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Journal of Thrombosis and Haemostasis, **3**: 915–921

ORIGINAL ARTICLE

A model-based algorithm for the monitoring of long-term anticoagulation therapy

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To cite this article: Pasterkamp E, Kruithof CJ, Van der Meer FJM, Rosendaal FR, Vanderschoot JPM. A model-based algorithm for the monitoring of long-term anticoagulation therapy. *J Thromb Haemost* 2005; **3**: 915–21.

Summary. It has been shown that computerized algorithms for the prescription of coumarin derivates can improve the quality of long-term anticoagulation treatment. These algorithms are usually based on an empiric relationship between dosage and International Normalized Ratio and do not quantify the delaying effect of the drug's pharmacokinetics or the effect of alternating doses that are used to approximate a certain average dosage. Our objective was to develop a mathematical model that takes into account these effects and to develop a new algorithm based on this model that can be used to further optimize the quality of long-term anticoagulation treatment. We simplified a general model structure that was proposed by Holford in 1986 so that the parameters can be estimated using data that are available during long-term anticoagulation treatment. The constant parameters in the model were estimated separately for phenprocoumon and acenocoumarol using data from 1279 treatment courses from three different anticoagulation clinics in the Netherlands. The only variable parameter in the model is the sensitivity of the patient, which is estimated during the course of each treatment. A total of 194 dosage and appointment intervals that were proposed by the new algorithm were scored as 'good', 'acceptable', or 'bad' by two dosing experts. One hundred and seventy-eight (91.8%) proposals were considered good by at least one expert and bad by none. In 39 cases the experts disagreed. We believe that this algorithm will allow further improvement of anticoagulation treatments.

Keywords: algorithm, anticoagulation, pharmacokinetics.

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Received 31 December 2004, accepted 10 January 2005

Introduction

Oral anticoagulant therapy with coumarin derivatives is used for a variety of indications such as mechanical heart valve prostheses, deep vein thrombosis and atrial fibrillation [1]. Inadequate treatment with these drugs increases the risk of thromboembolic (under-anticoagulation) and bleeding (over-anticoagulation) complications [2]. Therefore, the intensity of anticoagulation is regularly monitored by assessment of the International Normalized Ratio (INR) and the INR is kept as much as possible within a predefined target range. In the Netherlands the monitoring of the INR is handled by approximately 70 anticoagulation clinics. Patients on anticoagulation therapy visit these clinics every 1–6 weeks to have their INR measured and to receive a new calendar with daily dose prescriptions by mail 1 day later (dose calendar). Acenocoumarol (Sintrom mitis®) and phenprocoumon (Marcoumar®) are the licensed coumarin derivates.

If the measured INR is outside the predefined target range the dosage needs to be adapted. Determining the new dosage is complicated by several factors. First, the sensitivity of patients to the drug is subject to a pronounced inter-individual and, in the course of time, intra-individual variability. Second, because of the influence of delaying processes such as pharmacokinetics, and the complex relationship between dose and INR, it is difficult to make accurate dose adjustments. Third, the INR shows fluctuations that are unpredictable and may be the result of differential sensitivity of the thromboplastin reagent used [3], and unknown variations in diet, medication, compliance or physical condition of the patient.

To facilitate anticoagulation dosing, several computerized algorithms have been developed in the past and have been shown to improve the quality of control [4–8]. In the Netherlands several anticoagulation clinics use an algorithm called TRODIS that was first developed in 1973 [9]. TRODIS uses a complex empiric decision-tree that determines whether the dosage has to be adapted and, if it has, whether a new dosage can be calculated by the algorithm (dosage proposal) or whether it has to be determined by the physician. In practice, TRODIS only proposes a dosage in approximately 60% of all cases,

25% of which are subsequently overruled by the physicians upon review. In the case that a new dosage has to be calculated, TRODIS uses a simple dose–INR relationship that calculates the new dosage based on the INR and previous dosage only. This approach has several weaknesses. First, it does not take into account the pharmacokinetics of the drug or the effect of previous dosage adjustments. Second, TRODIS does not use the actual daily doses that are prescribed on the last visit's dose calendar but the average. On the calendar, for instance, a patient receives instructions to alternately take two and one tablets per day, which TRODIS uses as a dosage of 1.5 tablets per day. Especially for acenocoumarol with its short half-life of 24 h [10] it is relevant to know how many (in this instance either one or two) pills were prescribed to the patient the day before the visit to the anticoagulation clinic. Finally, after the previous visit the dosing physician may have decided to either prescribe an extra loading dose if the INR was too far below target, or stop the dosing for one or more days if the INR was too far above target (stop-dose). These actions are not taken into account if the algorithm only uses the average dosage instead of using the actual prescriptions on the dose calendar.

In conclusion, TRODIS only makes use of a subset of all the information that is available to adjust the dosage. The anticoagulation process is simply too complex to derive an empiric relationship between all the available data and the right dosage that will yield an INR near the target at the next visit.

A common approach in engineering to control complicated systems is to develop a mathematical model that describes the effect of the input on the output. An algorithm that is based on such a model controls the output (INR) by choosing the input (dosage) that yields the desired output (target INR), as predicted by the mathematical model. In the case of computerized anticoagulation dosing it may be expected that an algorithm that uses such a mathematical model will lead to faster and more accurate corrections of the dosage. This in turn will lead to a higher percentage of time-in-range, and fewer visits to the anticoagulation clinic per year. A few mathematical models with this purpose have already been developed, but they either use input that is not available during the therapy, such as individual levels of clotting factors, or they only operate during the initiation of therapy [11–14].

This article describes three steps that were taken to develop an algorithm for the prescription of oral anticoagulants. First a model structure for the above mentioned mathematical model is determined. Second, the parameters of the model are optimized to data from three anticoagulation clinics in the Netherlands. Finally the algorithm is evaluated by two physicians who are expert at prescribing anticoagulation dosages at the anticoagulation clinic in Leiden.

Methods

Data

We imported data from the computerized databases of the anticoagulation clinics of Leiden, Utrecht and The Hague into a relational database. Data were related to one of three entities: patients, treatments and visits. For each patient we obtained both date of birth and sex. For each treatment course we imported the date of onset, indication and, if applicable, the end date of treatment. For each visit we collected the date of visit, the result of the INR measurement, the dose calendar, the target INR and recorded remarks from the physicians and nurses. The remarks are coded and can contain information about co-medication, initial doses and about loading or stop-doses.

We selected treatment courses that complied with the following inclusion criteria. Onset of treatment on or after 1 January 1994 (anticoagulation clinics in Leiden and Utrecht) or on or after 1 January 1997 (The Hague), and before 1 January 2000. The time span of each treatment course was restricted to one of the following end-points: recorded end of a treatment course, admission to hospital, or 1 January 2000. Only treatment courses with phenprocoumon or acenocoumarol as the prescribed anticoagulant were selected. Treatment courses with a shift of anticoagulant from phenprocoumon to acenocoumarol or vice versa were excluded. Treatment courses with INR targets other than 3.0 (range 2.5–3.5) or 3.5 (range 3.0–4.0) (the commonly used INR targets in the Netherlands during the time window of this study) were also excluded. To make parameter estimation possible, only treatment courses where patients did not use coumarins prior to their entry in the database of the anticoagulation clinic and where the initial dose (the dose between onset of treatment and first visit to the anticoagulation clinic) was available in the database were included. Each patient may have undergone several non-overlapping treatment courses, with each treatment course comprising one or more visits.

Mathematical model

To develop a mathematical model that can be fitted to the available data we took the general model structure that was presented in 1986 by Holford as a starting point [15]. This model comprises four submodels, which are explained below (Fig. 1a). The first submodel describes the *pharmacokinetics* of the oral anticoagulant. This submodel gives the plasma concentration of the anticoagulant agent as a result of the drug intake. The second submodel characterizes the direct relationship between the plasma concentration of the anticoagulant and the production rate of vitamin K-dependent clotting factors. This relationship is also referred to as the *pharmacodynamic* relationship. The third submodel describes the relationship between the production rate of vitamin K-dependent clotting factors and the resulting level of these factors, expressed as the activity of the prothrombin complex. Finally, the fourth submodel represents the relationship between the prothrombin complex activity and the measured INR.

Note that the first and third submodels together describe the delay on the effect of the anticoagulant. The parameters of these models are the half-life of the drug and the half-lives of the clotting factors.

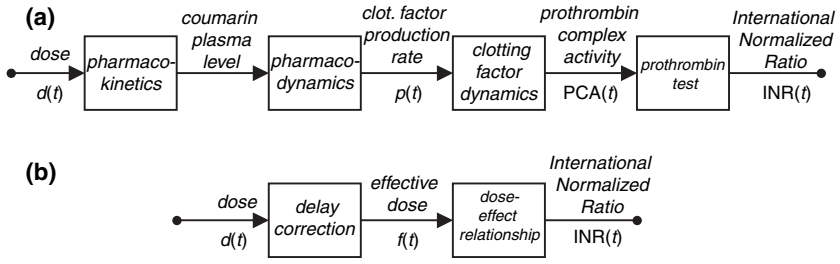

Fig. 1. (a) General model structure consisting of four submodels for the relation between dose and INR (Holford's model). (b) Lumping linear dynamics and static non-linearities in two separate submodels yields the simplified ICAD model structure.

Estimation of all variables of the four submodels is difficult in a practical setting, because:

1 only the INR is measured, so the plasma level of the anticoagulant and the prothrombin complex activity have to be inferred,
2 the time span between subsequent visits is variable and relatively long compared to typical clotting factor half-lives of approximately 12 h [16].

To overcome these difficulties, we simplified the structure of the model by combining the first and third submodels into one submodel, and the second and fourth submodels into another, thus obtaining a new model structure with only two submodels, referred to in the following text as the Improved Control of Anticoagulation Dosage (ICAD) model (Fig. 1b).

In the ICAD model, the first submodel describes the collective influence of all delaying processes, whereas the second submodel describes the relationship between the dosage and the corresponding INR. So instead of using the prescribed dosage directly as an input to the dose–effect relationship, it is first corrected for delays. We call this corrected dosage the *effective dose*. Imagine starting a prescription of a drug at two pills per day. If the half-life of the drug equals 1 day, then the *effect* of the drug after 1 day will be the equivalent of an average dose of one pill per day, whereas after two days the effect will be the equivalent of 1.5 pills per day. Only after several days will the effect of the average dosage (or the effective dose) approximate the effect of a long-term treatment of two pills per day. The only parameter of this first submodel is the half-life of the effect ($t_{½}$) which is approximately the same as the half-life of the drug.

Recall that the second submodel of the ICAD model is a direct cascade of Holford's second and fourth submodels. For Holford's pharmacodynamic submodel we adapted a sigmoid *E-max* model [16], thus:

$$p(t) = \frac{f_{1/2}^{\gamma}}{f_{1/2}^{\gamma} + f(t)^{\gamma}} \tag{1}$$

where $p(t)$ represents the production rate of vitamin-K dependent clotting factors and $f(t)$ represents the dose, and where the two parameters $f_{½}$ and γ determine the position and shape of the sigmoid curve. The measured INR depends on the level of the clotting factors, but also varies because of the differential sensitivity to the used thromboplastin reagent. Because during normal therapy these quantities are unknown, and because the thromboplastin reagent batch was not imported in the database, we assumed a simple hyperbolic relationship between the prothrombin complex activity (PCA) and the INR, such that:

$$\mathrm{INR}(t) = a + \frac{b}{\mathrm{PCA}(t)} \tag{2}$$

where PCA(t) is the relative prothrombin complex activity (between 0 and 1) and *a and b* are two parameters. Per definition a prothrombin complex activity of 100% (PCA = 1) corresponds to an INR that equals 1 which implies that a + b = 1. Cascading equations (1) and (2) with p = PCA yields the following effective dose–INR relationship:

$$\mathrm{INR}(t) = 1 + s \cdot (f(t))^{\gamma} \tag{3}$$

in which we introduced the parameter $s{=}b/f_{1/2}{}^{\gamma}$ called the *sensitivity* of the patient.

Parameter estimation

Up to this point, the only unknown parameters in the model are the sensitivity of the patient s (eqn 3), the effective half-life of the anticoagulant $t_{½}$ (first submodel) $_{\text{and}}$ the *E-max* parameter γ (eqn 3). We assumed $t_{½}$ and γ to be attributes of the anticoagulant and therefore constant during the treatment. The sensitivity s is patient-dependent and assumed to be variable during the treatment. Therefore, s needs to be calculated during the course of the treatment, while the other two parameters can be optimized with retrospective data.

With each new visit to the anticoagulation clinic a new sensitivity follows from eqn 3, the measured INR and the calculated effective dose. Because the prescribed dose calendar is stored in the database the effective dose at the next visit can also be calculated. Using eqn 3 again, the effective dose together with the sensitivity can then be used to predict the INR at the next visit. Depending on how accurate the model is there will be a difference between the predicted INR and the measured INR. This difference is known because the measured INR at the next visit is also stored in the database and it can be calculated for each visit (except the first one) and for all treatments. These differences can thus be used as a measure of accuracy for the model. The parameters γ and $t_{½}$ can subsequently be optimized by minimizing these differences.

This means that the parameters are varied until the differences are minimal. This is done using a computer program and a minimization criterion, which is described in the Appendix. The resulting set of parameters are then said to be optimized because the mathematical model gives the best predictions with these parameters.

For each anticoagulant (phenprocoumon and acenocoumarol) we randomly assigned all treatment courses to a derivation and validation data set (half–half). The derivation data were used for optimizing the parameters by using a Nelder–Mead simplex (direct search) method. Comparison of the minimization criteria in both data sets was used to assess whether the model would yield a comparable accuracy in an independent data set.

With all the parameters known, the model can be used in an algorithm to determine which dosage would result in an INR equal to the target. This *maintenance* dose should equal the effective dose in eqn 3 such that the INR equals the target:

$$d = \left(\frac{\mathrm{INR}^{\mathrm{target}} - 1}{s}\right)^{1/\gamma} \qquad (4)$$

where d equals the dosage proposal, $\mathrm{INR}^{\mathrm{target}}$ equals the target INR and s equals the sensitivity.

It is known that the INR shows random variations that are not related to prolonged changes in the sensitivity to the coumarin derivate. These random variations will affect the calculated sensitivity at each visit and would subsequently have an effect on the prescribed dosage. In the algorithm therefore, the calculated sensitivity is averaged with previously calculated values. The weight of these values decreases exponentially in time [17,18]. Figure 2 shows the resulting flow diagram that is used in the algorithm.

The algorithm is furthermore tolerant for small variations in the sensitivity (no dosage change) and puts a limit on the maximum allowable dosage change (either positive or negative). The change in sensitivity since the last visit to the anticoagulation clinic can be regarded as a measure of patient stability. The algorithm uses this value to calculate a new appointment period by applying a simple empiric relationship. The Appendix gives a short overview of the most important equations.

Expert evaluation

To assess whether the dosage proposals and appointment periods calculated by the algorithm are acceptable, prior to designing a study to clinically test the algorithm, 95 visits for acenocoumarol and 99 visits for phenprocoumon were randomly selected from the total number of included visits. The algorithm was used to generate dosage proposals for these selected visits. These proposals were independently analyzed by two physicians who are experts in dosing oral anticoagulation at the anticoagulation clinic in Leiden. The proposals were scored according to a three-point system. One point was assigned to dosage proposals and appointment periods that were in complete agreement with the expert opinion ('good'),

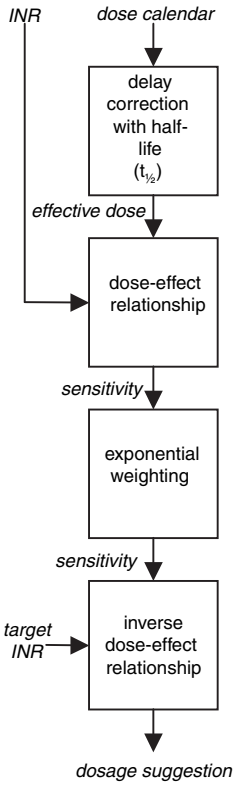

Fig. 2. Flow diagram showing the most important steps the algorithm takes to calculate a new dosage suggestion (bottom) from the measured INR and prescribed dose calendar (top). First the dose calendar is used to calculate the effective dose at the time of the visit, using the effective half-life parameter $t_{½}$. Together with the measured INR, the effective dosage is used to calculate the sensitivity of the patient. This sensitivity is averaged with previous measured sensitivities using exponentially decreasing weight factors. The averaged sensitivity is then used to calculate a new dosage suggestion from the target INR by applying the inverse dose–effect relationship.

2 points were assigned to proposals that were marked 'acceptable', which meant that the expert would have prescribed by himself or herself a slightly different dosage prescription or appointment period (the ICAD dosage proposal was, however, considered sufficiently safe to be accepted), 3 points were given if the dosage proposal or appointment period was different from the expert opinion in such a way that a serious under or over dosage was to be expected ('unacceptable'). Afterwards, the database was used to determine for which cases TRODIS made a dosage proposal in the past. The proposals made by TRODIS were not evaluated.

Results

Parameter estimation

From the computerized databases of the three anticoagulation clinics we imported 23 481 treatment courses (14 917 treatment courses with acenocoumarol and 8564 treatment courses with phenprocoumon) that fell within the specified time span. These

Table 1 Characteristics of included treatment courses

	Anticoagulant			
	Acenocoumarol		Phenprocoumon	
No. of treatments	1279		937	
(No. of visits)	(16 314)		(12 997)	
Male (%)	47		51	
Average age (years) at onset of treatment	57		58	
Average no. of visits	12.8		13.9	
Average visit interval (days)	13.3		16.4	
INR target range	2.5–3.5	3.0–4.0	2.5–3.5	3.0–4.0
No. of treatments	1141	138	808	129
(No. of visits)	(13 502)	(2812)	(9854)	(3143)
Average INR	2.67	3.15	2.92	3.33
SD	(1.24)	(1.28)	(1.10)	(1.27)

treatment courses comprised a total of 322 262 recorded visits (198 636 with acenocoumarol and 123 626 with phenprocoumon). From these data 1279 treatment courses (16 314 visits) with acenocoumarol and 937 treatment courses (12 997 visits) with phenprocoumon complied with our inclusion criteria. Most treatments were excluded because the patient used coumarins before the start of the treatment, or because the initial dose at the onset of treatment had not been correctly stored in the database and was not available.

Table 1 shows the characteristics for these treatment courses using the data stored in the database. From the total of 1279 treatment courses with acenocoumarol, 640 were assigned to a validation set, whereas 639 were assigned to a derivation set. From the total of 937 treatment courses with phenprocoumon 469 were assigned to a phenprocoumon validation set, whereas 468 were assigned to a derivation set. The parameters $t_{½}$ and γ that were estimated with the derivation data sets are presented in Table 2. For acenocoumarol an effective half-life of 2.08 days with a standard error (SE) of 0.08 days was found, whereas for phenprocoumon an effective half-life of 8.35 days (SE 0.15) was found. The estimate of parameter γ was 2.37 (SE 0.10) for acenocoumarol and 2.71 (SE 0.07) for phenprocoumon. When we compared the minimized criteria of the derivation data sets with the criteria of the validation data sets it became clear that the model performed similarly on an independent set of data.

Table 2 Results for the parameter estimation. Upper part of table shows the results of optimizing parameters γ and $t_{½}$ for both acenocoumarol and phenprocoumon and the resulting minimization criterion for both the derivation and validation data sets

	Anticoagulant	
	Acenocoumarol	Phenprocoumon
γ (SE)	2.37 (0.10)	2.71 (0.07)
$t_{½}$ (SE) days	2.08 (0.08)	8.35 (0.15)
Minimization criterion in derivation set	0.673	0.443
Minimization criterion in validation set	0.666	0.442

Table 3 Results of the expert evaluation

Total score dose/ appointment proposal	Anticoagulant		Total (%)
	Acenocoumarol (%)	Phenprocoumon (%)	
2	75 (78.9%)	75 (75.8%)	150 (77.3%)
3	13 (13.7%)	15 (15.2%)	28 (14.4%)
4 (two acceptable scores)	1 (1.1%)	4 (4.0%)	5 (2.6%)
Total of above	89 (93.7%)	94 (94.9%)	183 (94.3%)
4 (one bad, one good)	4 (4.2%)	2 (2.0%)	6 (3.1%)
5	2 (2.1%)	3 (3.0%)	5 (2.6%)
6	0	0	0
Total of all	95 (49%)	99 (51%)	194 (100%)

Expert evaluation

The 194 dosages and appointment periods proposed by the ICAD algorithm were independently analyzed by two experts. Table 3 shows the results. One hundred and seventy-eight (91.8%) ICAD proposals were considered good by at least one expert and bad by none. In 183 cases (94.3%) the proposal was qualified either good or acceptable by both experts. In 39 cases the experts disagreed: in 28 cases one expert qualified the ICAD proposal as good while the other qualified it as average, in six cases the proposal was qualified as good as well as bad and in five cases as acceptable and bad. In 61 of the 150 (77.3%) cases in which the ICAD proposal was qualified as good by both experts, TRODIS was not able to present a proposal.

Discussion

A simplified model with a reduced set of parameters was derived from Holford's theoretical model structure, and this model could be used to calculate dosage proposals for the physician. Using data from three anticoagulation clinics we optimized the parameters of the model for both acenocoumarol and phenprocoumon, while a similar procedure can be used to estimate parameters for other coumarin derivatives, such as warfarin. Finally, evaluations by two experts showed a high acceptance of the dosage and appointment period proposals of the algorithm.

Several earlier studies have modeled pharmacodynamics using a sigmoid *E-max* model. Although these studies use warfarin as the anticoagulant agent, the estimation of the *E-Max* parameter γ largely complies with our findings [19,20]. The first ICAD submodel describes the influence of all dynamic processes that determine the time-dependent relationship between dose and INR. Because pharmacokinetics is known to be of major influence, we expected the effective half-life to be at least as long as the half-life of the anticoagulant agent. The half-lives of acenocoumarol and phenprocoumon are, respectively, 24 h and 160 h, whereas we found longer effective half-lives of 50 and 200 h. It is likely that the difference of

approximately 1.6 days can be attributed to the remaining processes that have a time-dependent and delaying influence.

Based on data from six anticoagulation clinics, it has recently been shown that the variability in control of treatments with acenocoumarol is higher compared to that with phenprocoumon [21,22]. This could explain why with phenprocoumon a longer mean visit interval is found compared to treatment courses with acenocoumarol (13.3 days vs. 16.4 days), although the mean INR is closer to the center of the INR target range.

A combination of several factors makes it difficult for the dosing physician to determine a reliable new dosage. These are variability of the patient's sensitivity, the delay in the effect of the anticoagulant, the variability in the prescribed doses and the unpredictable variations in the measured INR. TRODIS uses an empiric dose–INR relationship that does not take into account the above-mentioned factors and the dose–INR relationship is chosen to be steep so that proposed dosage corrections are relatively small. As a result, TRODIS reacts slowly to changes in the sensitivity to the drug which leads to lower time-in-range. TRODIS resembles other algorithms that are described in literature like Coventry, Hillingdon and DAWN AC in a sense that they combine a decision tree or table with an empiric dose–INR relationship [5,7,10,23,24].

One drawback of the model-based strategy that we followed is that the quality of the dosage proposals is limited by the accuracy of the underlying mathematical model. In this study, the parameters were fitted using a large amount of historical data, but the equations themselves remain theoretical. A better model could be derived if not only the prescribed doses and measured INR were known, but also intermediate variables like the plasma level of the anticoagulant and the level of individual clotting factors. However, these measurements were not present in the available data of the anticoagulation clinics and are not used in daily practice, in which clotting factor measurements are not routinely carried out.

Another important drawback of the model-based approach is that the model is fitted on historic data and there is no guarantee that the inverse path, calculating the necessary dosage from the target INR, yields accurate dose prescriptions. Although the expert evaluation gives an indication of the quality of the dosage proposals, it cannot be used as a gold standard, because we expect that the new algorithm will yield better controlled anticoagulation therapies than those that are currently achieved by the physicians and TRODIS.

An important advantage is that improvements to the mathematical model can easily be incorporated into the algorithm. The model could, for example, be enhanced with more input variables like individual clotting factors or the sensitivity of the thromboplastin reagent.

The next step will therefore be to start a randomized controlled trial that compares the new algorithm against TRODIS. The expert evaluation shows that the dosage and appointment periods proposed by the algorithm were highly acceptable by the two experts, which makes such a randomized trial feasible and justified. We hope that a model-based and more quantitative approach to the prescription of oral anticoagulants, as proposed in this study, will lead to safer and more effective anticoagulation therapies.

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Appendix

Minimization criterion

The INR by definition is a ratio between two quantities and has a theoretical lower bound of 1. Therefore it is mathematically more correct to use the natural logarithm of the ratio of the predicted INR and measured INR, both corrected for the lower bound, as a measure of accuracy. The root mean square of this quantity was taken as the minimization criterion:

$$J = \sqrt{\overline{\log\left(\frac{\mathrm{INR}^{\mathrm{predicted}} - 1}{\mathrm{INR}^{\mathrm{measured}} - 1}\right)^2}} \tag{5}$$

The ICAD algorithm

The dose calendars with daily drug doses are used to calculate the effective dose up to the last day of the treatment course using the following formula:

$$f_{n+1} = \lambda \cdot f_n + (1 - \lambda) \cdot d_n \tag{6}$$

with f_n the effective dose at day n and d_n the dose that was taken at day n according to the dose calendar. The parameter λ corresponds to the relative decrease per day of the effective dose. It can also be expressed as the number of days that corresponds to a decrease of 50%, which yields the more intuitive effective half-time: $t_{½} = (\log ½)/(\log \lambda)$ (in days). Because only treatment courses were included where onset of treatment by the anticoagulation clinic also means initiation of anticoagulation therapy it is known *a priori* that the initial effective dose is zero ($f_0 = 0$).

After the k^{th} visit to the coagulation clinic the effective dose is combined with the measured INR to yield a first estimate of the sensitivity:

$$s_k = \frac{\mathrm{INR}_k - 1}{f_k^{\gamma}} \tag{7}$$

with s_k the sensitivity at visit k, INR_k the measured INR at visit k, and f_k the calculated effective dose at visit k.

This sensitivity is averaged with previous sensitivities using exponential weighting. The maintenance dose can subsequently be calculated from equation 4.