Monitoring Oral Anticoagulant Therapy by the Prothrombin Time: Reporting the Coagulation Activity or the International Normalized Ratio?

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In 1935, Quick et al. [1] described the one-stage prothrombin time (PT) test of the extrinsic pathway of the coagulation cascade. In the present nomenclature, the PT should be referred to as the tissue factor-induced coagulation time. With modifications, this test continues to be the principal method for monitoring oral anticoagulant therapy. Quick [2] recommended a detailed procedure for the preparation and use of rabbit brain thromboplastin to ensure consistent results at any time or place. In defiance of Quick's detailed description, many modifications of the test were developed and used. As a consequence of the modifications of the original test system, the results obtained by different laboratories could not be compared directly. Ideally, all laboratories should use the same well standardized thromboplastin preparation and should employ comparable techniques. This would require some form of central control but it is unlikely that this can be accomplished on a wide scale. Instead, standardization of the PT may be achieved by transformation of the PT values obtained with any reagent and technique into standardized values. It was soon realized that the percentage of prothrombin complex activity obtained with reference to dilutions of pooled normal plasma depends heavily on the thromboplastin reagent and the diluent used [3, 4]. For example, a therapeutic target range of 5-10% Thrombotest (Nycomed) activity was found to be equivalent to 10-20% Hepato Quick (Boehringer) and to 18-30% Thrombo-plastin-C (Dade).

In recent years, the international normalized ratio (INR) has been recommended as the universal scale for reporting the PT in oral anticoagulant monitoring [5]. It should be emphasized that the INR was defined only for this purpose and not for screening of the extrinsic pathway factors. The INR is based on two principles: (a) the establishment of an international reference preparation for thromboplastin together with a method to use this preparation, and (b) the calibration of other PT systems against the reference system by testing fresh samples from both healthy individuals and patients stabilized on oral anticoagulant therapy.

Although the INR system meets a number of practical problems (see below), it can reduce the differences between laboratories considerably [6].

In the present issue of Haemostasis two articles are published describing so-called simplified prothrombin time standardization methods [7, 8]. The proposed 'modified coag-

ulation activity method' depends on two principles that are similar to those of the INR system: (a) the use of a reference assay to define the scale (the authors suggest Thrombotest as reference assay), and (b) calibration of other PT systems against the reference system using samples from patients on oral anticoagulant therapy. The clotting times measured with the reference assay are then transformed into coagulation activities defined by dilutions of pooled normal plasma.

The authors maintain that the therapeutic target range in terms of INR covers more than 60% of the scale whereas the range expressed in terms of coagulation activities covers only 11 % of the scale. This may seem a big difference but it is only a mathematical difference. Each INR value corresponds to an activity value following a strict mathematical relationship. The width of the scale does not offer any advantage or disadvantage for precise monitoring of oral anticoagulant therapy.

Each standardization method has its own difficulties and pitfalls. In the INR system, the calibration line through the patients' points does not always cross the mean of the normals' points. This deviation may induce a small bias in the international sensitivity index and hence a small bias in the INR. In practice, this INR bias will be observed at the extremes of the range but hardly at the INR target level [9]. If more precise INRs are required, the correction according to Tomenson [10] can be applied. There are also difficulties and complexities with the modified coagulation activity method. If this method is to be applied by all laboratories monitoring oral anticoagulant therapy, each should use the same reference assay. This would require a gigantic reagent batch size. Furthermore, when the first reference batch is exhausted, it must be replaced by an identical batch in order to ensure identical coagulation activities. It is unlikely that a reagent manufacturer can meet the requirements of producing large, identical batches to cover the world's need. The second problem is the availability of sufficient standard pooled normal plasma. To obtain reproducible standard curves, pooled normal plasma must be prepared in a reproducible way. Obviously, 10 healthy blood donors are not sufficient to accomplish this [11].

Standardization of the PT is closely linked to interlaboratory trials and external quality assessment schemes. The success of any standardization method can only be assessed by comparing the values reported by a representative sample of clinical laboratories.

In the 1960s, the expression of the PT in terms of prothrombin complex activity was abandoned in the USA mainly because of large interlaboratory differences [3].

In Norway, the interlaboratory variation of Thrombotest and Normotest activities ranged from 7 to 22% CV [12]. The interlaboratory variation of the INR is also rather large in some countries, but in the Netherlands the range could be decreased to 5-7% CV in recent years [13]. These results suggest that acceptable standardization of the PT can be accomplished if manufacturers and clinical laboratories are willing and competent to implement the guidelines provided by national and international standardization committees.

Future research should be focused on simplified but accurate calibration of PT systems. In a recent publication, Poller et al. [14] suggested that local system calibration with lyophilized plasmas yields reliable INR values and also avoids some of the constraints on conventional thromboplastin calibrations.

The use of multiple different scales for reporting PT in oral anticoagulant control would lead to much confusion and should be avoided. The INR remains the recommended scale until the international standardization committees decide otherwise.

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Editorial

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