Monitor oral anticoagulant therapy – INR values for the Owren prothrombin time

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Oral anticoagulant therapy, the principal therapeutic intervention for preventing venous thromboembolism is monitored by the prothrombin time test using either the procedure of the Quick PT (1) or the Owren PT (2). The latter is frequently called Thrombotest™ after its commercial name. The prothrombin time is the most widely performed clotting test with nearly twice the number of PT’s performed as its nearest rival, the activated partial thromboplastin time (aPTT). Worldwide, the number of PT measurements in 2000 was estimated to be 800 million.

A great leap forward in monitoring oral anticoagulation occurred when the practice of reporting clotting times was replaced with the International Normalized Ratio or INR (3-5). Previously, clotting times were extremely dependent on the particular thromboplastin reagent, the instrumentation used to determine the PT, and the laboratory in which testing was performed. The advent of the INR afforded an acceptable means for comparing thromboplastins and results from different laboratories. Expressing PT results in terms of the INR has greatly improved the comparability of the PT between laboratories worldwide. The benefits of thromboplastin standardization through the ISI (4, 5) have led to the almost universal use of the INR reporting scheme (6).

Two papers published in Thrombosis and Haemostasis, one in this issue (Hillarp et al.), and the second in a later issue (Lindahl et al.) further advance the comparability of test results when monitoring vitamin K-antagonist oral anticoagulants. In their paper Lindahl, et al. provide a means for expressing results from prothrombin time measurements using the Owren PT assay as INR values (7). Although the Owren PT method is performed predominantly in Scandinavian countries, it is conceptually attractive because it reduces the influence of patient Factor V and fibrinogen levels on the measured clotting time and is thus potentially more sensitive to the activities of the vitamin K-dependent proteins than the Quick PT. Until now, expression of prothrombin time measurements as INR values has been limited to the Quick PT test, although not exclusively (8, 9). Lindahl, et al. demonstrate the feasibility of standardizing the PT test using only two plasma calibrators which is a greatly simplified procedure compared to the standardization of the Quick PT using the WHO procedure (4, 5, 10). The simplification in standardization should be of further benefit because of the financial pressures that laboratories face. In the second paper Hillarp, et al. provide evidence for further benefit from the two-plasma sample calibration method with the Owren PT assay (11). They report results that indicate the precision of both intra and inter laboratory results are improved by using this approach. Their conclusions are drawn from external quality assurance data collected between 1999 and the present day. Together these papers can be viewed as very important steps towards improving the comparability of test results from the two versions of the most widely performed coagulation test in laboratory medicine. If the application of the simplified two-calibrator method to the standardization of the Quick PT could be shown to offer similar improvement, the significance of these two reports will be even greater.

Many challenges remain for achieving method-independent comparability of PT testing. Some of these challenges are relatively new, arising as a consequence of the movement to point-of-care (POC) or near patient testing and home or self-testing for monitoring oral anticoagulant therapy. Almost without exception, self testing is proving to be as effective as the best specialized clinic for monitoring and maintaining control of the patient’s status (12-14). Recent studies advocate improved com-
parability of PT tests performed with different POC devices and different reagents, but do so principally on the basis of scaling “algorithms” for relating the results from POC devices to the results obtained from specialized expert laboratory instruments (15-17). Achieving universal comparability between POC PT measuring instruments and laboratory instrumental methods is a goal that demands vigorous pursuit.

In spite of the improvements made in the standardization of the PT test through application of WHO procedure for thromboplastin standardization via the International Sensitivity Index or ISI, inadequacies are still evident (18-23). Comparisons of INR values from the same patient samples, tested at the same time but with different thromboplastins, still do not always agree (24). Some of the non-comparability may be ascribed to different levels of Factor V, fibrinogen, etc., in the patient plasmas, which may affect the PT measurement due to the known differences in sensitivity to these components to the many commercially available thromboplastin reagents (25). It is here that the Owren PT might offer an advantage over the Quick PT, simply because it includes within the thromboplastin reagent, Factor V and fibrinogen from vitamin K-dependent factor-depleted bovine plasma, i.e. the “combined thromboplastin”. Data comparing same patient sample results tested with the Owren and Quick PT methods have not been published. It is hoped that the two studies reported in Thrombosis and Haemostasis will provide an incentive to do so. Perhaps these papers will also stimulate renewed efforts to identify the sources of variability observed between different PT measuring techniques and eliminate their effects on the reported PT test results.

Preanalytical variables such as, turbidity, haemolysis and icterus, may contribute to differences in clotting times, which are variously related to differences in clotting endpoint detection methodologies. Given the known differences in how the endpoint clotting time is determined in commercial instrumentation, it would be a surprise if there were not systematic differences between instruments that when identified and compensated could improve comparability even further (26, 27). POC instruments with their unique architecture and methods for determining the clotting endpoint merit particular attention in this regard.

Discoveries of new components in the extrinsic coagulation pathway also merit consideration for their contributions to the variability in the PT. Tissue factor pathway inhibitor (28-31) and the Protein Z-dependent inhibitor (32, 33) may, on biochemical grounds, both affect the prothrombin time. The arbitrary use of thromboplastin concentrations, which generate short clotting times, may mask the effects of these components, although not entirely eliminate them. Reports that there is a clinical relationship between risk for thrombosis and a combined deficiency of Factor V Leiden and Protein Z-dependent inhibitor (33, 34) suggest their possible influence on PT measurements should be expected. Perhaps this will require testing under conditions that provide longer clotting times to unmask such effects.

New discoveries provide opportunities for young investigators to attack the limitations of our current best practices. Solving old problems and integrating new discoveries into our testing methods can be a path to improved medical practice and professional success. May the advances continue.

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References