are the relatively small numbers of patients and controls investigated and the fact that thromboplastin reagents have not been calibrated as part of the study on the same instrument (1), or they have been calibrated by procedures not endorsed by WHO (2, 3). These limitations may be circumvented by a joint effort involving investigation of a larger number of patients from different centers. Plasmas from these patients should be centralized and the INR determined with different reagents, all calibrated against the same International Standard on the same instrument by the recommended WHO procedure with fresh plasmas from healthy individuals and anticoagulated patients (4). This approach would make it possible to separate the artefactual effects due to incorrect assignment of the ISI from the genuine effect of LAs on the PT test. We feel that any decision on the issue of oral anticoagulant monitoring in patients with LA should be deferred until more information becomes available.

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References


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In Vivo Photoactivation of Caged Thrombin

Dear Sir,

Arroyo and colleagues (1) claim to have produced intravascular thrombosis in abnormal vessels of the rabbit eye using photoactivation of intravenously injected caged-thrombin but have failed to present convincing histological verification for this. The black and white photomicrograph accompanying their article and its color counterpart on the front cover of the Journal are said to show “corneal vessels filled with blood cells that stain positive for fibrin” using the phosphotungstic acid hematoxylin (PTAH) technique. It is well known that the PTAH stain is a sensitive but nonspecific marker for fibrin since it binds equally well to red blood cells and a number of other structures (2). The photomicrographs exhibit no evidence of “intraluminal fibrin clots” as stated in the paper; the vessels are filled with erythrocytes and a few leukocytes with no sign of intravascular fibrin deposition. Blue-staining of the red cells does not indicate that fibrin has precipitated on those cells. The intensity of blue coloration of red blood cells and fibrin with the PTAH method varies with minor modifications of the staining technique (Fig. 1).

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Fig. 1 Photomicrograph of thin-walled, blood-filled vessels in subcutaneous tissue shows deep blue staining of red cells with phosphotungstic acid hematoxylin (original magnification = 400×).

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