Interpretation of Serial Measurements of International Normalized Ratio for Prothrombin Times in Monitoring Oral Anticoagulant Therapy

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Despite careful monitoring of oral anticoagulant treatment (OAT), some international normalized ratio (INR) for prothrombin time values will fall outside the therapeutic range. Considerable changes in serial INR results from OAT patients may be caused by random fluctuation alone, and, for statistical reasons, a fraction of the INR values will fall outside therapeutic range and interfere with dose adjustments. On the basis of therapeutic intervals and statistical evaluation of reference changes, we suggest and discuss an alternative method for interpretation of serial INR measurements. Retrospective evaluation of serial measurements of INR from OAT patients revealed an "overshooting" phenomenon. When a dose was adjusted on the basis of insignificant change in INR value, the subsequent INR value generally fell in the opposite direction. If a further change of dose was initiated because of the new INR value, a similar course in the opposite direction was observed. This "ping-pong" effect renders patients in a fluctuating state of anticoagulation and may introduce increased risk of complications. The suggested method provides an objective criterion for dose adjustments in OAT, which should reduce patients' risk.

Indexing Terms: statistics/therapeutic drug monitoring/therapeutic interval/coumarin derivatives

Oral anticoagulant treatment (OAT) with coumarin derivatives has a well-established efficacy in prophylaxis and treatment of various thromboembolic disorders (1). Although the pharmacological aspects of anticoagulation are reasonably well-described in general, the monitoring and management of OAT is still a complex task. Patients' responses during OAT are highly individual, and the average dose required for the maintenance of a therapeutic effect differs widely from patient to patient. For the individual patient this variation may cause problems in terms of erroneous dose adjustment. The efficacy and safety of OAT is directly related to the ability of avoiding thromboembolic and hemorrhagic complications (1). The risk is closely related to the intensity of OAT and correlates with the time spent by the patients outside a therapeutic interval set in accordance with indications (2). Management of OAT patients can be divided into a laboratory assessment of intensity of OAT and a therapeutic correction of dose of anticoagulant to keep the intensity of anticoagulation within the therapeutic interval (3). Application of the international normalized ratio (INR) for prothrombin times (PT) have substantially improved laboratory monitoring, and make it possible to address in more detail the causes of variability in the dose–response of coumarin derivatives in OAT (4). Despite monitoring, ~25–30% of INR values fall outside the therapeutic interval in large, prospective, randomized, controlled trials (5), as well as in centers with computer-assisted decision support systems in OAT monitoring (6). In the routine setting in primary healthcare and hospital outpatient clinics it seems to be even worse (7).

These observations might be explained by the interaction of factors such as dietary intake of vitamin K and alcohol, drug interactions, intercurrent infections, and liver diseases. However, those factors are fairly easy to recognize and correct for. More difficult are situations in which minor changes in factors affecting the biological variation on INRs from OAT patients go unnoticed by patients and physicians. This could occur with minor changes in dietary intake and intestinal uptake of vitamin K, as well as minor changes in patient compliance. The variability in procedures for blood drawing, handling, and processing also presents important factors for variation of PT determinations and adds to the total variation of INR measurements. These and other possible interactions could cause random fluctuation of INR values around a stable intensity of OAT (1, 4). Such fluctuation accidentally occurring at the day of venipuncture would interfere with the adjustment of coumarin derivative dose. One approach in optimizing therapeutic monitoring could be to use methods that take into account the random fluctuations in INR measurements. Thus, to improve the therapeutic monitoring of OAT, one must, before adjusting a coumarin derivative dose, consider whether a difference between two INR values represents a real change in intensity of OAT or is due to random fluctuation around a constant set point. Thus, there is a need for a very simple and easy-to-understand method that will be easy to introduce everywhere in routine clinical settings. The purpose of this paper is to discuss a tool for validation of the current INR values as well as their changes during the preceding period. The suggested tool for interpretation of consecutive INR values from patients on OAT is designed to combine the concept of

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4 Nonstandard abbreviations: OAT, oral anticoagulant therapy; INR, international normalized ratio; PT, prothrombin time; CD, critical difference; CVr, intradividual biological variation; CVa, analytical variation; CVt, total intraindividual variation; CVt, in treatment, intraindividual in-treatment variation; and TDM, therapeutic drug monitoring.

Received January 24, 1995; accepted May 8, 1995.
therapeutic intervals with the statistical evaluation of reference changes.

**Theoretical Settings**

Serial measurements of INR values can be interpreted with regard to (a) the therapeutic interval (i.e., being within or outside it) and (b) the difference between the actual and the latest measurement.

**Therapeutic Interval**

The individual OAT patient is seen at clinic visits at certain time intervals. Venipuncture and INR determinations are performed and interpreted according to the therapeutic interval, and, if necessary, the dose of vitamin K antagonist is adjusted (3). During pharmacological therapy the measured results are interpreted in relation to the therapeutic interval, which reflects considerations with regard to optimal pharmacological effect, toxicology, and minimal number of side effects (1). This is in contrast to biochemical analytes, which are usually interpreted in relation to reference values or reference intervals, based on results obtained from nontreated healthy individuals.

**Significance of a Change**

Evaluation of the significance of changes in results obtained from serial specimens from an individual requires knowledge about the magnitude of the total variation (i.e., within-subject variation as well as the analytical and preanalytical variations) in healthy subjects or in patients under well-defined conditions. The change in a biochemical variable must exceed the total standard deviation multiplied by the z-value (a constant dependent on the chosen probability) to be considered significant. The concept of critical difference (CD) or reference change incorporates these considerations (8, 9).

**Within-Subject Variation of INR in OAT Patients**

INR values are determined by the simultaneous measurement of activities of various vitamin K-dependent coagulation factors. Since the factors have different half lives, they show different sensitivities to fluctuations in the concentration of dietary vitamin K. This will add to the random fluctuation of serial INR measurements. Ideally, the within-subject biological variation of INR should be determined by the within-subject biological variation of each relevant coagulation factor. However, from a clinical point of view, use of a global estimate, in terms of INR measurements, seems appropriate.

Traditionally, the total variation is defined as the square root of the sum of biological, preanalytical, and analytical variances, based on measurements of analytes from healthy individuals (8, 9). Initiation of OAT introduces a suppression of the vitamin K-dependent coagulation factors in the patients. After ~96 h a pharmacodynamic steady state, in terms of a new homeostatic intensity of coagulation, is obtained. The new physiological set point (therapeutic set point) of coagulation corresponds to a point on the steep part of the dose–response curve of vitamin K antagonists (4).

Since the dose response in OAT patients is easily impaired, just a small variation in diet, health status, compliance, or medication can introduce a large change in the extent of coagulation. In contrast, healthy individuals have a homeostatic intensity of anticoagulation on the very flat part of the theoretical dose–response curve, such that even large changes in the above-mentioned extraneous factors will hardly be recognized in the coagulation response. In conclusion, the mean within-subject biological CV of INR measurements obtained from healthy volunteers is expected to be smaller than that for OAT patients (10–12) and not relevant for OAT. For OAT the concept of total variation of INR values needs to be redefined as total variation during steady-state conditions of treatment, and is referred to here as total in-treatment variation. Furthermore, the estimates of within-subject variation from patients in OAT do not describe a “true” biological variation. In the following, we will use the term “in-treatment within-subject variation” (S_{in treatment} or CV_{in treatment}) of estimates of variations obtained from patients in OAT treatment. In-treatment within-subject variation can be considered the within-subject variation combined with a pharmacologically determined variation (Appendix 1).

**Critical Difference**

For each measurement of INR a clinical decision must be made, either to continue treatment with unchanged dosage or to change the dose of anticoagulant. The difference between two consecutive measurements, INR_{i} - INR_{i-1}, may be caused by spontaneous variation (around the therapeutic set point) alone or it may reflect a clinical relevant change in coagulation. For a change to be considered significant, it must exceed the changes that may be expected from random variation with a certain probability. According to earlier studies, the change between two consecutive measurements, ΔINR,

\[ \Delta = \text{INR}_{i} - \text{INR}_{i-1} \]  

(1)

is significant at a given level if it exceeds

\[ \text{INR}_{i} \times Z \times \sqrt{\frac{2}{Z^2 + CV_a^2 + CV_b^2}} \]  

(2)

\( Z \) denotes the percentage points of the gaussian distribution in terms of CV, for a two-tailed probability of 5%, \( Z = 1.96 \). \( CV_a \) is the analytical variation, and \( CV_b \) is the intraindividual “in-treatment within-subject” variation when the dose is kept constant. This is identical to what in other reports has been defined as the CD (8, 9).

**Graphical Presentation**

**Difference Plot**

In clinical management of OAT, the clinician has to rely on INR values when assessing the intensity of anticoagulation. Before changing the dose of vitamin K antagonist, the present INR value must be interpreted in relation to the therapeutic interval and to the former
measurements of INR, as well as to regulability, risk factors, and present clinical state of the patient.

If the patient is considered to be in steady-state OAT and the measured INR value is within the therapeutic interval, then the variation in INR and consequently the \( \Delta \text{INR} \) must be small [i.e., below the CD in \((1 - F) \) differences]. The INR value may, however, also be within the accepted therapeutic range even if the patient's level of anticoagulation is unstable. In this situation the \( \Delta \text{INR} \) is expected to be significant, showing considerable fall or increase. Aiming for a presentation of data that facilitates interpretations, we think it reasonable, therefore, to compare the latest INR value (INR\(_{t} \)) with the most recently measured INR value (INR\(_{t-1} \)) only.

To ease the interpretation of consecutive INR values, we propose to plot the difference between the actual value and the most recently measured value (INR\(_{t} \) - INR\(_{t-1} \)) against the INR\(_{t} \), in a difference plot. This reveals the changes in INR, whether it is in a positive or negative direction \((13) \). Applying the therapeutic interval in the plot further reveals whether the latest measured INR is within or outside the therapeutic interval (Fig. 1A). If the measured INR is within the therapeutic interval, one must consider whether this indicates steady-state intensity of anticoagulation, or drifting or unstable OAT. To evaluate whether the present INR result is due to expected random variability or to a significant change in INR, we must also know the total variation of INR (including in-treatment within-subject variation) for the individual. We earlier estimated the mean total in-treatment variation for patients on constant dose of coumarin derivative to be 10.1\% \((4, 10) \). At the therapeutic target INR = 2.5, the CD is 0.7 INR (Eq. 2). At target INR = 3.5, the CD is 1.0 INR, at a 5\% level of significance, corresponding to a 95\% range for differences \((4) \). Given assumptions of linearity between the corresponding CDs for different therapeutic targets, decision limits for the CD can be illustrated graphically with sloping lines connecting the points, which equals the CDs for the different INR values. INR is defined only for PT obtained from patients on OAT, but since the CV\(_{\text{in treatment}} \) is assumed constant (10\%), the lines defining the CD will theoretically pass through zero (Fig. 1B).

**Interpretation of INR Measurements with the Model**

INR values above the upper or below the lower of the two lines determining the CD will indicate significant changes for any given \( \Delta \text{INR} \) value at the chosen level of significance. The area defined by the lines representing the CD and the therapeutic interval correspond to a therapeutic area where the differences between consecutive values represent insignificant changes in \( \Delta \text{INR} \); i.e., the area corresponds to steady-state intensity of anticoagulation. If the value is outside one of the lines but inside the therapeutic range, there is a significant change in \( \Delta \text{INR} \). Although the value is within the therapeutic range, one can reasonably consider whether the change reflects a biochemical change indicating that the dose of the coumarin derivative should be changed. Before making a change in dose, one must evaluate whether there is an otherwise sound explanation for the change to have taken place (e.g., the patient missing a tablet or having an intercurrent disease that may affect intensity of OAT). Furthermore, one may continue the treatment unchanged, even though the measured INR value is outside the therapeutic interval, if the \( \Delta \text{INR} \) is insignificant (i.e., within the lines indicating CD). By indicating different
levels of certainty for CD, different levels of probability of significance of change can be shown in the model (Fig. 1C).

Results from a patient in steady-state and with CV$_{\text{in treatment}}$ <10% are expected to be distributed within the therapeutic interval and the CD. However, results from a patient in steady-state (as well) but with a higher CV$_{\text{in treatment}}$ (e.g., 15%) will exceed the limit very often, which may result in frequent up- and downregulation of therapy (ping-pong effect).

**Retrospectively Evaluated Clinical Examples**

Patient in Steady-State OAT

This patient from our OAT clinic was retrospectively evaluated with the model. ΔINR was stepwise calculated and plotted against INR$_i$ in nine pairs of consecutive INR measurements without adjustment of dose of coumarin derivative (Fig. 2A). All paired observations of ΔINR and INR$_i$ are within the therapeutic interval and the limits for CD, indicating steady-state intensity of anticoagulation (e.g., CV$_{\text{in treatment}}$ <10%).

**INR Ping-Pong Effect**

When the dose of coumarin derivative is adjusted because of significant change between serial INR values, the next measured INR value is expected to increase or decrease accordingly. However, if dosage is adjusted on the basis of individual nonsignificant changes of serial INR values because of high CV$_{\text{in treatment}}$, overshooting of the next INR value must be expected. The same effect will be seen when the decision of dose adjustment is correct, on the basis of significant change in the serial INR values, but the change in dose exceeds what is necessary for correction of the following INR value. Such a ping-pong phenomenon will introduce severe fluctuation in the intensity of anticoagulation until adjusted by smaller changes in dose, as observed for another retrospectively evaluated patient from our OAT clinic (Fig. 2B).

**Discussion**

Despite monitoring of OAT it seems difficult to avoid INR values outside the therapeutic range. One explanation could be that even considerable changes in serial measurements of INR values are caused by random fluctuation of otherwise stable treatment, but with a larger CV$_{\text{in treatment}}$. Because of the marked variation in dose response between OAT patients, at least a fraction of the patient population must be expected to have a total CV$_{\text{in treatment}}$ that will result in a high proportion of INR values outside the range of the therapeutic interval. Thus, for statistical reasons alone, a fraction of the INR measurements will fall outside the therapeutic interval and interfere with dose adjustments. This implies that consideration of the random fluctuation leading to fewer adjustments of dose might improve management of OAT patients.

**Justification of the Suggested Method**

We suggest a simple and easy-to-understand method that allows for corrections of random fluctuations in INR measurements from OAT patients. The tool is a nomogram intended to be used by a general practitioner or a physician in an outpatient clinic, and the method should be generally applicable for all OAT patients. Methods for repeated calculations of estimates of true variance are not applicable, as the CV$_{\text{in treatment}}$ for an individual is changed each time the dose is adjusted. Furthermore, our suggested method is independent of assumptions of a free random process for INR values. The method for calculation of CD is based on an average within-patient standard deviation assumed to be the same for all patients (4). This method is, in principle, equivalent to the “delta-check” method (14) but is burdened with a proportion of false positives. In the clinical monitoring situation the physician must react to a high INR value because of the increased risk for bleeding. However, reducing the dose of anticoagulant because of a false-positive INR value is less serious (regarding side effects) than overlooking a true positive. In fact, we have introduced a very
conservative estimate of within-subject in-treatment variation in the calculation of the decision limits for CD. We are well aware that this will add more to the proportion of false-positive INR values, particularly since a proportion of the patient population must be expected to have a larger CTV than our estimate of 10.1%. However, wrong dose adjustment because of a misjudged INR value will promptly be disclosed by the nomogram, since the new INR plot will fall in the opposite direction. The chosen concept should be capable of correcting in part for the random fluctuation in INR values from OAT patients by indicating when it is reasonable to assume that an observed INR value is outside the therapeutic interval because of random fluctuations.

Our model is based on the assumption of steady-state anticoagulation. This implies that evaluation of the significance of change of an INR value after a change in dose may be impaired, as may interpretation of INR values during introduction of therapy. Steady-state conditions must be awaited, and this is normally obtained within 2 to 3 weeks. In other situations, changes in INR values must be expected and accepted. If the INR value, for instance, is expected to be low because of minor surgery or dentist visits, or if the drifting is explainable in terms of intercurrent infections, missing a tablet, or dietary abnormality, the next INR value should be expected to change significantly. Dose adjustment in this situation might result in overshooting. Again, one must await the steady-state condition. However, if the INR value is high, indicating an unacceptable increase in the risk for side effects, reduction of dose must be considered solely on the basis of clinical judgment.

Ping-Pong Effect

The average dose of coumarin derivative required for the maintenance of a therapeutic effect differs widely from patient to patient. Thus, the magnitude of the actual change in dose in response to INRs that exceed the significance level must be considered. One approach could be a percentage change in dose. Others have suggested a method based on an algorithm. A combination of the two methods, which also considers frequency of INR measurements, seems capable of reducing the fraction of INR measurements outside the therapeutic interval (15). Such a method can easily be introduced in the nomogram by adding decision limits for magnitude of dose adjustments. When overshooting is introduced because of a CTV<sub>ini-treatment</sub> > 10%, the next INR value must be expected to be in opposite direction. If the new INR value again is considered significantly different from the former, it will be further corrected and a state of positive feedback is introduced. The impact of differences in CTV<sub>ini-treatment</sub> can be assessed by use of calculations based on tables of the normal distribution. With a target of 2.5 INR and a therapeutic interval of 2.0–3.0 INR, 5% of the INR measurements will fall outside the interval if the CTV<sub>ini-treatment</sub> is 10%. For a patient with a CTV<sub>ini-treatment</sub> of 15% or 20%, the fractions of INR measurements outside the therapeutic interval are 18% and 32%, respectively. If the target for OAT is chosen not as the center of the interval, the fractions of INR measurements above or below the therapeutic interval will increase considerably according to the new set point and exceed the figures calculated above. In consequence, aiming for a target in the center of the therapeutic interval is necessary, and acceptance of an increased risk of false-positive INR values outside the therapeutic interval due to large values of CTV<sub>ini-treatment</sub> will correct for part of the ping-pong effect. A remaining ping-pong effect will immediately be recognized with the nomogram because the next measurement will be seen in the opposite direction.

Regression Towards the Mean

From a clinical point of view we presented the latest INR value at the x-axis in the model, since it provides a direct graphical evaluation of the present INR value to be within or outside the therapeutic interval. This approach, however, will introduce regression towards the mean when plotting ΔINR against the latest INR value. This effect could be avoided by using (x + y)/2 at the abscissa, but this approach would decrease the direct clinical information obtained by use of the latest INR.

Other Methods for Optimizing OAT

Future efforts to maximize the time OAT patients spend within the therapeutic interval could be based on prospective estimates of variation for the individual patient as a basis for deriving individual threshold values for monitoring. Such estimates could be incorporated in Bayesian forecasting programs for therapeutic drug monitoring (TDM) (16). Taking into account estimates of total in-treatment variation may improve the precision of the forecasting of TDM systems. This method, however, is still based on the assumption of random fluctuation of INR values, which hardly can be fulfilled in the routine monitoring of OAT, because change in dose of anticoagulants is based on the INR values. Another approach could be based on a sequential time-series model, which makes use of successive calculations of the patients' means and standard deviations (17). Such methods might prove useful in monitoring the individual OAT patient, by providing precise estimates of the "true" individual variances. This method needs clinical evaluation as well, since the INR values in monitoring OAT still do not fulfill the assumption of a free random process. The total variation of consecutive INR values from patients on stable OAT was estimated in a retrospective study. This estimate was obtained under very special conditions, i.e., no change in treatment during the study period. Because of the narrow therapeutic interval, only a limited number of patients could be used for calculation. Since dose changes were performed on the basis of interpretation of INR values in relation to therapeutic interval, we could not investigate whether the extreme INR values were caused by real change, by
use of a wrong set point, or by a CV >10%. In consequence, 32 patients used for calculation showed homogeneity of variance (4). Unselected data on CV \( T \) and CD in OAT patients on a constant dose of medication can be obtained by prospective studies and will provide more precise estimates of CD. Such estimates of individual variances and CV values must be expected to vary considerably compared with our present estimate and may not show homogeneity of variance. Application of a statistical method for calculating reference change, defined as the difference between two consecutive test results in an individual patient that is statistically significant in a given proportion of all similar persons, seems, in this situation, to be a better solution than just comparing mean variance from the population studied (14).

Components of Within-Patient Variability

The biological component of variation (CV\(_ b \)) might be specific for the individual patient, whereas the pharmacological component may be determined to a greater extent by external factors. The preanalytical component of variation could be reduced by careful instructions or education of patients with regard to these factors and, thereby, improve the controllability and minimize the risk of complication. Furthermore, standardization of the preanalytical procedures for blood drawing, blood processing, and handling must be expected to increase the precision of PT determinations and thereby reduce the total within-patient variation of INR.

The impact of such efforts, of course, needs evaluation in prospective randomized controlled trials.

In conclusion, we find that introduction of a method for interpretation of INR that takes into account the CD between two consecutive INR values will improve the controllability of OAT and thereby the efficacy and safety for the patients. Furthermore, presenting the INR result in a simple and useful graphical model could be educational and thereby ease the introduction of the combined therapeutic interval and reference change.

Appendix 1

Explanation of In-Treatment Variation

Biological variation is usually estimated from healthy individuals and expressed as SD/\( \bar{x} = CV \times 100\% \); thus CV\(_ b \) is proportional to the variance, SD\(^2 \). Both analytical and biological sources add to the total variance for a single measurement, which implies that:

\[
CV^2_T = CV^2_b + CV^2_p
\]

since preanalytical sources of variation are considered to be integrated parts of the biological sources of variation. When evaluating biological variation or random variation in specimens obtained from persons on pharmacological steady-state therapy, a new homoeostatic set point of the measured variable must be assumed within the individual. In this situation a pharmacologically introduced source of variation will add to the total biological variation and define CV\(_ b \) in treatment as

\[
CV^2_{\text{total in treatment}} = (CV_b)^2 + (CV_{\text{pharmaco}})^2
\]

and therefore CV\(_ T \) in treatment as

\[
CV_{\text{total in treatment}} = \sqrt{(CV)^2 + (CV_{\text{in treatment}})^2}
\]

The random variation on serially measured variables from pharmacologically treated patients must be assumed to be larger than for healthy individuals. When \( CV_{\text{in treatment}} \) differs considerably from \( CV \) of healthy individuals, as for INR from patients on OAT, then CV\(_ b \) may vary according to concentration. It may, however, be impossible experimentally to separate biological from pharmacological variation, but also under these conditions, the assumption will probably be valid.

We thank H.N. Nielsen for assistance in the preparation of the manuscript. This study was supported by a grant from “Sygekassernes Helsefond” (j.nr:11221-93).

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