Recombinant Thromboplastins vs Tissue-Extract Thromboplastins in Patients on Unstable Oral Anticoagulant Therapy

To the Editor:

In a previous report in Clinical Chemistry, we described much higher international normalized ratios (INRs) with recombinant Neoplastin R (Roche Diagnostics) than with tissue-extract Neoplastin Plus (Roche Diagnostics) in patients initiating oral anticoagulant therapy (1). For patients on stable oral anticoagulation, we observed no significant differences in INRs between the thromboplastins. The increased INR values with Neoplastin R during unstable anticoagulation, such as in the initial phase of oral anticoagulation treatment, could be explained by fluctuations in coagulation factor VII (FVII) concentrations owing to the low half-life of FVII. Recombinant thromboplastin exhibits an increased sensitivity for FVII compared with tissue-derived thromboplastin (2,3). The difference in sensitivity between Neoplastin R and Neoplastin Plus for FVII could implicate alterations in anticoagulation dosage and time period in obtaining stable anticoagulation. We investigated whether our findings could be extrapolated to other recombinant thromboplastins.

We collected and citrate-treated blood samples from 20 patients in the initial phase of oral anticoagulation treatment (between day 3 and day 7 after starting with a standard loading dosage of acenocoumarol: day 1, 6 mg; day 2, 4 mg; day 3, 2 mg), 20 patients with a highly increased INR (>5) not yet stabilized on oral anticoagulation, and 20 patients on stable oral anticoagulation (within the therapeutic INR interval of 2.0–4.0). Prothrombin time was measured on a STA-R analyzer (Roche Diagnostics). The international sensitivity index (ISI) was calibrated for each thromboplastin against reference plasma that had been primarily calibrated against the international reference standard, in accordance with guidelines (4). The mean normal prothrombin time (MNPT) for each thromboplastin was calculated from the prothrombin times for 20 healthy individuals. The ISI/MNPT values were as follows: Innovin (Siemens Healthcare Diagnostics), 0.97/9.48 s; RecombiPlasTin 2G (Instrumentation Laboratory), 1.13/11.57 s; Neoplastin Plus, 1.25/13.23 s; Neoplastin R, 1.08/14.34 s; Hepato Quick (Roche Diagnostics), 0.89/26.94 s; Thromborel S (Siemens Healthcare Diagnostics), 1.15/13.40 s.

We found increasing differences in the INR between recombinant thromboplastins (Innovin, RecombiPlasTin, Neoplastin R) and tissue-extract thromboplastins (Hepato Quick, Thromborel S, Neoplastin Plus) with increasing INR for all of the tested thromboplastins. In Fig. 1, the observed INR difference between Innovin and Neoplastin Plus is plotted against the mean of the INR values measured with the 2 thromboplastins for both patients on stable oral anticoagulant therapy and patients on unstable oral anticoagulation (including the patients initiating oral anticoagulation). A linear correlation ($y_{\text{Innovin}} = 1.3x_{\text{Neoplastin Plus}} - 0.2; r^2 = 0.94$) was observed for patients on unstable anticoagulant therapy. Similar plots and linear regression equations were observed for the other recombinant thromboplastin/tissue-extract thromboplastin combinations ($y_{\text{Innovin}} = 1.3x_{\text{Hepato Quick}} - 0.7 (r^2 = 0.94); y_{\text{RecombiPlasTin}} = 1.5x_{\text{Hepato Quick}} - 1.1 (r^2 = 0.96); y_{\text{Neoplastin R}} = 1.6x_{\text{Hepato Quick}} - 1.9 (r^2 = 0.89); y_{\text{Neoplastin Plus}} = 1.5x_{\text{Thromborel S}} - 1.0 (r^2 = 0.95); y_{\text{Neoplastin Plus}} = 1.4 (r^2 = 0.94)$).

The presented results are identical to our results previously reported for Neoplastin R vs Neoplastin Plus (1). Therefore, we conclude that for patients with INR values above the therapeutic interval, 1.5-fold increases in the INR may be observed more frequently for recombinant thromboplastins than for tissue-extract thromboplastins. A similar positive bias as INR values increase has been reported for studies that compared point-of-care INR instruments with plasma-based methods (5). According to our results, this bias might be explained by the recombinant thromboplastins used in the point-of-care instruments. It would be important for clinicians
to consider the thromboplastin source when making dosage adjustments for patients with high INRs.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: We acknowledge Dr. A.M.H.P. van den Besselaar, Department of Thrombosis and Hemositosis, Leiden University Medical Center, Leiden, the Netherlands, for providing the calibrated plasmas.

References

Jasper A. Remijn* Bertil Wildeboer Jeroen D.E. van Suijlen Henk J. Adriaansen

Department of Clinical Chemistry and Laboratory Hematology Gelre ziekenhuizen Apeldoorn/Zutphen, the Netherlands

* Address correspondence to this author at:
Department of Clinical Chemistry and Laboratory Hematology Gelre ziekenhuizen P.O. Box 9014 7300 DS Apeldoorn, the Netherlands Fax +31-55-581-1235 E-mail j.remijn@gelre.nl

Previously published online at DOI: 10.1373/clinchem.2010.161364

Noninvasive Prenatal Diagnosis of a Case of Down Syndrome due to Robertsonian Translocation by Massively Parallel Sequencing of Maternal Plasma DNA

To the Editor:

There has been much recent interest in the use of massively parallel sequencing of maternal plasma DNA for the detection of fetal Down syndrome, or trisomy 21 (1–4). DNA fragments in maternal plasma were sequenced at random to determine if an additional dose of chromosome 21 (chr21) sequences was contributed by the fetus. This approach has been shown to be highly robust in distinguishing trisomic and euploid cases. In these studies, however, all re-