ADOPTION AND VALIDATION OF THE INTERNATIONAL NORMALIZED RATIO FOR MONITORING ORAL ANTICOAGULANT THERAPY: THE SITUATION IN 1989*

Antonius M. H. P. van den Besselaar

Haemostasis and Thrombosis Research Unit, Department of Haematology, University Hospital, Leiden

The expression of prothrombin time determinations for oral anticoagulant control in terms of the international normalized ratio (INR) is recommended by the International Committee for Standardization in Haematology (ICSH) and the International Committee on Thrombosis and Haemostasis (ICTH) since 1985. The INR is based on a system of international reference preparations for thromboplastins as recommended by the World Health Organization (WHO). In this system it is proposed to determine the international sensitivity index (ISI) for each prothrombin time method to be used for oral anticoagulant control. Using the ISI it is possible to calculate the INR according to the equation:

\[ \text{INR} = R^{\text{ISI}} \]

in which R is the prothrombin time ratio obtained with the calibrated method.

The INR/ISI system has been tested for many thromboplastin methods. Generally speaking, the system serves its purpose very well. However, there are still some practical problems. Furthermore, the question can be asked to what extent the system is adopted by the four groups of people involved, i.e.:

1. manufacturers of commercial thromboplastins;
2. laboratories controlling oral anticoagulant therapy;
3. physicians prescribing coumarin congeners, and
4. organizers of (national) external quality assessment (EQA) programs.

This paper is an attempt to evaluate the practical problems and to assess the adoption of the INR/ISI system.

Key-words: External quality assessment; International normalized ratio; International sensitivity index; Oral anticoagulant therapy; Prothrombin time; Thromboplastin.


ADOPTION AND VALIDATION OF THE INR

International reference preparations for thromboplastins

At present, three WHO international reference preparations are currently held on behalf of WHO by the Central Laboratory of The Netherlands Red Cross Blood Transfusion Service in Amsterdam:

- RBT/79: second WHO international standard of rabbit, plain thromboplastin;
- OBT/79: second WHO international standard of the bovine, combined thromboplastin;

WHO standards are available in limited amounts, and are as a rule supplied to national institutes. National authorities are encouraged to prepare national standards calibrated against the appropriate WHO standards.

Reference materials for thromboplastins are also available from the Bureau of Reference of the European Communities (BCR) in Brussels. These materials are used regularly by the commercial reagent manufacturers for calibration of their products. Recently, the BCR reference material for rabbit plain thromboplastin required replacement. The new material (CRM 149R) was calibrated against its predecessor (RBT/79) in an international multicenter study involving 11 European laboratories. In this study, the BCR reference material for human plain thromboplastin (BCT/099) was included to verify that the relationship between RBT/79 and BCT/099 was maintained since 1979, when the first assessment was made. The results of the study offered reassurance with regard to the stability of both RBT/79 and BCT/099, confirming the conclusions drawn from long-term stability monitoring. The multicenter study also offered evidence that the calibration of a thromboplastin is more precise when comparisons are made between similar preparations from the same species (tab. 1).

Manufacturers’ thromboplastin calibration

Most thromboplastin manufacturers, at least in Europe, now calibrate their reagents according to WHO recommendations and provide the ISI or a table with INR in the reagent’s box insert. Only a few manufacturers fail to do so. A commercial photometric prothrombin time test is calibrated and used by a major Thrombosis Service in The Netherlands since 1983. However, the manufacturer does not provide the ISI or INR table.

Some manufacturers have recognized the method-dependency of the ISI. The knowledge of ISI values for specific methodologies (instruments) is important for accurate monitoring of oral anticoagulant therapy.

Calibrations should be carried out by comparison with the appropriate standard of the same species. Since the ISI is method-dependent, it should be realized that the WHO standards and BCR reference preparations should be used with the manual technique only. The certified ISI values for these preparations were obtained with the manual technique. Only one BCR reference material (CRM 149R) was calibrated with a semiautomatic mechanical coagulometer (Schnitger and Gross) in a multicenter study. The ISI of this particular thromboplastin/instrument combination was not significantly different from the ISI with the manual technique.