biopsies), it should be demonstrated that the results of testing are really useful to improve life expectancy. Some authors suggest the usefulness of extensive screening including abdominal and pelvic CT scan, with or without additional gastro-intestinal endoscopy (5, 9, 12). Others, such as Cornuz et al. (13) propose a simplified approach which includes history, physical examination, routine laboratory tests and chest x-ray (i.e. the standard clinical evaluation performed at admission in the hospital), with more extensive screening procedures in few selected patients only. Unfortunately, the sample size of the published studies is generally too small to draw any conclusion and to suggest reliable guidelines. In a recent paper Barosi et al. (14) showed that the only cost-effective strategy in patients with idiopathic VTE includes the search of colon and breast cancer in females and colon cancer in males.

A large, prospective clinical trial on the effect on survival of an extensive screening for occult cancer in patients with idiopathic VTE is ongoing (15), and it should give us the definitive answer. However, the starting point (i.e. the increased risk of subsequent cancer in these patients) seems to be solidly demonstrated.

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Successful Calibration of a Reagent from Human Placenta against rTF/95, the WHO International Reference Preparation for Thromboplastin, Human Recombinat, Plain

Dear Sir,

The World Health Organization (WHO) recommends to express results of the prothrombin time (PT) test for patients on oral anticoagulants by the scale named International Normalized Ratio (INR). To this end WHO established a scale of calibration that requires different steps. In the first step, International Reference Preparations (IRPs) for thromboplastin are established and distributed to national control laboratories and reagent manufacturers. In the second step the IRPs are used to calibrate national or manufacturers house standards.

These are in turn used in the third step to calibrate working reagents (1). Until recently, there were three different IRPs characterized by the species from which they have been derived and by their composition with respect to whether or not fibrinogen and factor V have been added (combined, or plain reagent): rabbit, plain (coded RBT/90); bovine, combined (OBT/79) and BCT/253, human, plain. The latter was very recently replaced by a new preparation (coded rTF/95) made of relipidated human recombinant tissue factor (2). According to the guidelines issued by the WHO, national and working reference preparations must be calibrated against the appropriate IRP (1). It is recommended that plain reagents from rabbit origin be calibrated against RBT/90; combined bovine and combined rabbit reagents against OBT/79 and human reagents against rTF/95. The idea behind this recommendation is to perform like-to-like calibration in order to
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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 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)</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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Monitoring Warfarin Therapy in Patients with Lupus Anticoagulants (LA)

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-

References


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