International Normalized Ratio for Prothrombin Times in Patients Taking Oral Anticoagulants: Critical Difference and Probability of Significant Change in Consecutive Measurements

Jens Flensted Lassen,1 Ivan Brandslund, and Steen Antonsen

To determine when a change in serial measurements of prothrombin time in patients receiving oral anticoagulant therapy (ACT) is a statistically significant biological change necessitating dose adjustment, one must know the size of the "critical difference" in statistical terms (i.e., probabilities). In a cohort of 32 ACT patients at pharmacological steady-state, we studied the within-subject total variation of prothrombin time, expressed as International Normalized Ratio (INR), over 6 months. The total within-subject variation (CV) of INR was 10.1%. The corresponding critical differences required for significance of change in serial INR results was 0.7 at a therapeutic target of 2.5 INR and 1.0 at a therapeutic target of 3.5 INR. The data presented allow generation of objective criteria for monitoring ACT patients and deciding dose adjustments. We recommend that estimations of critical differences for significant change of INR in ACT patients should be based on results obtained in the specific clinic investigated to mirror the routine total variation of INR measurements they obtain.

Indexing Terms: monitoring therapy/quality goals

Oral anticoagulant treatment (ACT) with coumarin derivatives has a well-established efficacy in prophylaxis and treatment of various thromboembolic disorders (1).2 The risks of ACT side-effects in terms of thromboembolic or hemorrhagic complications are closely related to the intensity of anticoagulation and correlate to the length of time patients spend outside a certain therapeutic interval (2). The dose of coumarin derivative and the anticoagulant response is a direct relation in normal subjects. However, marked variation in the dose–response exists between subjects and in patients during extended ACT. For the individual patient, this variation may cause problems in terms of wrong dose adjustments (3).

Management of ACT can be divided into laboratory and therapeutic monitoring. The aim of laboratory monitoring is to measure the intensity of ACT, whereas therapeutic monitoring is done to adjust the dose of coumarin according to the therapeutic interval and the actual clinical state of the patient. The causes of variability in the dose–response of coumarin derivatives is theoretically related to both parts of the monitoring. However, application of the International Normalized Ratio (INR) for variation in prothrombin time (PT) and use of internal and external control procedures have substantially improved the performance of laboratory monitoring (1). In contrast, therapeutic monitoring of ACT in clinical trials (4) as well as in routine settings still does not perform very well (5). Thus, the question of how to maximize the time a patient spends within the therapeutic interval is important (6).

Reducing within-patient variability of the dose–response relationship of coumarins could be one approach to optimizing therapeutic monitoring. The causes of variability in dose response include interactions of such factors as dietary intake of vitamin K and alcohol, intercurrent infections, liver diseases, concomitant treatment with other drugs, and other factors affecting pharmacodynamics and pharmacokinetics of the drugs (1). In that these factors affect the therapeutic response of coumarin derivatives, they may introduce random fluctuation in measured INR values. Before changing the dose of anticoagulant, it is imperative for the clinician to know whether a difference between two INR values represents a significant biological change in intensity of ACT or is due simply to random and (or) systematic variation around a pharmacological set-point (7). Data on the total variation of INR results of individuals (i.e., the sum of within-person, analytical, and preanalytical variations) are required for one to evaluate the significance of a change in serial INR results from individual patients (8). However, only data on within-subject variation of PT in healthy subjects have been reported, and these are not directly applicable to the therapeutic situation of ACT. Accordingly, we investigated total variation of INR from ACT patients as the basis for estimating critical differences of serial INR values at different intensities of ACT.

Materials and Methods

Design of the Study

The procedures followed in this study were in accordance with the second Declaration of Helsinki (amended in 1989). The Danish law on biomedical research and the Scientific Ethical Committee system of October 1, 1992, excepts from approval by a scientific ethical committee the research on existing data without inter-
vention and with the purpose of technical and medical quality assurance; accordingly, no approval was applied for. The total variation (i.e., within-subject, pre-analytical, and analytical variation) of PT measurements was retrospectively estimated for 32 patients from our ACT clinic. Patients' record forms from the clinic were analyzed, and patients were identified whose phenprocoumon dose needed no adjustment through at least six control visits at the clinic. Sets of six serial INR values, obtained during at least 6 months of treatment, were used for calculations. The INR series were selected from the years 1989–1992, and values for each patient were included only once. The subjects were 10 women (median age 60.5 years, range 21–73) and 22 men (median age 62.5 years, range 29–77). The patients were all on long-term ACT because of prosthetic heart valves, atrial fibrillation, or recurrent venous thrombosis. The target INR value was 2.5 in eight patients and 3.5 in the remaining; however, in five of the remaining patients the target had been reduced to 3.0 because of minor contraindications.

Blood Sampling and Analysis

According to the laboratory standard procedure, blood samples had been obtained from sedentary patients at rest, being drawn from antecubital venipuncture by experienced staff. The samples were collected about every 5 weeks (range 4–6 weeks) as part of routine monitoring in the outpatient ACT clinic. Blood specimens obtained from blood anticoagulated with 0.1 volume of 38 g/L trisodium citrate were kept at 18–22°C and centrifuged at 1500g for 15 min within 1 h of collection, after which the plasma was separated. The anticoagulant effect was measured in fresh plasma with the Amelung (Lieme, Germany) coagulometer KC 4A, with a combined ox brain thromboplastin [Thrombotest™; Nycoderm, Pharma, Oslo, Norway; International Sensitivity Index (ISI) of the thromboplastin = 1.0]. PT values were expressed in terms of INR, as follows: INR = (patient's PT/mean normal range PT) × ISI. The analytical quality was assessed each working day, with use of control material with INR values of 2.5 and 4.1; total CV did not exceed 3.5%.

Statistical Method

Total variation was estimated by nested analyses of variance. Tests for outliers and for heterogeneity were performed as stated by Fraser and Harris (3). No outliers and no heterogeneity were found. Estimates were made for both sexes, for groups of different target values, and for three age groups: ≤55 years (n = 8), 56–64 years (n = 14), and ≥65 years (n = 10). The between-run analytical variation was assessed, from results for the "physiological" control material included in every run. To document the general quality of care in the clinic, we calculated for patients in long-term treatment the fractions who were within and outside the therapeutic range, from the last control results for individual patients ("last check in files") in 1990, 1991, and 1992 (9). The critical difference (CD) was calculated as

\[
CD = Z \times \sqrt{\frac{2}{n}} \times CV_{\text{total}}
\]

where CV_total denotes the total variation of the analyte, and Z is the Z-score, the number of SDs appropriate for the level of probability selected to indicate significance. For P ≤0.05, commonly used in clinical medicine, Z is 1.96 for a two-sided (any change) critical difference and 1.65 for a one-sided (rise or fall) difference (10).

Results

Table 1 lists the estimates of total variation during 6 months. The mean variation (CV) was 10.1%. A probability plot of the individual variances is shown in Fig. 1. There were no statistical signs of differences between groups of gender, age, or therapeutic INR target. Table 2 lists the critical differences determined at two therapeutic targets and at different levels of significance. The clinical quality of the therapeutic control of ACT patients was assessed by the proportion of INR

<table>
<thead>
<tr>
<th>Table 1. Total variation in INR values in patients on pharmacological steady-state anticoagulant therapy.</th>
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<td><strong>Groups</strong></td>
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<tr>
<td>Total</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Target (3.5)</td>
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<tr>
<td>Target (2.5)</td>
</tr>
<tr>
<td>≤55 years</td>
</tr>
<tr>
<td>56–64 years</td>
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<td>≥65 years</td>
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No statistically significant difference between groups by gender, therapeutic target, or age was detected.
measurements within the therapeutic interval, 70% within this interval being considered the gold standard for quality of ACT outpatient clinics (9). In our clinic, the proportion (and 95% confidence interval) of patients with INR values within the therapeutic interval was 69% (60–77%, n = 138), 74% (66–81%, n = 150), and 76% (68–83%, n = 149) in 1990, 1991, and 1992, respectively.

Discussion

Critical Differences in ACT Patients

In estimating critical differences of INR values for patients on pharmacological steady-state ACT, we selected for study patients without dose adjustments during a 6-month period and excluded patients with dose adjustments because of having INR values outside the therapeutic interval. As this implies, we evaluated the most easily managed patients attending our clinic and, as expected, the therapeutic interval was reproduced when target INR values ±2 SD were calculated. This means, therefore, that the present estimates of critical differences must be considered a minimum value. Unselected data on total variation, CV, and critical differences in ACT patients on constant doses of medication can be obtained by prospective studies and will provide more theoretically correct estimates; however, such an investigation will be difficult to perform because of practical and ethical reasons. From a clinical point of view, therefore, use of a global estimate of INR measurements seems appropriate.

From our data, two INR measurements in the same subject (e.g.) of 3.1 and 3.9 might, with 10% probability, differ from the therapeutic target of 3.5 solely because of random variation. The probability of finding a critical INR difference of 1.0 purely for reasons of random variation is, at the same therapeutic target value, 5%. When monitoring ACT, one will probably react by adjusting the dose at an observed change in INR that is much less than this. Still, at a 25% significance level, INR changes of 0.4 and 0.5, respectively, are required at INR therapeutic targets of 2.5 and 3.5. These considerations can be simplified into a nomogram, based on the results from Table 2. The nomogram (Fig. 2) provides the probabilities of significant changes at different amounts of anticoagulation and will ease the interpretation of serial measurements of INR. The nomogram may be useful in medical decision support electronic data processing systems to indicate to the physician at what level of probability is a change reflecting enough real biological change to warrant a dose adjustment.

This gives the doctor a tool for reacting to even a small probability of change, if the consequences for nonadjustment of dose are serious. Thus, a doctor might not change a dose at the 2.5 INR target before the probability of change between two consecutive INR measurements exceeds 95%, whereas a dose adjust-

Table 2. Critical differences for significance between two consecutive INR results from patients on pharmacological steady-state anticoagulant therapy.

<table>
<thead>
<tr>
<th>Probability of difference, P</th>
<th>Critical differences for INR therapeutic target of</th>
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<tbody>
<tr>
<td>0.75</td>
<td>2.5</td>
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<tr>
<td>0.90</td>
<td>0.4</td>
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<tr>
<td>0.95</td>
<td>0.6</td>
</tr>
<tr>
<td>0.99</td>
<td>0.7</td>
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<tr>
<td></td>
<td>0.9</td>
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<td>1.3</td>
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![Fig. 2. Probability of significant difference between to consecutive INR measurements from patients on oral anticoagulant therapy.](image)

For example, a change in INR from 2.7 to 3.5 means a ΔINR of 0.8. From the nomogram, a ΔINR of 0.8 that results in an INR of 3.5 (x-axis) corresponds to a probability of biological change of ~90%.
ment even at a 25% probability of change would be warranted at 4.5 INR because of the serious risk of spontaneous bleeding at high INR values.

Within-Subject Variation in Healthy Individuals

Others have estimated within-subject variation (CV_w) from healthy individuals not taking anticoagulant medication. Dot et al. reported a CV_w of 2.3% (mean) in a study of 39 individuals (11), and Costongs et al. reported a CV_w of 5.8% (median) in 274 healthy individuals (12). From our data, the CV_w from patients in ACT can be estimated as ∼9% (subtracting the analytical CV of 3.5% from the total CV), without taking preanalytical variation into account. This difference between the estimates is probably due to the various factors known to affect the coagulation system and to differences in therapeutic response to anticoagulants (1, 3). When oral anticoagulants are taken, the vitamin K-dependent coagulation factors are suppressed and a new homeostatic intensity of anticoagulation is obtained (3). The new pharmacological set-point of anticoagulation corresponds to the steep part of the dose–response curve of vitamin K antagonists. The dose–response in an ACT patient is easily affected by extraneous factors, and only a small variation in diet, health status, compliance, or medication will introduce a large response in intensity of anticoagulation. Normal individuals may be expected to have a homeostatic intensity of anticoagulation on the flat part of the theoretical dose–response curve, and large differences in the above-mentioned factors will therefore hardly be recognized in their coagulation response. Thus, within-subject biological variation of INR measurements obtained from normal volunteers should presumably be smaller than for ACT patients. This seems consistent with the data in this study.

Quality Specifications of ACT

In our opinion, quality specifications of management of ACT should take into account not only indications of treatment, risk of major complications, frequency of control visits, and analytical quality but also the random variation of serial INR values. Introduction of the concept of a critical difference in serial INR measurements in the therapeutic control in our ACT clinic may be able to further reduce the fluctuation of INR values and ease the control of the patients’ coagulation status. Of course, final evaluation must await controlled studies.

Future improvements in the clinical monitoring of ACT patients await the development of prospective estimates of variation for the individual patient as a basis for deriving individual threshold values for ACT monitoring. This approach requires further evaluation.

In conclusion, we recommend estimation of the critical difference in INR values for patient populations in every ACT outpatient clinic and use of this difference to assess threshold values above or below which ACT dose adjustment can be decided. Such decisions should be based on statistically significant changes between consecutive INR values, in relation to the risk of clinical consequences, be it bleeding or embolism, at high or low INR values.

References