International Normalized Ratio for monitoring therapy with vitamin K antagonists

Ton van den Besselaar

Leiden University Medical Center, Coagulation Reference Laboratory, Leiden, The Netherlands

International Normalized Ratio (INR) is a mathematical transformation of a prothrombin time (PT) determined with a thromboplastin (tissue factor) reagent and a measurement technique. The measurement technique may be a manual technique (e.g. tilt-tube) or a semi-automatic or a fully automated instrument. The PT is transformed to the PT-ratio using the mean normal PT (MNPT) as denominator. INR is based on the availability of established International Standards for thromboplastin and a mathematical model for calculations. An accepted model is the International Sensitivity Index (ISI) which is used as exponent for the PT-ratio. The ISI model assumes that there exists a linear relationship between log-transformed PT's with an International Standard and log-transformed PT's with a working thromboplastin reagent and instrument. Although in reality there are deviations from the ISI model, the magnitude of the deviations is small for most thromboplastin reagents and appears to be acceptable for reliable monitoring of therapy with vitamin K antagonists. In case the INR deviations are greater than 10%, an alternative model may be used, e.g. Tomenson's equation.

The PT is a non-specific test because it is sensitive to multiple different coagulation factors. Thromboplastin reagents of different make may have different sensitivities to individual coagulation factors. For this reason there exists genuine variation of INR between reagents of different make.

The technique or instrument for PT determination may have a significant effect on the PT-ratio with a particular thromboplastin reagent. This means that the ISI of a thromboplastin reagent depends on the technique or instrument used. Some thromboplastin manufacturers provide instrument-specific ISI values for their reagents. Alternatively, the user may perform local calibration of the thromboplastin/instrument combination by using a set of certified plasmas with assigned INR values. Certified plasmas for local calibration may be prepared in different ways. They may be obtained by artificial depletion of coagulation factors or may be obtained from patients treated with vitamin K antagonists. They may be provided either as freeze-dried or as deep-frozen aliquots. Manufacturers of certified plasmas should inform the user about the thromboplastin reagents for which the plasmas may be used. The commutability of the certified plasmas should be demonstrated.

Handheld devices for PT/INR determination which measure the PT from capillary whole blood, are used on an increasing scale for clinical point-of-care (POC) testing, as well as self-testing and self-management by patients at home. Test strips or cartridges for whole blood POC devices are for single use and must be manufactured in a reproducible way. Primary calibration of POC devices should be performed with a split-sample procedure: each patient's blood specimen should be tested as whole blood in the POC device and subsequently as citrated plasma sample with an International Standard for thromboplastin. The ISI model may be used for calibration of POC devices but this is not absolutely required. Alternative mathematical models may be used to transform the measured PT into INR for display on the device's screen.

It is widely accepted that analytical performance goals should be based on biological variation. Requirements for desirable analytical imprecision are based on within-subject biological variation of the analyte. For the INR, it has been suggested that the desirable imprecision may be derived from the within-subject variation observed in patients in the steady state of vitamin K antagonist treatment, in whom the dose of the vitamin K antagonist was constant and there were no changes in conditions which may influence the INR such as intercurrent diseases, invasive procedures, and starting or stopping drugs interacting with the vitamin K antagonist. Within-subject variation of the INR has been assessed in patients receiving phenprocoumon, acenocoumarol, and warfarin. Furthermore, within-subject variation of the INR has been assessed in patients monitored with automated laboratory methods, and in patients who performed self-testing with a POC whole blood device (CoaguChek XS). In self-testing patients, the median within-subject coefficient of variation (CV_B) was 10.2% in patients receiving acenocoumarol and 8.6% in patients receiving phenprocoumon. According to Fraser and coworkers, the desirable imprecision goal is $CV_A = 0.5 \times CV_B$ which is 5.1% for acenocoumarol and 4.3% for phenprocoumon patients.

External Quality Assessment (EQA) is an important component of quality assurance. Participation in an independent EQA scheme permits individual laboratories to identify problems relating to their own practice. There are two limitations to EQA of the INR. First, between-laboratory variation in preanalytical conditions cannot be evaluated. Second, systematic differences between reagent groups can be introduced if the freeze-dried survey samples are not commutable. In that case it is not possible to determine a single INR value for a survey sample that is valid for all samples.